Análisis longitudinal de potenciales biomarcadores neurofisiológicos asociados a disfunción sináptica en una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante

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RESUMEN

Comprender la enfermedad de Alzheimer como un continuum biológico trae consigo el reto de la búsqueda de biomarcadores preclínicos sensibles, accesibles y económicos que permitan la identificación temprana de personas en riesgo de sufrir esta enfermedad. Se ha descrito la disfunción sináptica como un fenómeno patológico que se presenta en etapas tempranas de la enfermedad y que es transversal en el proceso de la misma. La disfunción sináptica puede ser desencadenada por la presencia de productos intermedios de las proteínas amiloide y Tau, exacerbado por procesos inflamatorios y muerte neuronal. Esta disfunción sináptica genera un cambio en la dinámica cerebral, en el procesamiento de la información comprometiendo redes implicadas en procesos cognitivos que finalmente llevarán a la presentación de síntomas clínicos manifiestos descritos en esta patología. En este sentido surgen algunas opciones como los biomarcadores plasmáticos o biomarcadores derivados del procesamiento del qEEG. Se desconoce el comportamiento de estos biomarcadores en población preclínica con EA de origen genético y su asociación con los procesos de disfunción sináptica. Para responder estas preguntas, en esta tesis se llevaron a cabo 5 estudios independientes. El primer estudio fue una revisión sistemática en búsqueda de genes causales de demencia en Latinoamérica, se identificaron 9 variantes patogénicas en el gen de PSEN1, tres de ellas reportadas previamente en Colombia. Este estudio puso en evidencia la necesidad de realizar una búsqueda exhaustiva de variantes genéticas patológicas en Colombia para EA. En el segundo estudio se realizó un análisis de 900 genomas de pacientes con demencia temprana esporádica o con agregación familiar, se identificaron 21 variantes patogénicas, la mayoría de ellas con las 3 ascendencias continentales (Amerindio, europeo, Africano), 11 de ellas en el gen de PSEN1 con fenotipo amnésico en la mayoría de los pacientes con edades de inicio extremas desde los 32 años hasta los 57 años. Se seleccionó a la población PSEN1-E280A como modelo ideal de estudio para esta tesis por ser una población extensa ampliamente caracterizada. Con el tercer estudio se demostró una asociación entre los valores plasmáticos de p-tau217 con la patología *in vivo* en PET amiloide, PET TAU y

marcadores cognitivos en esta población. En un análisis regional en las neuroimágenes funcionales se resalta el compromiso de la precuña asociado a p-tau217 plasmática, previamente reportada como una región de interés en la fisiopatología de EA. Con el cuarto estudio se identifica la banda de frecuencia Beta como un potencial marcador neurofisiológico que en estadios preclínicos de ADAD muestra diferencias estadísticamente significativas entre portadores asintomáticos y no portadores. Esta señal se relaciona con componentes cuyo origen se estima en regiones posteriores, lo que resalta la importancia de los hallazgos previos en la precuña. Finalmente, el último estudio es una revisión sistemática que respalda los hallazgos de la disfunción sináptica como un modelo fisiopatológico en EA que genera alteraciones a diferentes niveles moleculares y celulares. En general, los hallazgos derivados de estas investigaciones permiten concluir que las variantes genéticas patológicas para EA son un modelo ideal de estudio donde la disfunción sináptica es un proceso fisiopatológico temprano y transversal al proceso de enfermedad, biomarcadores como p-tau217 permite predecir la patología in vivo y la banda de frecuencia Beta medida por qEEG se postula como un potencial marcador neurofisiológico con una edad media de aparición a los 30 años, sin embargo, los tamaños del efecto fueron modestos y con baja precisión. Se recomiendan muestras más amplias y un seguimiento más prolongado en futuras investigaciones.

Palabras Clave: Enfermedad de Alzheimer, PSEN1, Biomarcadores, p-tau217, electroencefalograma.

ABSTRACT

Understanding Alzheimer's disease as a biological continuum brings with it the challenge of searching for sensitive, accessible, and inexpensive preclinical biomarkers that allow the early identification of individuals at risk for this disease. Synaptic dysfunction has been described as a pathological phenomenon that occurs in early stages of the disease and is cross-cutting in the disease process. Synaptic dysfunction can be triggered by the presence of amyloid and Tau protein intermediates, exacerbated by inflammatory processes and neuronal death. This synaptic dysfunction generates a change in brain dynamics, in information processing, compromising networks involved in cognitive processes that will eventually lead to the presentation of manifest clinical symptoms described in this pathology. In this sense, some options arise such as plasma biomarkers or biomarkers derived from qEEG processing. The behavior of these biomarkers in preclinical population with AD of genetic origin and their association with synaptic dysfunction processes are unknown. To answer these questions, 5 independent studies were conducted in this thesis. The first study was a systematic review in search of causal genes of dementia in Latin America, 9 pathogenic variants in the PSEN1 gene were identified, three of them previously reported in Colombia. This study highlighted the need to conduct a comprehensive search for pathogenic genetic variants in Colombia for AD. In the second study, an analysis of 900 genomes of patients with sporadic early dementia or with familial aggregation was performed, 21 pathogenic variants were identified, most of them with the 3 continental ancestries (Amerindian, European, African), 11 of them in the PSEN1 gene with amnestic phenotype in most patients with extreme onset ages from 32 years to 57 years. The PSEN1-E280A population was selected as the ideal study model for this thesis because it is a large population that has been extensively characterized. The third study demonstrated an association between plasma p-tau217 values with in vivo pathology in amyloid PET, TAU PET and cognitive markers in this population. A regional analysis in functional neuroimaging highlights the involvement of the precuneus associated with plasma p-tau217, previously reported as a region of interest in the pathophysiology of AD. The fourth study identifies the Beta frequency

band as a potential neurophysiological marker that in preclinical stages of ADAD shows statistically significant differences between asymptomatic carriers and non-carriers. This signal is related to components whose origin is estimated in posterior regions, which highlights the importance of previous findings in the precuneus. Finally, the last study is a systematic review that supports the findings of synaptic dysfunction as a pathophysiological model in AD that generates alterations at different molecular and cellular levels. Overall, the findings derived from these investigations allow concluding that pathological genetic variants for AD are an ideal model of study where synaptic dysfunction is an early pathophysiological process and transversal to the disease process, biomarkers such as p-tau217 allow predicting pathology in vivo and Beta frequency band measured by qEEG is postulated as a potential neurophysiological marker with a mean age of onset at 30 years, however, effect sizes were modest and with low precision. Larger samples and longer follow-up are recommended in future research.

Keywords: Alzheimer's disease, PSEN1, Biomarkers, p-tau217, electroencephalogram.

1. INTRODUCCIÓN

I. Impacto de las demencias a nivel mundial y nacional

A. Epidemiología global de las demencias

Las demencias, son un grupo de trastornos que causan marcada discapacidad y dependencia funcional. Para el 2019 habían 55.2 millones de individuos con demencia; se estima que para el 2030 este número va a incrementar a 78 millones y para el 2050 a 139 millones de individuos, el 50% de los afectados viven en países de medianos a bajos ingresos, como es el caso de Colombia (1). Lo anterior está mediado por el crecimiento poblacional, el aumento multifactorial de la esperanza de vida global y el incremento de ciertos factores de riesgo para el desarrollo de enfermedades neurodegenerativas. Esto tiene como resultado el incremento de las muertes asociadas a pacientes con demencia, por eso se ha convertido desde el 2019 en la séptima causa de muerte en población adulta (2).

Se estima que la incidencia anual de demencia en adultos entre los 65 y 70 años es de 5/1000 habitantes. Para adultos mayores de 85 años la incidencia puede llegar a ser de 80/1000 habitantes (3). En total, el estimado es de 9.9 millones de nuevos casos por año (1). Esto se refleja en un mayor reto financiero para los sistemas de salud de los diferentes países dado el alto costo de la enfermedad, no solo por gastos médicos directos, sino también los indirectos y los gastos sociales no médicos (2).

Para el 2013, en Estados Unidos se estimó que el monto destinado al manejo de las demencias estuvo alrededor de los 157-215 mil millones de dólares (4). La estimación global para el 2030 es de 1.7 - 2.8 trillones de dólares. Las cifras anteriores se traducen en un alto impacto socioeconómico y social, lo que ha permitido que en los últimos años esta enfermedad sea considerada una prioridad en salud pública (2,4) y que la mayoría de los esfuerzos estén encaminados hacía la prevención y el diagnóstico temprano, especialmente en los estadios preclínicos de la enfermedad.

B. Epidemiología de las demencias en Latinoamérica y Colombia

En Latinoamérica, la prevalencia estimada de demencia es del 11%. Con respecto al sexo es más frecuente en mujeres (6%) en comparación de los hombres (5%), y es más prevalente en áreas urbanas que en áreas rurales. El factor de riesgo más importante es la edad: La prevalencia en adultos entre los 67-69 años es de 4.4% y 61.6% en mayores de 90 años. Se predice que para el 2050 la prevalencia va a aumentar 4 veces su valor en la región (5).

En Colombia, en el 2015 se llevó a cabo el Estudio de Salud, Bienestar y Envejecimiento (SABE Colombia 2015), donde se tomó información de una muestra representativa de la población adulta mayor colombiana que estaba conformada por 23.694 individuos de áreas urbanas y rurales. En ella se encontró que la prevalencia de deterioro cognitivo leve (DCL) en Colombia es del 17.9%, la prevalencia global de demencia fue del 9.4% (8.1% en hombres y 10.7% en mujeres) (6,7).

Por lo anterior, la demencia representaría un problema de salud pública dado que se trata de un grupo de enfermedades crónicas no transmisibles con discapacidad por pérdida de la autonomía, que no tienen hasta el momento, tratamiento para modificar su curso y que con la progresión de la enfermedad se va aumentando la necesidad de cuidado. Esto no solo representa un problema para el individuo que padece la enfermedad, sino también para sus familiares, quienes en muchos casos encabezan el cuidado de los pacientes hasta el final de sus días, igualmente para el sistema de salud. Estudios de estimación del gasto han determinado que, en Colombia, en promedio, un paciente con demencia puede gastar entre 1.200 y 2.300 dólares por año. Esta cifra es mucho mayor (5.400 dólares aproximadamente) en estadios severos de la enfermedad (8).

C. Demencia precoz en el mundo

El término demencia precoz hace referencia a los trastornos neurocognitivos que aparecen antes de los 65 años. Estos casos son de especial relevancia porque

pueden iniciar tan temprano como la 4ta o 5ta década de la vida, tiene un curso más agresivo que las formas tardías de la enfermedad y afecta la vida laboral, ocupacional y social de una manera más drástica. De hecho, su aparición antes de los 60 años está dentro de las 10 principales causas de años de vida saludable perdidos por discapacidad (YLDs por sus siglas en inglés) (2).

Se estima que la prevalencia global de este tipo de demencia es de 119 personas por 100.000 habitantes, que se refleja en 3.9 millones de personas en el mundo con demencia precoz (9). En un metaanálisis llevado a cabo en 2021 se estimó que la incidencia anual es de 370,000 casos nuevos por año utilizando la población mundial estimada para 2019. Adicionalmente, en este estudio no hubo reporte de incidencia ni prevalencia de demencia precoz en Colombia por ausencia de estudios poblacionales relacionados con esta condición (10).

Entre las etiologías de la enfermedad, destaca con una mayor prevalencia la Enfermedad de Alzheimer (EA), seguido de la demencia vascular (VaD) y la demencia frontotemporal (9). En otras cohortes, se han identificado también como causas de demencia precoz los traumas craneoencefálicos, la demencia con cuerpos de Lewy y la demencia relacionada a los trastornos por consumo de alcohol (11).

II. Enfermedad de Alzheimer

A. Definición

La EA es la principal causa de demencia en el mundo y está caracterizada por la acumulación anómala de beta-amiloide (Aβ) en forma de placas neuríticas y de proteína tau hiperfosforilada que forma ovillos neurofibrilares. Esto conlleva a la pérdida progresiva de la memoria episódica, con subsecuente compromiso del resto de procesos cognitivos como función ejecutiva y lenguaje, afectando la funcionalidad de los individuos (12).

La principal causa de demencia de inicio temprano es la EA, que representaría aproximadamente un tercio de los casos (13). Alrededor del 5-10% de los casos con enfermedad de Alzheimer de inicio temprano (EOAD) son de origen familiar (FAD) por herencia autosómica dominante; patología explicada por variantes genéticas

patogénicas de penetrancia completa en los genes de la proteína precursora de amiloide (APP) (<1%), en el gen de la presenilina 1 (PSEN1) (6%) y en el gen de la presenilina 2 (PSEN2) (1%). Las variantes genéticas patológicas en PSEN1 son la causa más común de FAD (14).

Si bien es cierto que el origen familiar y temprano de la EA es de menor frecuencia que las formas esporádicas, éstas son de especial interés porque tienen un curso clínico más agresivo, con mayor riesgo de mortalidad (13), un alto número de afectados entre las familias y su presentación generalmente es en edades reproductivas y productivas. Adicionalmente, representan un modelo ideal de estudio que permite realizar un seguimiento longitudinal desde etapas preclínicas hasta etapas clínicas de la enfermedad, permite explorar en la población en riesgo intervenciones tempranas que conlleven a un diagnóstico preclínico y potencialmente a terapias modificadoras del curso de la enfermedad.

Además de las particularidades previamente descritas, estos pacientes también tienen diferentes fenotipos clínicos. Se han descrito la presencia de cefalea, mioclonías tempranas, convulsiones, alteraciones de la marcha, afecto pseudobulbar, síntomas comportamentales marcados e hiperreflexia (13,14).

B. Variantes genéticas

A diferencia de la enfermedad de Alzheimer de inicio tardío (LOAD) la cual es una enfermedad de etiología heterogénea, la EOAD está determinada principalmente por la genética con una heredabilidad del 92-100%. De hecho, entre el 30-65% de los individuos con EOAD tienen un familiar afectado en el primer grado de consanguinidad. Como se describió previamente, la APP, PSEN1 y PSEN2 son los genes principalmente implicados en el desarrollo de EOAD (15).

El gen de la APP está ubicado en el cromosoma 21q.21, contiene 19 exones y los 16-17 son los que producen Aβ. Su localización se ha comprobado en estudios llevados a cabo en individuos con trisomía 21, quienes al tener una copia adicional del gen expresan las características patológicas y clínicas de EOAD (16). La APP es una proteína transmembrana tipo 1 que está involucrada en procesos de neurogénesis y de regulación de la diferenciación celular. Postransduccionalmente, esta proteína puede tomar dos vías que están mediadas por las enzimas β-secretasa, α-secretasa

y γ-secretasa (17). El clivaje de la APP por la α-secretasa y la γ-secretasa conducen a la vía no amiloidogénica en la cual se produce una molécula soluble o sAPPa, que es posteriormente degradada intracelularmente por vía endosomal/lisosomal. En la vía amiloidogénica, el primer clivaje de la APP se lleva a cabo por la β-secretasa, lo cual produce Aβ40 y 42, este último el mayor implicado en la formación de placas seniles por su hidrofobicidad (18).

Hasta el momento, 73 variantes genéticas patógenas en el gen de la APP se han reconocido en el mundo. Algunas revisiones estiman que estas variantes están presentes en 119 familias (19). La mayoría de las mutaciones en este gen son de tipo no sinónimas, seguidas de las mutaciones *missense* las cuales tienen una penetrancia completa y por último las duplicaciones, que tienen una menor penetrancia y mayor variabilidad en su presentación (15).

La PSEN1 es una proteína transmembrana que posee 467 aminoácidos. Esta es miembro del complejo de la γ-secretasa y por ende tiene un rol en el procesamiento de la APP (20). Con respecto a las variantes genéticas, en el gen de la PSEN1 se han reportado más de 350 variantes genéticas patogénicas en más de 475 probandos. El rango de edad de inicio de síntomas en individuos con la mutación en esta proteína suele estar entre los 30-50 años, tiene una penetrancia completa y puede tener distintas formas de presentación: paraparesia espástica, síntomas extrapiramidales, síntomas comportamentales marcados, episodios convulsivos temprano en el curso de la enfermedad y ataxia cerebelosa (15).

La PSEN2 también es una proteína transmembrana que comparte un 65% de homología con la PSEN1. Su función además de catalítica en el complejo de la enzima γ-secretasa, es la regulación de la homeóstasis del calcio intraneuronal, refuerzo del acople mitocondria-retículo endoplásmico y regulación de la autofagia. Hasta el momento hay 87 variantes genéticas reportadas en el gen que codifica para esta proteína. Clínicamente, el inicio de la enfermedad es a los 40-70 años, aún no se conoce con exactitud la penetrancia por el número reducido de individuos con mutaciones en este gen (21).

C. Familias con variante genética PSEN1-E280A

En el año 1987, Cornejo y colaboradores, reportaron el primer caso de enfermedad Alzheimer de origen familiar por herencia autosómica dominante en Colombia. Esta familia, conformada por 6.000 miembros aproximadamente, presenta una variante genética patogénica en PSEN1 y es el resultado del cambio de glutamina por alanina en la posición 280 del gen que codifica para esta proteína (E280A). Esta es la comunidad emparentada con una variante genética que produce FAD más grande reportada en el mundo (22,23).

Clínicamente, estos individuos presentan deterioro cognitivo leve entre los 43 - 45 años, demencia entre los 49 - 50 años y la media de edad de muerte es de 59 años. En cuanto a los síntomas, el más frecuente es la alteración de la memoria episódica, seguida de cambios comportamentales, alteraciones del lenguaje, cefalea, alteraciones en la marcha, convulsiones y mioclonías, signos cerebelosos y parkinsonismos.

Esta variante genética, al ser de penetrancia completa y estar presente en un número importante de individuos en Antioquia, la cual ha tenido un seguimiento continuo desde 1994, representaría un modelo nativo ideal para el estudio de la enfermedad de Alzheimer como un continuo biológico y no como una condición derivada de un evento único (24). La presencia de esta mutación explica completamente la presentación de la enfermedad en estos individuos, es decir, todos los portadores con una probabilidad cercana al 100% van a padecer la enfermedad. Por ende, en ellos se puede estudiar el comportamiento de distintas variables (síntomas cognitivos o conductuales, biomarcadores en plasma, suero, o líquido cefalorraquídeo, neuroimágenes, variables electrofisiológicas y biomarcadores no convencionales) desde las etapas presintomáticas de la enfermedad. Conocer cómo estas variables se comportan en el tiempo aumenta el entendimiento de la fisiopatología de la enfermedad y en consecuencia permite la identificación de posibles blancos terapéuticos.

2. PLANTEAMIENTO DEL PROBLEMA

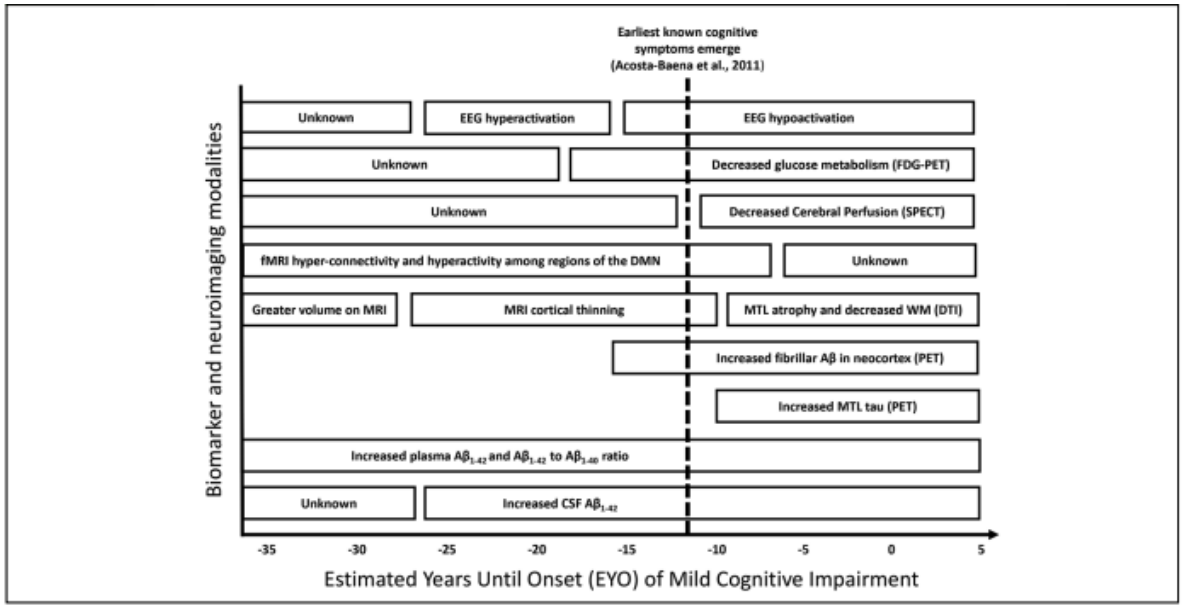
I. Proceso fisiopatológico

Actualmente se entiende la EA como un continuo biológico y clínico, en el cual la enfermedad inicia mucho antes de la aparición de los síntomas clínicamente significativos. Esto implica entonces una etapa preclínica o presintomática, que en el caso de las personas con la variante genética PSEN1-E280A se estima que inicia en la segunda a tercera década de vida; y una etapa clínica o sintomática que inicia con el deterioro cognitivo leve (DCL) que progresa en 4-5 años a demencia (25).
En la variante genética de PSEN1-E280A, se han propuesto dos etapas clínicas pre-sintomáticas:

- El pre DCL-asintomático, el cual es una etapa donde el sujeto no presenta quejas subjetivas de memoria, pero si es posible detectar un declive asintomático significativo en las pruebas neuropsicológicas.
- El pre DCL-sintomático, etapa en la cual el sujeto presenta quejas subjetivas de memoria y declive significativo en las pruebas neuropsicológicas (26).

Lo anterior hace parte del continuo si se mira desde la óptica clínica, sin embargo, la trayectoria de la enfermedad no solo involucra los síntomas sino también los cambios fisiopatológicos. En este orden de ideas, se ha demostrado que en estas modificaciones fisiopatológicas aparecen en individuos todavía con desempeño cognitivo normal, por esto el estudio en etapas presintomáticas de la enfermedad cobra relevancia (27).
Los biomarcadores que determinan la presencia de la enfermedad son la acumulación de Aβ y de proteína tau hiperfosforilada. Ambos se pueden medir en líquido cefalorraquídeo (LCR), con imágenes funcionales de tomografía por emisión de positrones (siglas en inglés PET) para Beta-Amiloide, en plasma o suero. En el caso particular de los individuos con la variante genética en PSEN1-E280A, se ha realizado

un seguimiento longitudinal que permite describir las edades promedio de aparición de cada uno de estos biomarcadores (ver figura 1) (28). Esto ha permitido comprender la organización de los eventos fisiopatológicos determinantes de la enfermedad en la línea del tiempo en esta población.



A synthesis of the Colombian kindred biological marker literature is presented as a function of the estimated years until the median age of onset of mild cognitive impairment in this cohort. The hypothetical trajectories of the biological markers of ADAD in this cohort are displayed relative to the earliest known signs of cognitive decline at a median age of -12 EYO (dashed line; Acosta-Baenta et al., 2011). Note: fMRI = EEG = electroencephalogram; FDG-PET = fludeoxyglucose positron emission tomograph; SPECT = single-photon emission computerized tomography; FMRI = functional magnetic resonance imaging; DMN = default mode network; MRI = structural magnetic resonance imaging; WM = white matter; DTI = diffusion tensor imaging; Aβ = amyloid-beta; PET = positron emission tomography; MTL = medial temporal lobe; CSF = cerebral spinal fluid.

Figura 1: Modelo hipotético de progresión de marcadores biológicos de enfermedad de Alzheimer debido a la variante genética PSEN1-E280A. Tomado de Fuller et al. (28).

En estudios en población con riesgo genético y en modelos animales, se ha demostrado que el evento inicial en la fisiopatología de la EA es el acúmulo de Aβ (29,30). Sin embargo, la amiloidosis, en términos del modelo causal, es necesaria pero no es suficiente para generar deterioro cognitivo clínicamente significativo, se requiere la asociación con otros cambios: Disfunción sináptica, la formación de ovillos neurofibrilares, neurodegeneración y pérdida neuronal. De estos anteriores, el mejor correlato de deterioro cognitivo en EA es la presencia de taupatía y disfunción sináptica, que como se describe más adelante, en parte es consecuencia de la amiloidosis cerebral (30).

La acumulación de Aβ, aparte de ser el evento inicial, es el desencadenante del resto de la cascada fisiopatológica. La hiperfosforilación de Tau, aunque es un hecho multifactorial, está propiciado por la acumulación de Aβ en cualquiera de sus formas.

Esto se ha demostrado en modelos animales y en sistemas de cultivos celulares 3D, en los cuales cuando se bloquea la producción de Aβ también se inhibe la hiperfosforilación de proteína Tau (29). Con base en esto, se puede intuir que la disfunción sináptica es un evento que ocurre tanto en etapas preclínicas como clínicas, y que es transversal a los dos eventos fisiopatológicos principales.

II. Amiloidosis

A. Desbalance entre agregación y acumulación

La agregación y acumulación de Aβ es el evento patológico que determina la EA. En la génesis de esta molécula, la APP es proteolizada por β-secretasa, la enzima BACE1 (Por sus siglas en inglés que corresponden a *β-site APP cleaving enzyme 1*), y la γ-secretasa. De este clivaje se obtiene Aβ42 y Aβ40. La primera es el principal componente de las placas, la última está más relacionada con angiopatía amiloide y tiende a acumularse en los vasos sanguíneos de las leptomeninges.

El proceso de fibrinogénesis inicia con la formación de monómeros de Aβ, estos posteriormente atraviesan un proceso de nucleación primaria del cual se obtienen estructuras oligoméricas, algunas tóxicas (*On-pathway oligomerization*) y otras que se consideran no tóxicas (*Off-pathway oligomerization*). Posteriormente, los oligómeros tóxicos pasan por el proceso de elongación donde se obtienen protofibrillas y luego fibrillas. Estas últimas son altamente hidrofóbicas y son resistentes al clivaje por proteólisis por lo que se acumulan en placas.

El primer producto, los monómeros, no son moléculas tóxicas y se ha demostrado en modelos animales que lo que causa la alteración de la transmisión sináptica, deterioro cognitivo y la muerte neuronal es la agregación de estos monómeros, es decir, las estructuras oligoméricas.

Los oligómeros, son moléculas de bajo peso molecular, hidrosolubles, que tienden a ser más tóxicas que las hebras beta y las placas. Lo anterior está explicado porque los oligómeros, al ser solubles, interactúan con las membranas celulares alterando su integridad e inducen mayor respuesta inflamatoria.

Con respecto a las placas, estas se ubican principalmente en el espacio extracelular (aunque pueden pasar al espacio intracelular con facilidad) (31,32), alrededor de las neuronas y las células de la glía. Una vez formada la placa, esta interacciona con las membranas celulares y genera poros, activa los canales de calcio por estimulación de receptores NMDA y genera desestabilización de la polaridad celular.

Normalmente, las neuronas mantienen un alto gradiente de calcio en reposo mediado por altos niveles extracelulares y bajos niveles en el citosol. El Aβ cuando entra en contacto con las membranas celulares, se adhiere a ellas, las expande y genera poros que funcionan como canales iónicos. Por tanto, hay un alto influjo de calcio a la neurona, se pierde el gradiente, lo que se expresa en neurodegeneración por alteración de la polaridad celular. Este fenómeno, también llamado dishomeostasis del calcio, altera el transporte de vesículas, la función mitocondrial, aumenta las especias reactivas de oxígeno y en últimas conlleva a muerte neuronal.

B. Acción de la variante PSEN1 en el sitio de corte de APP

La PSEN1 es una proteína transmembrana que posee 9 dominios que están conectados por puentes hidrofílicos tanto en la cara intracelular como en la extracelular. Su función enzimática está mediada por la presencia de ácido aspártico en los dominios transmembrana 6 (TM6) y 7 (TM7), y por la región N-terminal que se ubica en el dominio y puente 1 (TM1 y HL1 respectivamente).

Una vez la β-secretasa ha realizado la primera proteólisis de la APP, la porción extracelular se remueve casi completamente, dejando el extremo C terminal libre para ser dividido por el complejo de la γ-secretasa (33). Es en esta parte del proceso que se forma el complejo PSEN1/2, nicastrina y anterior pharynx-defective 1 (Aph1), y es por este que se termina el clivaje de la APP. Las variantes patogénicas en PSEN1 pueden generar ganancia o pérdida de la función de la enzima, esto se resume en sobreproducción de Aβ y aumento del índice Aβ largo/corto (Aβ42/40). Además de esto, la PSEN1 puede afectar el procesamiento de múltiples sustratos diferentes a la APP, como Notch, Wnt y β-catenina (20).

C. Placas de amiloide y ambiente inflamatorio

Alrededor de la hipótesis amiloidea, la neuro-inflamación ha tomado un papel relevante como un factor que contribuye a la exacerbación de síntomas y como un factor diferencial en la presentación de la enfermedad. Para que exista neuro-inflamación debe haber un estímulo que desencadena la activación de la microglía, en este caso es la acumulación de Aβ. Una vez esto ocurre, las células de la microglía secretan citoquinas (interleuquina 1 Beta, interleuquina 6 y factor de necrosis tumoral alfa) y quimioquinas proinflamatorias, que en últimas reclutan más células de la microglía y astrocitos en el sitio de la injuria (34).

En condiciones normales, este mecanismo de depuración inmune es autolimitado y finaliza cuando el patógeno o el daño ha sido resuelto. En el caso de la EA esto no ocurre porque las células del SNC no tienen la capacidad de eliminación del Aβ, lo que genera una liberación excesiva de moléculas proinflamatorias. A esto se le suma el daño celular provocado por esta reacción inflamatoria, que a su vez genera reactividad a nivel microglial y astrocítico (34).

Otra vía propuesta por la que se desencadena la neuro-inflamación es a través de la disfunción mitocondrial. La mitocondria es el principal organelo involucrado en la producción de energía celular y es particularmente vulnerable a la toxicidad por acumulación de Aβ. Los mecanismos propuestos reportan que la interacción entre las placas y este organelo generan una alteración en el funcionamiento de las enzimas que conforman la cadena de transporte de electrones, principalmente el citocromo c oxidasa. Asimismo, la interacción del Aβ con la enzima alcohol deshidrogenasa de unión a amiloide, hace que haya un cambio conformacional en esta última, alterando la permeabilidad de la membrana mitocondrial y de la cadena respiratoria (32).

Lo anterior provoca un aumento en las especies reactivas de oxígeno (ROS), una disminución de los mecanismos compensatorios para la eliminación de estas moléculas y subsecuentemente un aumento del estrés oxidativo. Este fenómeno puede aparecer tempranamente en la patogénesis de la enfermedad una vez haya placas neuríticas en el espacio extracelular (32).

Adicionalmente, se pierde la capacidad de utilizar eficientemente la glucosa y se disminuye la producción de energía (32). Esto es deletéreo especialmente en las mitocondrias que se ubican en los botones sinápticos donde la demanda de energía es alta por la liberación de neurotransmisores. Por ende, la disfunción mitocondrial en

EA se asocia con daño en la plasticidad sináptica y activación de vías pro-apoptóticas (32).

III. Taupatía

A. Mecanismos de hiperfosforilación, acumulación y agregación

La proteína Tau es una molécula asociada a los microtúbulos que está implicada en el transporte axonal y ensamblaje microtubular. Su función principal es servir como estabilizador de los microtúbulos en los extremos distales de axones y dendritas. Desde el punto de vista genético, esta proteína es producto de la codificación del gen *MAPT* en el cromosoma 17 y en el SNC se expresan 6 isoformas diferentes.

En condiciones normales, 1 mol de proteína tau tiene 2-3 moles de fosfato, por tanto, sufre procesos de fosforilación y desfosforilación, de manera equilibrada, para poder mantener la adecuada función de la molécula. Las enzimas implicadas en la fosforilación están divididas en tres grupos: Proteínas quinasas dirigidas por prolinas (PDPK), proteínas quinasas no dirigidas a prolina (*Non-PDPK*), proteínas tirosina quinasa (TKP).

En condiciones patológicas, esta molécula se fosforila entre 3 y 4 veces más de lo normal, con una predilección por los procesos de fosforilación por encima de los de desfosforilación. Este proceso de hiperfosforilación se lleva a cabo en el extremo C-terminal de la proteína tau. En primera instancia esto genera un autoensamblaje de la proteína que a su vez lleva a la formación de los filamentos helicoidales. Tau hiperfosforilada (TauP) se trasloca al soma, generalmente en forma de filamento helicoidal, y estos a su vez se ensamblan para formar los ovillos neurofibrilares (NFTs), el segundo componente neuropatológico de la EA.

Los NFTs se pueden observar histopatológicamente y se identifican tres fases en su formación:

- Pre-NFTs: Acumulación anormal de TauP en el citosol de las neuronas

- NFTs maduros: Agregados en el pericarion de TauP que desplazan el núcleo a la periferia.
- NFTs fantasmas: Depósitos de TauP en el espacio extracelular por muerte neuronal.

Generalmente este proceso ocurre en presencia de variantes genéticas en las enzimas o por estimulación por parte de los oligómeros de Aβ a las enzimas Quinasa C-jun amino-terminal (JNK) y la Glucógeno sintasa quinasa 3 (GSK3) (35–37). Las placas de Aβ juegan también un papel importante y en modelos animales se ha demostrado que pueden generar la conversión patológica de Tau a TauP, lo que nos permite intuir que la amiloidosis precede a la taupatía en EA.

Con respecto a su localización, la acumulación de TauP típica inicia en la región trans-entorrinal (Etapas 1 y 2 de Braak), luego involucra la corteza límbica (Etapa 3 y 4 de Braak) y finalmente se extiende a la neocorteza (Etapas 5 y 6 de Braak). La progresión a través de estas estructuras se correlaciona con la severidad de la demencia (27). Sin embargo, hasta en el 25% de los casos se pueden reportar formas atípicas en su distribución: predominantemente en corteza límbica o un patrón de conservación hipocampal. En el primer patrón, generalmente la progresión de la enfermedad es más lenta y las características clínicas son típicas de EA, mientras que en el patrón de conservación hipocampal la progresión es más rápida y se presenta con signos focales atípicos (38).

B. Neurodegeneración asociada a tau

La homeóstasis microtubular es esencial para mantener una adecuada morfología celular, conservar las funciones y viabilidad de la célula. La hiperfosforilación de tau no solo afecta la actividad biológica celular, sino que adicionalmente se convierte en una molécula altamente tóxica para las neuronas. De hecho, TauP irrumpe la interacción entre moléculas de tau normales y los microtúbulos, así como otras moléculas implicadas en el ensamblaje de los mismos (39). Tau hiperfosforilada en últimas genera una axonopatía por bloqueo del tráfico celular de organelos y moléculas implicadas en la transmisión sináptica y en procesos de plasticidad. Esto último resulta en neurodegeneración y deterioro en la cognición.

IV. Disfunción Sináptica

A. Concepto de disfunción sináptica

La disfunción sináptica es un evento fisiopatológico que altera las conexiones neuronales a múltiples escalas: Molecular, celular, redes cerebrales, corteza cerebral, entre otros (12). Este fenómeno ocurre antes de la muerte neuronal y está caracterizado por el daño de las membranas celulares en las uniones axodendríticas y axo-axonales. Esto permite discernir que las alteraciones cognitivas en las etapas tempranas de la enfermedad es producto de la pérdida de las sinapsis más que la pérdida de neuronas. Existen diferentes mecanismos que interactúan para desencadenar alteraciones en la homeostasis de la función sináptica, entre ellos los más destacados son la amiloidosis, taupatía y la inflamación (32) .

En los últimos años se ha propuesto la disfunción sináptica como un evento que ocurre temprano en el proceso fisiopatológico de la EA, y una vez instaurado permanece presente de manera transversal durante las diferentes etapas de la enfermedad. Se ha encontrado que, en etapas tempranas, las formas solubles oligoméricas de Aβ y tau son las responsables de la sinaptotoxicidad.

B. Toxicidad de los productos intermedios

En el inicio del estudio fisiopatológico de la EA se pensó que las formas poliméricas tanto de Aβ como de TauP, eran las únicas responsables del daño y muerte neuronal, sin embargo, se ha prestado atención recientemente a los efectos de los oligómeros en el adecuado funcionar neuronal y se ha determinado que son responsables, en gran parte, de la disfunción sináptica y la citotoxicidad. De hecho, estudios han reportado que la presencia de formas poliméricas de ambas moléculas se correlaciona pobremente con la aparición de deterioro cognitivo (40).

Con respecto a los oligómeros de Aβ (oAβ), estos son moléculas hidrosolubles, que se encuentran en una ubicación intermedia en el desarrollo de las placas neuríticas. Estas moléculas pueden ser de bajo peso molecular (LMWO) o de alto peso molecular (HMWO), los primeros se han descrito como los más implicados en los procesos de citotoxicidad (30). Estudios realizados en modelos animales *in vivo,* se ha demostrado que a nivel de SNC lo que más abundan son los HMWO, pero estos sirven como producto intermedio en la formación de los LMWO, dado que en ambientes ligeramente alcalino logran disociarse (41). Posterior a la disociación de los HMWO y la formación de LMWO, se ha evidenciado mayor actividad citotóxica: Alteración de la potenciación a largo plazo (LTP), disminución de los receptores β2- adrenérgicos y sobreactivación de la microglía (41).

Además de su efecto citotóxico regional, los oAβ tienen un mecanismo replicativo que asemeja a la proteína priónica, lo que les permite posteriormente transmitirse de célula a célula por mecanismos mediados por estructuras vesiculares como los exosomas (42). En este sentido, aparte de ser altamente tóxicos, las estructuras oligoméricas amiloides juegan un papel fundamental en la disfunción neuronal y en la propagación de la enfermedad.

En el mismo orden de ideas, se ha evidenciado que los pre-filamentos de tau son más citotóxicos que los NFTs. Modelos animales han encontrado que los procesos de apoptosis y microgliosis preceden al acúmulo de NFTs y están mediados por las formas oligoméricas de Tau. Los pre-filamentos de Tau también se han relacionado con alteración en proteínas involucradas en la regulación del tráfico de vesículas presinápticas lo cual interfiere de forma aguda en la liberación de neurotransmisores, en el reciclaje de vesículas sinápticas y en procesos de plasticidad neuronal.

C. Amiloidosis y disfunción sináptica

1. Disfunción presináptica

Tomando en cuenta lo mencionado en secciones previas, la EA se puede comprender como una sinaptopatía, en la cual hay alteraciones de la conectividad cerebral en etapas tempranas de la enfermedad. Estos procesos de afectación sináptica comprometen principalmente las terminales axonales y las espinas dendríticas (43).

Estas últimas son estructuras dinámicas en las cuales se generan cambios bioquímicos, eléctricos y morfológicos que permiten aumentar la plasticidad y que se consoliden elementos de la cognición como el aprendizaje y la memoria (44).

En el hipocampo se han estudiado procesos específicos de plasticidad neuronal, entre estos la potenciación a largo plazo (LTP) y la depresión a largo plazo (LTD). La potenciación a largo plazo (LTP) es un proceso que está mediado por activación de los receptores NMDA (rNMDA) y alto influjo de calcio, también promueve el reclutamiento de receptores AMPA lo que genera elongación de las espinas dendríticas. Por el contrario, en la depresión a largo plazo (LTD) hay internalización de los rNMDA, activación de los rNMDA peri-sinápticos, disminución del influjo de calcio a la neurona, pérdida de las sinapsis y contracción de las espinas dendríticas (31,32,45). Se ha encontrado que las formas oligoméricas de AB1-42 tienen el potencial de suprimir la LTP y facilitar la LTD (46).

Adicionalmente, los procesos de plasticidad pueden ser alterados por modificaciones presinápticas y postsinápticas. Entre los mecanismos presinápticos, la disrupción de la homeostasis excitación/inhibición y la hiperactividad neuronal están primordialmente influenciados por disregulación presináptica, así como la regulación y distribución de las vesículas sinápticas (VS).

En estudios previos se ha determinado que sAβ1-42 soluble bloquea la LTP, la sinaptogénesis y el tráfico inter-vesicular. Este último proceso está críticamente relacionado con la formación sináptica porque es la forma que tienen las neuronas de aportar neurotransmisores a las estructuras sinápticas nuevas y de promover el fortalecimiento de las mismas (47).

Con respecto a las moléculas involucradas en la regulación presináptica, la sinaptofisina es una de las más estudiadas. Esta es una proteína transmembrana que se ubica en las VS y juega un papel importante en la formación del poro en la membrana celular en el momento de la liberación de los neurotransmisores. Se ha demostrado que Aβ interactúa con la sinaptofisina, evitando su unión con VAMP2 y consecuentemente la formación del complejo SNARE, un elemento clave en la unión VS-membrana neuronal (48).

Otras moléculas también se han correlacionado con los efectos deletéreos de la amiloidosis. La endofilina 1 es una proteína involucrada en la endocitosis de VS y en presencia de Aβ los niveles de esta se aumentan, provocando un incremento en las corrientes excitatorias postsinápticas miniatura (mEPSC) y en consecuencia

alterando los procesos plasticidad neuronal (46). Los oAβ también pueden interactuar directamente con otras proteínas involucradas en el anclaje y fusión de las VS como la sintaxina (49), y con proteínas involucradas en el reciclaje y disponibilidad de las VS como la sinapsina (47) y la dinamina 1 (50).

2. Disfunción postsináptica

Desde el punto de vista postsináptico, los oAβ pueden funcionar como ligandos, uniéndose a múltiples receptores en las membranas celulares y desencadenando vías de señalización que generan alteración de la plasticidad sináptica y pérdida neuronal. Los receptores principalmente involucrados son los glutamatérgicos, alfa-7 nicotínicos, receptores de acetilcolina, proteína priónica celular y receptores de Wnt. La relevancia de estos receptores en la alteración sináptica es desconocida, los más estudiados son los receptores de glutamato.

Los receptores ionotrópicos de mayor importancia a nivel de SNC son los AMPA y NMDA, estos son de especial importancia en los mecanismos de plasticidad sináptica y almacenamiento de información por medio de la LTP y LTD.

En EA el proceso que prima es la LTD, no solo por mecanismos de internalización de rNMDA, sino también por procesos de desensibilización. Reciente evidencia sugiere que en una primera instancia se aumenta la neurotransmisión glutamatérgica pero los altos niveles de este neurotransmisor en la hendidura sináptica terminan provocando desensibilización de los receptores y favorece la LTD. De igual forma, los altos niveles de glutamato en la hendidura y la poca disponibilidad de rNMDA provoca la estimulación de receptores peri-sinápticos metabotrópicos, los cuales están implicados en la LTD (45).

Lo anterior ha sido comprobado en modelos experimentales en los cuales la aplicación de oAβ sintético disminuye la expresión de rNMDA, se inhibe la LTP y se disminuye la densidad de las espinas dendríticas (51). Otras investigaciones han determinado que los oAβ producen disminución de la densidad de espinas sinápticas y disminución de las sinapsis electrofisiológicamente activas en las neuronas hipocampales. Adicionalmente, el daño inducido por la presencia de oligómeros se previene con anticuerpos contra el Aβ y con moléculas inhibidoras de la agregación de Aβ. Lo anterior permite intuir que la presencia de los oligómeros altera las vías de señalización mediadas por el rNMDA que están involucradas en la LTD (51).

Aunque estos mecanismos no han sido completamente dilucidados, aparentemente los efectos deletéreos de los péptidos de Aβ son dependientes de la concentración, es decir, se producen con la exposición a altos niveles de oAβ. Se ha reportado que bajos niveles de péptidos Aβ tienen el potencial de aumentar la LTP, mientras que los altos niveles o la exposición prolongada disminuyen las corrientes excitatorias postsinápticas e inhiben la LTP mediada por rNMDA. Una posible explicación a esto es que los oAβ afectan la actividad NMDA por el aumento gradual de glutamato en la hendidura sináptica, además de funcionar como agonistas de los rNMDA. Otras observaciones han propuesto que las bajas exposiciones a péptidos Aβ generan disfunción presináptica, mientras que las altas concentraciones son necesarias para generar disfunción postsináptica (40).

D. Hipótesis Tau y disfunción sináptica

Al igual que ocurre con los oAβ, la disfunción sináptica y la citotoxicidad inducida por TauP está mediada por la presencia de las formas solubles más que por su conformación fibrilar. La forma en que TauP afecta la función sináptica y por ende genera alteración de la función cognitiva se ha relacionado con su interacción con la neurotransmisión glutamatérgica. La plasticidad sináptica depende principalmente de la activación del receptor NMDA que está a su vez regulado por el complejo PSD95-Fyn-NMDA en el extremo neuronal postsináptico. Se teoriza que TauP establece interacción especialmente con Fyn alterando la formación de este complejo en el lado postsináptico y por ende altera la transmisión glutamatérgica y los mecanismos de neuroplasticidad (52). Los mecanismos que explican lo anterior no están completamente dilucidados. Sin embargo, otros estudios han demostrado que la interacción TauP-Fyn exacerba la excitotoxicidad inducida por Aβ, mientras que la inhibición de Fyn aminora la disfunción neuronal y el déficit cognitivo en modelos animales con ratones portadores de variantes genéticas patogénicas en APP (53,54). La alteración en la liberación de VS también se ha propuesto como un mecanismo relacionado con la sinaptotoxicidad inducida por TauP. Una de las moléculas estudiadas es la sinaptogyrin-3, una proteína transmembrana de las VS, que al interactuar con TauP se genera una afectación de la movilidad de las VS y una disminución de la neurotransmisión (55). De forma similar, la sinaptofisina y la septina-

11, moléculas de unión a VS y de tráfico de VS respectivamente, se reducen en presencia de tau oligomérica específicamente en la región CA1 del hipocampo. (56). Otras moléculas que interaccionan con TauP y generan alteraciones en la señalización intracelular como la TIA1 (*T cell intracellular antigen 1*) (57) y la nectina-3 (58).

Por otro lado, también se ha relacionado la acumulación aberrante de TauP con la función de los astrocitos. Estos últimos están regulados principalmente por la concentración intracelular de calcio y se ha encontrado que en presencia de formas oligoméricas de Tau las corrientes de calcio inducidas por ATP son menores en amplitud. De igual forma, la transmisión de moléculas como glutamato y serina de los astrocitos al espacio extracelular se disminuye, alterando la transmisión sináptica de los astrocitos hasta la hendidura sináptica (59).

E. Inflamación y disfunción sináptica

La microglía juega un papel importante en los procesos de plasticidad neuronal y de conectividad sináptica a través de la secreción controlada del factor neurotrófico derivado del cerebro. Sin embargo, en ambientes pro-inflamatorios, la microglía tiene un efecto negativo en la maduración y diferenciación celular, en la formación de nuevas conexiones sinápticas y en la neuroplasticidad. Entonces, la función de esta célula es dependiente del microambiente en el que se desenvuelve (34).

La reacción del sistema inmune innato se caracteriza por activación del sistema fagocítico para intentar eliminar los detritos y agregados de moléculas anómalas. Ante la imposibilidad de eliminar estos acúmulos anormales de proteínas la respuesta inflamatoria se cronifica, provocando neurotoxicidad (60). En modelos animales se ha demostrado que la activación de C1q, la proteína que inicia la cascada de activación del complemento se aumenta tempranamente en el curso de la fisiopatología de la EA y sucede antes del depósito de Aβ en forma de placas neuríticas. La inhibición de C1q, C3 o de la microglía reduce el número de células fagocíticas y disminuye el daño temprano en las conexiones sinápticas (61).

En relación con el complemento, otros estudios han demostrado su relación con la disfunción sináptica en la presencia de acúmulos de TauP. Se ha propuesto que el complemento juega un papel importante no solo en los procesos de neuro-inflamación

sino en los procesos de agregación de proteína tau. La expresión aumentada de C3 y su receptor C3aR1 se ha correlacionado con deterioro cognitivo en modelos animales in vivo, en consecuencia, la deleción del gen que codifica C3aR1 mejora la función neuronal a través del aumento de la LTP (62).

Desde el punto de vista genético, las deficiencias en la respuesta inmune innata mediadas por las variantes patogénicas en el gen TREM2 (por sus siglas en inglés *triggering receptor expressed on myeloid cells 2*) se han correlacionado con formas de presentación tardías de la EA. Esta variante permite comprender el papel de la actividad microglial y la inmunidad innata en la patogénesis de la EA (63).

F. Plasticidad sináptica

Existe un ciclo de retroalimentación positiva patológica entre la producción Aβ y un ambiente de hiperexcitabilidad neuronal aberrante, lo que favorece la inhibición de LTP, inducción de LTD y una acumulación patológica de Aβ (64). Esto se ha explicado por diferentes mecanismos, entre ellos, la activación temprana de rNMDA que contiene GluN2B.

Para evitar los efectos deletéreos de la LTD prolongada como el silenciamiento o eliminación sináptica, las redes neuronales han implementado mecanismos de retroalimentación negativa conocidos como “plasticidad sináptica homeostática”, aumentando de forma compensatoria la fuerza sináptica y el umbral de acción de la LTD (65). Sin embargo, fallos en esta plasticidad hebbiana producto de la acumulación de oAβ y un ambiente postsináptico previo alto debido a la hiperexcitabilidad neuronal aberrante en pacientes con EA, producirían fallos en la metaplasticidad llevando a una pérdida constante y no controlada de la fuerza sináptica que puede conducir a la eliminación de la sinapsis por un favorecimiento de la LTD subumbral. Se ha evidenciado disminución de la densidad sináptica en pacientes con EA en región hipocampal que podría estar explicado por este mecanismo (66).

V. Cambios en la actividad eléctrica

En la fisiopatología de la EA, las alteraciones que se generan en los neurotransmisores (glutamato, GABA, acetilcolina) a través de las modificaciones a la homeóstasis del calcio, contribuyen a la disfunción de redes neuronales y la actividad eléctrica cerebral. En modelos animales se ha demostrado que la acumulación prolongada y a altos niveles de Aβ produce redes excitatorias aberrantes que son compensadas con el aumento de la actividad neuronal inhibitoria especialmente en las redes de aprendizaje y memoria (45). Entre estos cambios destacan la desaceleración del ritmo alfa (8-12 Hz) con tendencia a ritmo theta (4-8 Hz) y actividad gamma aberrante (67).

Lo anterior puede ser en parte explicado por la alteración de las redes excitatorias glutamatérgicas y la pérdida sináptica asociada, lo que provoca patrones aberrantes de actividad eléctrica neuronal de sincronización entre las sinapsis glutamatérgicas funcionantes, en vez de aumento de la actividad excitatoria. Este fenómeno de sincronización puede a su vez generar actividad eléctrica epileptiforme caracterizada por la presencia de *spike and sharp waves* (45). Esto ha sido previamente evidenciado en estudios en humanos con electroencefalograma (EEG) (68).

A. EEG y generadores de la señal eléctrica

La actividad eléctrica registrada por el electroencefalograma (EEG) refleja un conjunto de procesos y dinámicas neurofisiológicas que subyacen al funcionamiento cerebral. El entendimiento de dichos sustratos fisiológicos es esencial para abordar la señal obtenida por EEG y para interpretar de manera correcta las variaciones, patrones y características de los diferentes componentes de las señales eléctricas (69). A nivel celular, la sinapsis entre dos neuronas provoca un potencial excitatorio o inhibitorio postsináptico que conlleva a cambios en gradientes de potenciales a lo largo de la membrana neuronal. Estos gradientes evidencian movimientos iónicos a lo largo del medio intra y extracelular, este último sería el que aporta a la generación de los potenciales de campo extracelulares, contribuyentes principales de la actividad eléctrica que es registrada por el EEG (70).

Los electrodos de superficie del EEG registran actividad eléctrica que resulta de la suma de los potenciales de campo extracelulares, tanto potenciales postsinápticos excitatorios como inhibitorios. Estos se originan en las neuronas piramidales de la corteza cerebral. La disposición perpendicular de estas neuronas en relación con la superficie y su arreglo paralelo una con otra, permiten el efecto sumatorio de esta actividad eléctrica y finalmente su identificación en el EEG (71).

Existen algunos fenómenos básicos que componen la actividad registrada en el EEG, que determinan los patrones y disposiciones observados en la señal. Dentro de estos fenómenos están las oscilaciones y la sincronización. Grupos sincronizados de potenciales de acción en las fibras aferentes a las neuronas piramidales conllevan a la generación de potenciales postsinápticos con disposiciones similares a ondas (69).

La amplitud y duración de la despolarización dependen de la frecuencia y patrón de descarga de las fibras aferentes. De esta forma, ráfagas aferentes de potenciales de acción sincrónicos y agrupados, con secuencias periódicas determinadas, generan que el registro de los potenciales de campo por el EEG muestre las fluctuaciones sinusoidales características. Así mismo, la actividad tónica de alta frecuencia de las fibras aferentes resulta en potenciales postsinápticos de mayor duración, con fluctuaciones más pequeñas, que en el registro se evidencian como cambios en la polaridad de la señal de menor amplitud y mayor frecuencia (69).

La actividad sincrónica y oscilatoria está determinada por múltiples variables intrínsecas del sistema nervioso. Entre estas se encuentran las comunicaciones intracorticales directas, las conexiones talamocorticales, interacción con la glía, tipos de neurotransmisores, circuitos de retroalimentación, entre muchas otras. Finalmente, estas características en conjunto permiten y conllevan a la aparición de los ritmos oscilatorios tradicionales que se establecen en el EEG: delta, theta, alfa, beta y gamma. Estos ritmos se agrupan en bandas anchas de frecuencia, que conservan grafo-elementos típicos y agrupan varias frecuencias individuales diferentes en cada banda (69).

Los ritmos que se evalúan en el registro del EEG evidencian características similares de forma intrínseca y se ha demostrado que cambian según los estados fisiológicos

de los sujetos. En las aproximaciones para comprender las dinámicas electrofisiológicas, se ha postulado que dichos ritmos explican el funcionamiento subyacente del sistema nervioso. De esta manera, se ha demostrado que algunas características intrínsecas de las dinámicas neurofisiológicas -como la frecuencia y variabilidad de disparo neuronal, la habituación y sensibilización de circuitos neuronales, el acoplamiento de fase, la tonicidad, periodicidad, temporalidad y cadencia de la actividad eléctrica, entre muchas otras-, subyacen a los patrones oscilatorios y sincrónicos observados por el EEG (69,71).

Lo anterior conduce a comprender que el abordaje e interpretación del registro electroencefalográfico debe estar determinado por la aproximación, mediante el uso de diferentes métricas y tipos de análisis en EEG cuantitativo (qEEG). Este abordaje permitiría visualizar y obtener información de cada una de las propiedades neurofisiológicas que, si bien no son aparentemente evidentes en el registro del EEG, subyacen y dan sustento a las señales obtenidas por este medio (69).

B. EEG y alteración de la señal en EA

A escala macroscópica y en un modelo *in vivo*, se sabe qué técnicas electromagnéticas, como el electroencefalograma (EEG), reflejan el funcionamiento de las redes neuronales como una herramienta útil para la evaluación y detección temprana de los impactos fisiopatológicos en la EA (72,73).

El EEG, por medio de su análisis cuantitativo (qEEG), emplea métodos computacionales que mejoran la adquisición, procesamiento de información, el análisis y clasificación de datos de investigación aumentando su precisión. A partir del qEEG se pueden desarrollar múltiples tipos de análisis de la señal obtenida.

En el análisis de frecuencia, aún en estadios tempranos de demencia por EA se evidencia un "*enlentecimiento*" de los ritmos occipitales alfa y de la Frecuencia Individual Alfa pico (iAPF), dichas variaciones también han sido encontradas en sujetos con Deterioro Cognitivo Leve (74,75). La disminución de la frecuencia

promedio y de la potencia alfa ha sido correlacionada significativamente con la gravedad de la demencia y el grado de atrofia hipocampal (72,74).

Otras investigaciones, centradas en el análisis de potencia espectral, demuestran diferencias significativas en pacientes con EA: enlentecimiento de las señales de base del qEEG acompañados con disminución de la potencia en bandas de intermedia y alta frecuencia (Alfa, Beta y Gamma) e incremento de la potencia en bandas de baja frecuencia (Delta y Theta) (76–78). Este aumento en la potencia theta ha sido asociado clínicamente con disminución de la alerta y con el grado de deterioro cognitivo del individuo (estadio y severidad de la demencia) (74,77,78), evidenciando un incremento en la potencia de la banda theta y una disminución en la potencia de la banda beta durante los cambios fisiopatológicos tempranos de la enfermedad, y, consecuentemente, una predominancia progresiva del incremento de la actividad en la banda delta y de la disminución de la actividad en la banda alfa a medida que avanza la enfermedad hasta estadios clínicos más severos (73).

En población con EA con variante genética PSEN1-E280A se han realizado estudios donde tomaron qEEG a 15 sujetos portadores pre-sintomáticos comparados con 15 sujetos sanos no portadores durante una tarea de reposo (con ojos cerrados) y una de memoria; encontrando diferencias estadísticamente significativas entre los grupos en la potencia en banda theta y alfa-2 para ambas tareas, posteriormente, se comprobó en un análisis de componentes independientes (ICA) y método de solución inversa que la región de la precuña estaba afectada en esta población con estas dos medidas de potencia espectral (76,79). Otro estudio en esta misma población confirma este hallazgo, encontrando en estadios clínicos de EA cambios espectrales significativos en la banda de frecuencia theta (75).

Finalmente, en un estudio con 28 sujetos con DCL comparándolo con PET amiloide, PET FDG (fluorodesoxiglucosa), resonancia magnética cerebral y pruebas cognitivas, se demostró que en presencia de Aβ se observa aumento de la banda de frecuencia alfa en regiones frontales. Incremento de banda delta en estas mismas regiones se correlacionó con atrofia e hipometabolismo entorrinal. El aumento de Theta global se asoció con atrofia hipocampal pero no se encontró como medida específica de EA al encontrarse en sujetos con ausencia de Aβ. (80)

VI. Formulación del problema

La enfermedad de Alzheimer se reconoce como un problema de salud pública global con un aumento exponencial en cuanto a personas afectadas y retos para el sistema de salud; el entendimiento de la enfermedad de Alzheimer como un continuo biológico trae consigo la tarea de una búsqueda de biomarcadores accesibles y económicos que permitan identificación temprana de personas en riesgo de sufrir esta enfermedad, con el objetivo de vincularlas en terapias modificadoras o preventivas.

Las formas genéticas de la EA se convierten en un modelo ideal de estudio que han permitido identificar diferentes biomarcadores con 20-30 años de antelación al inicio de los síntomas clínicos. Sin embargo, algunos de estos métodos son invasivos, costosos y requieren infraestructuras complejas para su realización, lo que limita su generalización y aplicabilidad en ámbitos clínicos. Por otro lado, algunos de estos biomarcadores se presentan en etapas tardías del proceso fisiopatológico como los cambios en PET Tau o los hallazgos en neuroimágenes funcionales; este tipo de biomarcadores reportados tienen limitaciones en su técnica como la incapacidad de rastrear productos intermedios de la taupatía o la amiloidosis como la presencia de oligómeros de Aβ en LCR, plasma o neuroimágenes.

La disfunción sináptica es un fenómeno patológico que se presenta en etapas tempranas de la enfermedad y que es transversal en el proceso de esta. Esto puede ser desencadenado por la presencia de productos intermedios de las proteínas amiloide y Tau, exacerbado por procesos inflamatorios y muerte neuronal. Esta disfunción sináptica genera un cambio en la dinámica cerebral, en el procesamiento de la información comprometiendo redes implicadas en procesos cognitivos que finalmente llevarán a la presentación de síntomas clínicos manifiestos descritos en esta patología.

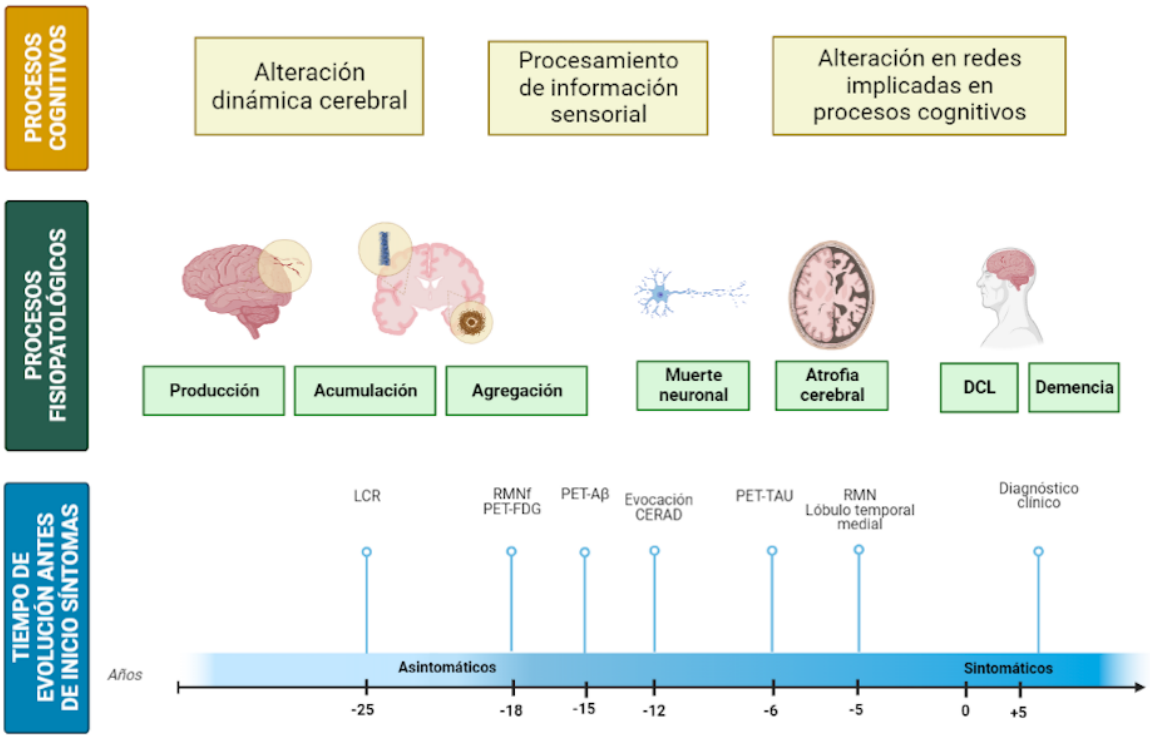


Figura 2: Modelo Fisiopatológico de la Enfermedad de Alzheimer.

Se reconocen grandes avances en investigación en EA y la inminente búsqueda de biomarcadores en etapas preclínicas de la enfermedad, sin embargo, hay algunos aspectos que deben ser considerados y serán discutidos a lo largo de esta tesis:

Primero, en países de medianos a bajos ingresos como es el caso de la mayoría de los países en Latinoamérica y el Caribe no se cuenta con información suficiente en la literatura sobre poblaciones o familias con origen genético para enfermedades neurodegenerativas como EA o Demencia Frontotemporal, entre otras. Las variantes genéticas que se encuentren en otros países de Latinoamérica y Centroamérica podrían también encontrarse acá en Colombia y ser una población susceptible de ser estudiada en búsqueda de biomarcadores tempranos y beneficiarse de terapias preventivas en un futuro.

Segundo, exámenes como la tomografía por emisión de positrones (PET) permiten realizar el estudio, diagnóstico y monitoreo de la EA, sin embargo, su técnica no permite rastrear los productos intermedios de amiloidosis o taupatía. Por su parte, el

examen de LCR ha mostrado utilidad en la medición de patología específica de EA, pero tiene la limitación de requerir una técnica invasiva para su obtención. Es creciente la necesidad de biomarcadores sensibles, costo-efectivos y mínimamente invasivos que permitan rastrear la progresión de la EA desde etapas muy tempranas. En este sentido surgen algunas opciones como los biomarcadores plasmáticos o biomarcadores derivados del procesamiento del EEG. Se desconoce el comportamiento de estos biomarcadores periféricos en población pre-clínica como en poblaciones con EA de origen genético.

Finalmente, la mayoría de los estudios de EEG, se han desarrollado en un número reducido de personas, en estudios transversales, en poblaciones con factores de riesgo genético como la presencia del genotipo ApoE4 o adultos mayores con riesgo cardiovascular. Todas estas características limitan sus resultados y la generalización de sus hallazgos. El objetivo principal de este trabajo es evaluar los potenciales biomarcadores neurofisiológicos asociados a disfunción sináptica en un seguimiento longitudinal de esta población con riesgo genético para EA.

Dadas estas consideraciones, este trabajo está dirigido a responder la siguiente pregunta de investigación: **¿Cómo se asocian los biomarcadores neurofisiológicos plasmáticos y en qEEG con los procesos de disfunción sináptica en una población con la con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante?**

3. OBJETIVOS

I. OBJETIVO GENERAL

Analizar los potenciales biomarcadores neurofisiológicos asociados a disfunción sináptica en un seguimiento longitudinal, usando como modelo una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante.

II. OBJETIVOS ESPECÍFICOS

1. Describir las poblaciones con riesgo genético para enfermedad de Alzheimer en Latinoamérica y Colombia como modelos ideales de estudio de disfunción sináptica

Estudio #1: Describir las variantes genéticas de causalidad para Demencia en Latinoamérica.

Estudio #2: Describir las variantes genéticas de causalidad asociadas con neurodegeneración en el contexto de sus orígenes ancestrales y mestizaje en una cohorte colombiana de 900 sujetos.

2. Identificar marcadores neurofisiológicos de disfunción sináptica en etapas preclínicas de una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante.

Estudio #3: Evaluar una asociación entre los niveles plasmáticos basales de p-tau217 con marcadores posteriores de patología cerebral in vivo medidos por PET.

3. Evaluar el comportamiento de las medidas neurofisiológicas en un seguimiento longitudinal en una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante.

4. Correlacionar los hallazgos en las medidas neurofisiológicas con el seguimiento clínico y neuropsicológico en una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante.

Estudio #4: Evaluar el comportamiento en un seguimiento longitudinal de medidas de potencia espectral y reactividad Alpha/Theta en una población con la mutación E280A en PSEN1 para enfermedad de Alzheimer precoz.

5. Establecer un modelo neurofisiológico de la alteración en la señal eléctrica asociado al proceso fisiopatológico en etapas preclínicas de la enfermedad de Alzheimer en una población con la variante genética PSEN1-E280A para enfermedad de Alzheimer autosómico dominante.

Estudio #5: Realizar una revisión sistemática de la literatura sobre disfunción sináptica y electroencefalograma en poblaciones con enfermedad de Alzheimer precoz.

4. METODOLOGÍA

El desarrollo de los objetivos planteados condujo al diseño y ejecución de 5 estudios independientes; dos de ellos fueron revisiones sistemáticas, uno enfocado en neuro genética, 1 estudio clínico de biomarcadores periféricos y 1 estudio neurofisiológico. Por esta razón, la sección de materiales y métodos de cada uno de ellos es específica e independiente y se describe con mayor detalle en cada uno de los artículos anexos.

5. RESULTADOS

Para dar cumplimiento a los objetivos de la investigación, se desarrollaron 5 estudios: 2 revisiones sistemáticas, 1 estudio de neuro genética, 1 estudio de carácter clínico y 1 estudios de tipo neurofisiológico. Los resultados derivados de dichos estudios se publicaron en revistas internacionales. A continuación, se describe el abordaje de cada uno de ellos.

La primera revisión sistemática se detalla en la publicación **"Genetics of Dementia: Insights from Latin America"** (ver publicación No. 1). Esta revisión fue necesaria para conocer las variantes genéticas que se han descrito en Latinoamérica y que ante la ausencia de estudios poblacionales en estos países no han sido descritas en revisiones previas. Esta revisión sistemática sirvió como base para la búsqueda genética realizada en la segunda publicación: **"A neurodegenerative disease landscape of rare mutations in Colombia due to founder effects"** (ver publicación No. 2). Este artículo presenta nuevas variantes genéticas identificadas para Enfermedad de Alzheimer o Degeneración Lobar Frontotemporal en población colombiana, resalta una mayor proporción de frecuencia de variantes raras en Colombia derivadas de poblaciones ancestrales y manifestaciones fenotípicas diferentes en un mismo gen. Abre la posibilidad de estudio y seguimiento clínico de poblaciones raras y únicas que permitirán un mejor entendimiento del proceso fisiopatológico de las enfermedades neurodegenerativas.

Los resultados del tercer estudio se encuentran detallados en la publicación: "**Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer 's disease**" (ver publicación No. 3). Esta publicación demuestra una asociación entre los niveles plasmáticos basales de p-tau217 y las subsecuentes medidas de patología in vivo a través de PET y medidas de cognición. Estas medidas soportan la utilidad de p-tau217 como un posible biomarcador de EA y un posible marcador neurofisiológico de disfunción sináptica como un evento temprano y previo a la aparición de hallazgos anormales en PET; esto da soporte teórico al proceso de

disfunción sináptica como un evento temprano en la enfermedad y al objetivo de rastrear a través de EEG estos cambios neuropatológicos.

Los estudios neurofisiológicos tuvieron inicialmente una colaboración cuyo objetivo en el marco de un estudio transversal era evaluar la capacidad del aprendizaje de máquina para clasificar pacientes portadores asintomáticos de la variante PSEN1-E280A de los no portadores, usando características de potencia espectral del EEG y componentes independientes a través de ICA. Con este estudio logramos discriminar estos dos grupos con un 83% de exactitud. Los resultados se pueden visualizar en la publicación: **"Automatic Classification of subjects of the PSEN1-E280A Family at risk of developing Alzheimer's Disease using Machine Learning and Resting State electroencephalography**" (datos en "otras publicaciones y trabajos colaborativos").

El segundo estudio neurofisiológico tenía como objetivo evaluar las medidas de potencia espectral en un seguimiento longitudinal y buscar un marcador de progresión de la EA. Este mismo estudio realizó otros análisis como el índice de reactividad alfa/theta. Los resultados del estudio se encuentran descritos en el manuscrito titulado: **"Longitudinal analysis of qEEG in subjects with autosomal dominant Alzheimer 's disease due to PSEN1-E280A variant."** (en proceso de sometimiento para publicación (ver manuscrito No. 4)).

Finalmente, para dar respuesta al modelo neurofisiológico de disfunción sináptica, se realizó una segunda revisión sistemática de la literatura sobre los mecanismos que desencadenan la disfunción sináptica a partir del proceso fisiopatológico de la enfermedad de Alzheimer. Los datos de esta revisión sistemática se encuentran descritos en el manuscrito: "**Pathophysiological basis of synaptic dysfunction in Alzheimer 's disease: A systematic review**" (en proceso de sometimiento para publicación (ver manuscrito No. 5)).

A continuación, se presenta el resumen de cada estudio y se anexa su correspondiente artículo:

5.1. Publicación No. 1: “Genetics of Dementia: Insights from Latin America”

Resumen

La enfermedad de Alzheimer (EA) y la demencia frontotemporal (FTD) son trastornos neurodegenerativos que resultan en una carga significativa tanto para los pacientes como para los cuidadores. Para el 2050, el número de personas con demencia en América Latina se cuadruplicará. Una comprensión profunda de los factores genéticos relevantes de la EA y la DFT es fundamental para abordar esta realidad a través de la prevención. Se realizó una revisión de las diferentes variantes genéticas que causan EA o DFT en América Latina. Se realizaron búsquedas en las bases de datos Medline utilizando las palabras clave "enfermedad de Alzheimer", "demencia frontotemporal", "mutación", "América" y "América Latina", además de países latinoamericanos específicos. Se eligieron y analizaron cuarenta y cinco artículos. Las mutaciones de PSEN1 son la causa más común de la enfermedad de Alzheimer de aparición temprana genética (EOAD), seguidas de las mutaciones de PSEN2 y APP. La DFT genética puede explicarse principalmente por mutaciones en GRN y MAPT, así como por la expansión repetida de C9orf72 G4C2. APOE ε4 puede modificar la prevalencia e incidencia de la enfermedad de Alzheimer de inicio tardío (LOAD), además del rendimiento cognitivo en los portadores afectados.

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Genetics of dementia
Insights from Latin America

Claudia Ramos[1], David Aguillon[1], Christian Cordano[2], Francisco Lopera[1]

ABSTRACT. Alzheimer's disease (AD) and frontotemporal dementia (FTD) are neurodegenerative disorders that result in a significant burden to both patients and caregivers. By 2050, the number of people with dementia in Latin America will increase 4-fold. A deep understanding of the relevant genetic factors of AD and FTD is fundamental to tackle this reality through prevention. A review of different genetic variants that cause AD or FTD in Latin America was conducted. We searched Medline and PubMed databases using the keywords "Alzheimer's disease," "frontotemporal dementia," "mutation," "America," and "Latin America," besides specific Latin American countries. Forty-five items were chosen and analyzed. *PSEN1* mutations are the commonest cause of genetic early-onset Alzheimer's disease (EOAD), followed by *PSEN2* and *APP* mutations. Genetic FTD can be mainly explained by *GRN* and *MAPT* mutations, as well as *C9orf72 G4C2* repeat expansion. *APOE ε4* can modify the prevalence and incidence of late-onset Alzheimer's disease (LOAD), in addition to the cognitive performance in affected carriers.

Keywords: Alzheimer's disease, frontotemporal dementia, Latin America, genetics.

GENÉTICA DAS DEMÊNCIAS: PERCEPÇÃO A PARTIR DA AMÉRICA LATINA

RESUMO. A doença de Alzheimer (DA) e a demência frontotemporal (DFT) são distúrbios neurodegenerativos que causam uma sobrecarga significativa para pacientes e cuidadores. Em 2050, o número de pessoas com demência na América Latina aumentará 4 vezes. Uma compreensão profunda dos fatores genéticos relevantes da DA e da DFT é fundamental para enfrentar essa realidade por meio da prevenção. Foi realizada uma revisão de diferentes variantes genéticas que causam a DA ou a DFT na América Latina. Pesquisamos os bancos de dados Medline e PubMed usando as palavras-chave "doença de Alzheimer", "demência frontotemporal", "mutação", "América" e "América Latina", além de países latino-americanos específicos. Quarenta e cinco itens foram escolhidos e analisados. As mutações do *PSEN1* são a causa mais comum da doença de Alzheimer genética de início precoce (DAIP), seguida pelas mutações do *PSEN2* e da *APP*. A DFT genética pode ser explicada principalmente por mutações no *GRN*, *MAPT* e expansões repetidas da *C9orf72 G4C2*. O *APOE ε4* pode modificar a prevalência e a incidência da doença de Alzheimer de início tardio (DAIT), mas também o desempenho cognitivo em portadores afetados.

Palavras-chave: doença de Alzheimer, demência frontotemporal, América Latina, genética.

Worldwide, there is nearly one new case of dementia every 3 seconds.[1] In 2018, the global prevalence of dementia was 50 million cases, and this rate is projected to reach 152 million by 2050.[1] By 2020, lower-middle-income countries (LMIC) will have 89.28 million people with dementia. In addition, upper-middle-income countries (UMIC) will experience the greatest dementia impact.[2] In Latin America, dementia is an important public health issue, due to the predicted four-fold increase in subjects with dementia from 2015 to 2050.[2]

Prevention is considered a key factor for tackling this reality, while the study of genetics allows both an accurate characterization of subgroups of patients and personalized

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prevention.[3] The purpose of our work is to describe Alzheimer's disease (AD) and frontotemporal dementia (FTD) genetics in Latin America.

GENETIC VARIANTS RELATED TO ALZHEIMER'S DISEASE

Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) genes carry the active site of the γ-secretase complex.[4] Besides them, other proteins are encoded by different risk genes related to late-onset AD (LOAD) and involved in Aβ clearance. *SORL1*, *PICALM*, and *CD2AP* genes regulate amyloid precursor protein (APP) endocytosis and the production of Aβ in the endosomal-lysosomal system.[4,5] On the other hand, *APOE*, *CLU*, *TREM2*, *ABCA7*, *PICALM*, *CD33*, *CD2AP*, and *CR1* are involved in Aβ elimination.[4,5]

In a recent genetic meta-analysis involving 94,437 individuals with LOAD, 20 previous LOAD loci were confirmed.[5] The authors also described five new genome-wide loci (*IQCK*, *ACE*, *ADAM10*, *ADAMTS1*, *WWOX*), identified when investigating relatives of people diagnosed with AD or dementia. The possible pathways related to these variants involve protein-lipid complex, Aβ formation and degradation, cholesterol metabolism, tau processing, and immunity. Remarkably, the authors identified a genetic correlation between LOAD, family history of dementia, and education. For example, they found that common genetic LOAD variants were positively correlated to a maternal history of dementia.[5] Also, they detected a significant negative correlation between AD and educational level: more years of schooling and better cognitive scores behaved as protective factors against LOAD.[5]

FRONTOTEMPORAL DEMENTIA

FTD is the second most common cause of dementia in individuals under the age of 65. FTD is a neurodegenerative disorder characterized by:

- behavioral difficulties (disinhibition, compulsions, stereotypic movements, hyperorality) and personality and affective changes (loss of empathy, apathy, inertia);
- language and executive dysfunction;
- frontal and/or anterior temporal brain atrophy;
- heritability: 40% of affected patients have a relative with this condition, and the inheritance pattern in 10% of them is autosomal dominant;[6]

Three genes are often associated with FTD:

- *MAPT*, which is found on chromosome 17q21.31 and encodes the microtubule-associated protein tau protein, *MAPT*;
- *GRN*, which is found on chromosome 17q21.31 and encodes the granulin protein, *GRN*;
- *C9orf72*, which is found on chromosome 9p21.2 and consists of a segment of deoxyribonucleic acid (DNA) with six DNA nucleotides — four guanines and two cytosines (written as GGGGCC).[6]

MAPT is an important protein for microtubule stabilization and assembly.[6] Mutations in this protein cause diseases by 1) altering tau splicing, which affects the normal 3R/4R tau ratio (usually the 3R/4R ratio in the adult human brain is very stable); 2) promoting cytoplasmic tau aggregation; and 3) causing tau hyperphosphorylation, which generates microtubule instability.[6,7] *MAPT* mutations are related to several phenotypes, mainly the behavioral variant FTD (bvFTD).[6] Notoriously, *MAPT* mutation carriers can develop episodic memory impairment.[6] Brain neuroimaging can show symmetric involvement of anterior temporal, lateral prefrontal, and orbitofrontal regions.[6] The neuropathology of *MAPT*-mutation syndromes is characterized by frontotemporal lobar degeneration (FTLD), a neurodegenerative process involving neuronal loss and gliosis of the frontal and temporal brain regions, in the presence of hyperphosphorylated tau inclusions.[8] Alternative splicing of *MAPT* generates six different tau isoforms; the inclusion of exon 10 produces tau isoforms with either four (4R tau) or three (3R tau) microtubule-binding domain repeats. In FTLD-tau, Pick's disease is characterized by predominant deposition of 3R tau aggregates, whereas corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are 4R tauopathies.[8]

GRN is a protein necessary to activate signaling cascades for neuronal growth, inflammation, and wound repair.[6,8] Mutation carriers have a 50% decrease in *GRN* mRNA progranulin levels in plasma and cerebral spinal fluid (CSF).[8] *GRN* mutations are usually related to bvFTD.[6] As in some *MAPT* cases, *GRN* carriers can present episodic memory impairment, besides neuropsychiatric symptoms, such as psychosis and isolation.[6] Neuroimaging shows asymmetric atrophy of frontotemporal regions.[6,8] Carriers' pathology is characterized by a pathologic form of TAR DNA-binding protein 43 (TDP-43), distributed in cytoplasmic aggregates leading to microtubule phosphorylation, ubiquitination, and degradation.[8] Specifically, the neuropathology of *GRN* mutation carriers is the TDP-43 type A.[8]

As mentioned before, the *C9Orf72* gene has a hexanucleotide repeat expansion in its first intron: GGGGCC. Normal alleles have three to thirty repeat units, while people with the repeat expansion mutation can present hundreds to thousands of them.[9] Its encoded protein,

C9orf72, has been involved in coupling cytoskeleton modulation and autophagy with endocytosis.[9] *C9Orf72* mutations have been related to bvFTD, frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS), nonfluent variant primary progressive aphasia (nfvPPA), corticobasal syndrome (CBS), and rarely semantic variant primary progressive aphasia (svPPA).[6] As with *GRN*, *C9Orf72* carriers can develop neuropsychiatric symptoms, such as psychosis and anxiety. Moreover, as in *MAPT* and *GRN*, these patients can present visual and verbal episodic memory impairment.[6] Neuroimaging shows symmetric and sometimes minimal atrophy of the cerebral hemispheres, thalamus, and cerebellum.[6] TDP-43 type A can be found in *C9Orf72* carriers, but the commonest pathology in this population is TDP-43 type B, consisting of less neuronal cytoplasmic inclusions and dystrophic neurites in both cortical layers and lower motor neurons. Another interesting pathological finding is the presence of ubiquitin-positive, TDP-43-negative inclusions in the cerebellum, neocortex, and hippocampus.[8]

Other important mutations associated with FTD include *VCP*, *CHMP2B*, *TARDBP*, *FUS*, *SQSTM1*, *UBQLN2*, *TDK1*, *TREM2*, *CHCHD10*, and *PRNP*. Some of them will be mentioned in the next sections.

METHODS

We searched the PubMed and Medline databases using the keywords "Alzheimer's disease," "frontotemporal dementia," "mutation," "America," and "Latin America," filtering for "human" research, without restricting dates for relevant articles. The initial search produced 205 hits. We searched specific Latin American countries to ensure the articles found were relevant to specific regions. After reading the abstracts and discarding articles unrelated to the genetics of AD and FTD in Latin America and the Caribbean, we selected and reviewed a total of 45 studies.

ARGENTINA

Alzheimer's disease

Presenilin 1 mutations

T119I

Two members of an Argentine family of Italian descent underwent both clinical evaluation and genetic testing, and a mutation in *PSEN1 T119I* was found.[10]

The proband's first cognitive complaints happened when he was 49 y.o. Next, the patient developed depression after a sibling's death. Finally, the participant was diagnosed with Alzheimer's dementia nine years after the memory complaints (58 y.o.). One of the proband's parents and several uncles and cousins were also affected by the same condition. After DNA analysis, Itzcovich et al. found a heterozygous C>T transition at position c.356 of *PSEN1*, a variant that predicts a threonine-to-isoleucine substitution at codon 119 (p.T119I), located in the first extracellular loop of the protein (HL-I loop).

Clinical symptoms include memory, executive, and attention impairment.[10] Neuroimaging showed bilateral amyloid accumulation in the neocortex (frontal, parietal, and lateral temporal lobes), cingulate, and striatum.[10]

Mean age of onset was 56 years, but one family member was diagnosed with LOAD at the age of 71 years, suggesting that this mutation can cause autosomal dominant AD of both early and late onset in this population.[10]

M146L

This autosomal dominant mutation was found in an Argentine family and described in 1998. It consists of an A>T transversion in codon 146 of *PSEN1*, a variant that causes a methionine-to-leucine substitution.[11] Mean age of onset was 38.9±3.9 years, and mean age at death was 41.7 through 51 years. Carriers developed symptoms such as memory loss, early language impairment, myoclonus, and cerebellar signs, besides some neuropsychiatric symptoms, including aggressiveness and apathy. All subjects in that report were *APOe3* homozygotes.

M146V

Riudavets et al.[12] described an Argentine family originally from Portugal. This case of familial dementia associated with a PS-1 M146V mutation presented with typical clinical features of FTD (gradual apathy, disinhibition, executive dysfunction, anomia, and memory loss followed by extrapyramidal manifestations, including rigidity, akinesia, and movement disorders, without tremor). Afterward, the proband clinical state worsened and progressed to myoclonus, seizures, and mutism.

Presenilin 2 mutations

N141I

Researchers from the Centro de Neuropsiquitría y Neurología de la Conducta (CENECON), Universidad de

Buenos Aires, characterized these clinical phenotypes in two Argentine pedigrees with clinical symptoms of early-onset AD (EOAD) and found *PSEN2 Asn141Ile* (*N141I*) in all affected subjects.[13] The carriers developed early episodic memory impairment, visuospatial impairment, limited verbal fluency, and executive dysfunction, as well as neuropsychiatric symptoms like apathy. Noteworthily, epilepsy was rare.[13]

Even though *N141I* is the most frequent *PSEN2* mutation, this research was the first *PSEN2 N141I* report in South America. Moreover, these families share the same Volga German (VG) ancestry, that is, their ancestors moved from Germany to the southern Volga region in the 1760s, generating the founder effect of this mutation.

Affected members' mean age of onset was 52.7±3.2 years, the mean age at death was 60.7±3.6 years, and the mean disease duration was 7.9±3.1 years. This mutation has a penetrance of 100%.

The *APOE* polymorphism phenotype of the carriers was: ε3/ε3 and ε2/ε3, with no impact on onset and progression of the disease, and ε4/ε4, although determining the impact of this last genotype at the age of onset or disease progression was not possible.

Frontotemporal dementia

Allele repeat expansions

C9ORF72 G4C2

The first case of FTD due to *C9orf72 G4C2* repeat expansion in Argentina was described in 2016.[14] It involved a 51-year-old proband who developed behavioral disorders (anxiety, aggressiveness due to feeling offended in public places, psychotic ideation, and delusions), followed by language difficulties and cognitive impairment for over 3 years. The psychotic symptoms, in addition to a family history of parkinsonism and ALS, made the clinicians suspect *G4C2* hexanucleotide repeat expansion in *C9ORF72*. The presence of an expanded *G4C2* allele in the patient was then confirmed (more than 50 repetitions).

Itzcovich et al. genotyped the *C9orf72 G4C2* repeat in patients with FTD (n=33), ALS (n=50), and age-matched healthy controls (n=73) in Argentina.[15] They found a male to female ratio of 1:1 in the ALS group, while 60.6% of FTD individuals with *C9orf72* repeat expansion were women. The overall G4C2 expansion frequency among FTD cases was 18.2% (6 out of 33 FTD cases). Among ALS patients, only two cases (one with positive family history and one sporadic) carried a G4C2 expansion. In the six G4C2 expansion carriers with FTD, five had bvFTD and just one had primary progressive aphasia; curiously, most of these patients (3 out of 5 or 60% of this group) showed motor neuron disease during follow-up.

MAPT mutations

P301L

In 2017, Gatto et al. reported an intrafamilial variable phenotype in a family with a missense mutation (p.P301L; rs63751273) in exon 10 of the *MAPT* gene.[16] This family of Basque ancestry had 26 members over 6 generations and 9 affected individuals. The two living subjects analyzed had different phenotypes: CBS (1 female) and FTD (1 male), while the 7 deceased family members over 4 generations, whose cases were described as early-onset dementia, presented with apathy and disinhibition as the main symptoms. The CBS proband also had cognitive complaints that were evident in the neuropsychological tests, with attention deficit and dysexecutive impairment.

During the follow-up, the CBS proband developed gait disturbance, high risk of fall, worsening of motor symptoms in her right arm (focal dystonia and alien limb syndrome), myoclonus, hyperreflexia, apraxia, and frontal release signs.[16] Attention and executive function worsened, and she developed problems with memory and language.[16]

The second case (FTD) involved a man with symptoms such as logorrhea, tangentiality, disinhibition, inappropriate behavior such as waking his son up at night just to talk (the authors of the report considered it a lack of empathy), isolation, compulsions (alcoholism), repetitive behaviors (eating the same meals every day), emotional apathy (he seemed not to care about his difficult financial situation), and grooming neglect.[16] Neuropsychological tests led to the conclusion that he had attention problems and executive impairment (as in the proband's case). Finally, a brain magnetic resonance imaging (MRI) showed asymmetrical frontal atrophy of the frontal lobes, a finding highly suggestive of bvFTD.[16]

BRAZIL

Alzheimer's disease

Presenilin 1 variants

Barbosa Abdala et al.[17] performed a mutational screening of *PSEN1* among 53 samples of people with a fam-

ily history of AD from Rio de Janeiro. Four variants were identified: two missense variants (*rs63750592*; *rs17125721*) and two intronic variants (*rs3025786*; *rs165932*). Prediction results and other articles showed that *rs17125721* (*Glu318Gly* or *E318G*) is a risk variant and not a monogenic cause of AD, while *rs63750592* (R35Q) is a variant of unclear pathogenicity.

A subsequent case-control study evaluated the role of *rs17125721* or *E318G* on AD risk. A sample of 120 sporadic AD cases and 149 healthy older adult controls was analyzed, and a risk association for *s17125721* or *E318G* was identified in familial AD cases (*Odds Ratio* — OR=6.0; 95% confidence interval [95%CI] 1.06–33.79; p=0.042); no statistical association was found between the *APOE* ε4 allele and *rs17125721* or *E318G*.[17]

APOE4

In 1997, Almeida and Shimokomaki[18] examined the association between the *APOE* ε4 allele and AD, which was being reported in developed countries. After analyzing a sample of 55 AD patients and 55 controls, they found that *APOE4* was more frequent among the AD patients (20.9% versus 8.9%; p=0.038), establishing that one *APOE* ε4 allele was enough to increase by 2.63 times the odds of being diagnosed with dementia. Interestingly, they also noticed a trend toward earlier onset among *APOE* ε4 carriers.

Recently, De Luca et al.[19] explored the influence of *APOE* ε4 on the age of onset of AD. To that end, they analyzed three groups from three different sources: 414 patients from Italy, 135 patients from Brazil, and 376 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) consortium. *APOE* ε4 showed a significant anticipatory effect among people with LOAD in the three samples. The Brazilian group presented a particularly significant *APOE* ε4 anticipatory effect (p=0.001; beta= -10.2; 95%CI -11.0 to -9.4).

Besides *APOE* ε4, the authors found other polymorphisms related to LOAD, such as *SOR1*, *GAB2*, and *GSK3B*. Since none of these last variants are considered etiological factors, despite being able to interact with other genetic forms to modify the risk of AD, Izzo et al.[20] conducted a study to explore the interaction of these polymorphisms with *APOE* ε4. The authors found an association between the *SORL1* GG genotype and AD (OR=2.07; 95%CI 1.17–3.68; p=0.047), regardless of the presence of *APOE* ε4. They also discovered a positive association between the *GAB2* GG genotype and AD (OR=1.8; 95%CI 1.01–3.18; p=0.021), which was higher in *APOE* ε4 carriers (OR=5.08; 95%CI 1.45–18.98; p=0.006). Finally, the authors identified an association between the *GSK3B* GG genotype and AD (OR=2.48; 95%CI 1.19–5.20; p=0.018), which was higher in the absence of the ε4 allele. Also, they found a protective effect related to the A allele of *GSK3B*, irrespective of the *APOE* status.

Frontotemporal dementia

Allele repeat expansions

C9ORF72 G4C2

In 2012, this expansion was described in relatives with several affected members.[21] Similar to previous reports, the main clinical syndromes seen in this *C9orf72* family were bvFTD and ALS. In many members, subtle personality changes started decades before dementia was diagnosed. Interestingly, one of the subjects was diagnosed with bvFTD at an earlier age than the previous generation, raising the hypothesis of an anticipation phenomenon. Two patients had inflammatory bowel disease. As in other *C9orf72* cases, hallucinations were a characteristic symptom (rare in sporadic bvFTD). Furthermore, neuroimaging showed a moderate posterior pattern of atrophy, described as more important parietal and occipital atrophy with reduced temporal tissue loss when compared to sporadic bvFTD.

In 2016, Chadi G et al.[22] evaluated the clinical features of subjects carrying *C9orf72* repeat expansions within a Brazilian cohort of ALS patients and identified a patient diagnosed with FTD.

In 2018, a study about the frequency of this expansion in the Brazilian population was published.[23] Among the 471 patients analyzed (404 with ALS/motor neuron disease, 67 with FTD, and 63 healthy controls), the highest frequency of the expansion was in the FTD-ALS group (50% of familial and 17.6% of sporadic cases), followed by 5% of pure ALS/motor neuron disease patients (11.8% of familial and 3.6% of sporadic cases) and 7.1% of pure familial FTD individuals.

GRN, MAPT, and TARDBP mutations

In 2016, Takada et al. investigated the frequencies of *GRN* and *MAPT* mutations in FTD cohorts from two Brazilian dementia research centers.[24] They analyzed blood samples from 76 probands diagnosed with bvFTD (n=55), svPPA (n=11), or nfvPPA (n=10). A total of 25% of the cohort had at least one relative affected by FTD.

The authors found *GRN* mutations in seven probands (9.6%), and *MAPT* mutations in two probands (7.1%).

GRN and *MAPT* mutations explained 31.5% and 10.5% of the familial cases, respectively. In individuals with *GRN* mutations, three novel *GRN* mutations were identified (patients with bvFTD): p.Q130X, p.D317Afs*12, and p.K259Afs*23. Other *GRN* mutations found in that sample were: *p.Q257Pfs*27* (proband with nfvPPA), *p.Q300X* (proband with nfvPPA), *p.V200Gfs*18* (proband with nfvPPA/mixed PPA), and *p.S301Cfs*61* (proband with bvFTD).

Subjects with the *Q130X GRN* mutation (or some of their relatives) showed memory difficulties, especially of the semantic type, language impairment (nfvPPA), irritability, apathy, and other bvFTD symptoms, such as diet changes, loss of empathy, and executive impairment.[24] One patient developed delusions. On the other hand, a *GRN D317Afs* mutation carrier showed bvFTD symptoms that included disinhibition, impulsive behavior, and apathy at the age of 63. Later, the patient developed motor impairment (parkinsonism). Asymmetric but bilateral atrophy was identified in the brain MRI, and pathology revealed the involvement of frontal, parietal, and temporal lobes. His mother also had bvFTD and motor symptoms.[24] Finally, a person with *K259Afs GRN* mutation and some relatives developed anomia, logorrhea, apathy, disinhibition, diet changes, and asymmetric brain atrophy, especially of the temporal lobes.[24]

Regarding *MAPT*, an *Asn279Lys* (*N279K*) mutation was found in a 45 y.o. proband with bvFTD and PSP. The other proband had a g.120998 cytosine to thymine change, an intronic variant that affects the alternative splicing of exon 10 (IVS10+16 C>T), which does not lead to a protein change but could explain the bvFTD phenotype of this subject.[24]

TARDBP is a gene in chromosome 1 that encodes a protein called TDP-43, an important riboprotein with functions such as mRNA stabilization, transcription regulation, and alternative splicing.[6,25] Mutations in this gene have been associated with FTD, FTD-ALS, and ALS.[25] In 2012, Machado-Costa screened a sample of 47 FTD cases for *TARDBP* mutations and found a *p.I383V* mutation in a proband diagnosed with svPPA at the age of 54.[25] The mutation carrier also had neuropsychiatric symptoms like irritability, apathy, disinhibition, and obsessive-compulsive behavior; his brain MRI showed bilateral temporal atrophy.

Valosin-containing protein mutations

Katsuyuki-Shinjo et al.[26] reported a Brazilian family with inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD), an autosomal dominant disease linked to chromosome 9p21-p12. This condition is attributed to missense mutations in the valosin-containing protein (VCP) gene, whose protein has been involved in proteolysis.

Ten family members from three generations were evaluated. The proband's (male, 58 y.o.) first symptom was distal progressive muscle weakness of the four limbs. Myopathy was confirmed by electromyography and muscle biopsy. Afterward, he developed personality changes and cognitive impairment. MRI and single-photon emission computed tomography (SPECT) showed atrophy and hypoperfusion in the frontal and temporal brain areas, specifically. A computed tomography (CT) revealed increased density, coarse trabeculation, and cortical thickening of the cervical spine. His mother had AD, and his father had chronic asymmetric limb muscle weakness. He tested positive for *VCP* mutation: *c.290G>A*, *p.Gly97Glu*, or *p.G97E*. Two of his siblings and a nephew had this mutation as well.[26]

Abrahao et al.[27] also described three clinical cases of relatives with intrafamilial phenotype variability: each participant had either myopathy with rimmed vacuoles, ALS, or FTD, but none had Paget disease of bone (PDB). After the whole-exome sequencing, they confirmed the segregation of a novel mutation, *p.Asn91Tyr* or *N91Y*, in an autosomal dominant pattern. The proband with FTD was diagnosed with probable bvFTD, with onset at the age of 66.

Fanganiello et al.[28] also described a family with IBMPFD. The proband presented mild progressive proximal myopathy, PDB (onset at the age of 55 years), behavioral disturbances, and cognitive impairment (onset at the age of 56 years). The patient developed FTD with features of both bvFTD and semantic dementia. Mutation analysis of the propositus revealed a heterozygous nucleotide transition in exon 3 (c.277C → T) of the *VCP* gene, resulting in an arginine substitution with cysteine in codon 93.

Prion protein mutations

PRNP is a gene encoded by chromosome 20, responsible for the prion protein (PrP), a 208 amino acid membrane glycoprotein, whose exact function is unclear, but that could participate in processes such as neuronal protection, cellular adhesion, cell signaling, and circadian rhythm control.[29]

In 1996, Nitrini et al.[30] reported a *PRNP* mutation, *Thr183Ala* or *T183A*, which had an autosomal dominant genetic pattern and led to a rapidly progressive FTD (disease duration: 4.2±2.4 years) at the age of 44.8±3.8 years. The proband showed apathy, memory problems, time and visuospatial disorientation, slurred speech, parkinsonism, and frontal release signs. The electroen-

cephalogram was normal, but he had diffuse cortical atrophy. The brain pathology revealed spongiform changes and neuronal loss in the putamen, besides minimal gliosis in the remaining affected regions. Other family members were also affected by this condition.

CHILE

Alzheimer's disease

M146I

In 2010, Sinning et al.[31] reported an extended Chilean pedigree affected by EOAD for 4 generations. The cause in all affected members was a heterozygous G to C transversion at position 438 of the mRNA in *PSEN1* (*14q24*), which results in a methionine to isoleucine substitution at position 146 of the protein (*M146I*). The age of onset of dementia ranged between 38 and 42 years. They had early neuropsychiatric manifestations, such as anxiety and depression, and other neurological issues, including myoclonus and generalized epilepsy.

Frontotemporal dementia

C9Orf72

In 2017, Miranda et al.[32] described the case of a 77 y.o. woman who developed symptoms such as apathy, less fluent language, anomia for common items, and circumstantial speech when she was 68 y.o. Later, she developed inattention, problems with semantic memory and frontal test, and nfvPPA, besides parkinsonism without rest tremor or rigidity. Other relatives also had a history of dementia, parkinsonism, and ALS (several brothers and a sister, the mother, and many maternal aunts and uncles). Severe atrophy of frontal and temporal lobes was identified in this proband. Genetic testing showed a GGGGCC *C9orf72* abnormal expansion (approximately 60 repeats). This was the first described case of familial FTD due to *4G2C C9Orf72* repeat expansion in Chile.

COLOMBIA

Presenilin 1 E280A

E280A is a glutamic acid to alanine mutation at codon 280 of the *PSEN1* gene. The consequence is an early-onset familial AD at a mean age of 49 years, with fully penetrant autosomal dominant transmission.[33] It was first discovered in a family from the state of Antioquia, Colombia, with over 6000 members subsequently identified and described.

PSEN1 E280A carriers will undergo four AD stages:

- asymptomatic pre-mild cognitive impairment (MCI) (median age: 35 y.o.; 95%CI 30–36);
- symptomatic pre-MCI (38 y.o.; 95%CI 37–40);
- MCI (44 y.o.; 95%CI 43–45);
- dementia (49 y.o.; 95%CI 49–50).[34]

In affected carriers, the main neurological features are: memory impairment (100%), behavioral changes (94%), language impairment (such as aphasia, 81%), headache (migraine and non-migraine, 73%), gait difficulties (65%), seizures and myoclonus (45%), cerebellar signs (19%), and parkinsonism (19%).[35] This symptomatology is supported by pathological changes, such as brain atrophy, cerebellar damage, and severe amyloid and tau-related pathology.[35]

Regarding *APOE* polymorphisms in this population, Pastor et al.[36] found no association between *APOE* ε4 and age at disease onset in *PSEN1 E280A* mutation carriers. On the other hand, *APOE* ε2 delays the age of onset, making it a protective factor.[37]

Presenilin 1 I416T

I416T is the cause of dementia in the second largest family with EOAD in Antioquia, Colombia. Ramírez-Aguilar, Acosta-Uribe et al.[38] recently found the variant *c.1247T.C* in codon 416 of *PSEN1*, which causes isoleucine to threonine substitution and impairs a highly conserved residue in the 8th transmembrane domain of presenilin 1.

The age of onset was 42.35 years (standard deviation [SD] 6.28) for memory complaints, 47.6 years (SD 5.83) for MCI, and 51.6 years (SD 5.03) for dementia. Among the several neuropsychiatric symptoms are depression, anxiety, delusions, hallucinations, and insomnia. Besides memory impairment, the affected carriers develop myoclonus and tonic-clonic seizures. Neuropsychological symptoms include amnestic MCI, and, interestingly, these patients show better performance in language and attention than praxis and executive function. *APOE* ε4 does not behave as an age modifier in this population.

APOE3ch

In 2019, Arboleda-Velasquez et al.[39] described a mutation in *APOE3* called *APOE3ch*, caused by an arginine to serine substitution at amino acid 136 (*R136S*). The mutation was found in homozygous form in a *PSEN1*

E280A carrier who developed MCI in her seventies, even though the median age of MCI onset is usually 44 y.o.[40] The subject had problems with recent memory, and her neurological exam was normal. Neuroimaging techniques such as positron emission tomography (PET) showed an important amyloid-β burden, with a distribution volume ratio (DVR) of 1.96 — much higher than that of younger people with MCI and the same *PSEN1* mutation (DVRs 1.49–1.60). Nevertheless, PET tau burden and neurodegeneration were limited (only medial temporal and occipital regions were affected), and the fluorodeoxyglucose PET did not detect the glucose metabolism abnormalities typical of people with this familial AD type. Also, her MRI showed atrophy similar to that of carriers with MCI in their forties.

The *APOE3ch* mutation is located in a region that plays a role in binding to lipoprotein receptors and heparan sulfate proteoglycans (HSPGs).[41] HSPGs seem to promote amyloid-β aggregation and neuronal tau uptake through processes like APOE binding.[42] APOE3ch presents the lowest heparin-binding ability (compared to other *APOEs*), becoming a protective genetic variant against the early onset of autosomal dominant AD when a person has homozygosity.[39]

The authors concluded that *APOE3ch* homozygous people might be resistant to the clinical onset of AD by limiting tau pathology and neurodegeneration despite the significant amyloid-β burden in those subjects.[39]

Other mutations

In 2001, Arango et al.[43] published a systematic genetic analysis of *APP*, *PSEN1,* and *PSEN2* mutations in a Colombian sample of 76 subjects with AD, identifying several mutations. In *APP,* they found a silent *Gly708 (G708*) mutation in a proband with sporadic AD. In *PSEN1*, they discovered a new *PSEN1* mutation, *Val94Met*, in a subject with sporadic AD, which was absent in the 53 asymptomatic controls; they also identified other three *PSEN1* mutations: *Ile143Thr* (*I143T*, autosomal dominant), *Glu280Ala* (*E280A*, autosomal dominant and previously described), and *Glu318Gly* (*E180G*, in sporadic and familial cases). Nowadays, *PSEN1 E318G* is considered a risk modifier of this disease.[44] Finally, in *PSEN2,* they found two silent mutations: *Pro129* or *P129* (in a patient with autosomal dominant AD) and *Ser236* or *S236* (in three sporadic cases). *APOE* polymorphisms were not measured, which was considered a limitation of the study.

In the state of Valle del Cauca, in western Colombia, a *PSEN1 Pro117Ala (P117A)* mutation was found in eight patients. This mutation causes autosomal dominant EOAD during the fourth decade of life (Table 1).[45] The first *PSEN1 Pro117Ala* mutation case reported involved three patients from the same family in France with early progressive ataxia (which occurs 1–7 years after the onset of cognitive decline) and dementia.[46] Ataxia was not reported in the Colombian pedigree with this mutation.

Triggering receptor expressed on myeloid cells 2 (*TREM2*) is an important protein for the phagocytosis of apoptotic neuronal cells by microglia in the brain. In 2013, Giraldo et al.[47] described a *TREM2 W198X* mutation that results in polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), an autosomal recessive condition related to early-onset dementia (an FTD-like syndrome). The clinical profile of these patients consisted of compulsive tobacco use and alcohol consumption, convulsive disorder, and neuropsychiatric symptoms, such as obsessions, compulsions, apathy, impulsivity, disinhibition, and cognitive impairment (bradyphrenia, executive dysfunction, apraxia, and memory loss). The frontal atrophy identified in the brain MRI was bilateral but asymmetric and worse on the right side. The authors of this report concluded that *TREM2* might be a risk factor for neurodegeneration and suggested that other neurodegenerative disease cohorts should be examined for its genetic variants.

In 2018, Arboleda-Bustos et al.[48] studied the association between several *TREM2* polymorphisms and LOAD. They found a relationship with the *TREM2* arginine to histidine substitution at amino acid 47 (*R47H*) in a sample of 358 AD cases and 329 controls; specifically, this variant was identified in six LOAD probands: five (5/558 or 1.4%) heterozygous and one (1/358 or 0.28%) homozygous. No control presented this polymorphism. The difference in the *R47H* allele frequency between cases and controls was statistically significant (p=0.010). They also detected a higher frequency of *APOE4* in AD cases (ε3/ε4 genotype presented an OR=1.738; 95%CI 1.233–2.450; p=0.0016, and ε4/ε4 genotype showed an OR=10.568; 95%CI 3.197–34.932; p=0.0001). Out of the five heterozygous *R47H* carriers, three were *APOE* ε3/ε3 and two, *APOE* ε3/ε4; the homozygous subject was *APOE* ε3/ε4, with a family history of LOAD, and age of onset of 66 y.o. The authors concluded that *TREM2 R47H* could be an important LOAD risk factor, but more studies are necessary to corroborate the relationship described.[48]

In Colombia, a recent study about LOAD genetics has also been performed.[49] It evaluated the association of 14 single-nucleotide polymorphisms in genes

that have been connected to LOAD and confirmed this relationship through a genome-wide association study. Indeed, significant associations were identified for variants in *BIN1* (*rs744373*; OR=1.42), *CLU* (*rs11136000*; OR=0.66), *PICALM* (*rs541458*; OR=0.69), *ABCA7* (*rs3764650*; OR=1.7), and *CD33* (*rs3865444*; OR=1.12). Likewise, a significant interaction effect was observed between *CLU* and *CR1* variants and *APOEe*. These results reflect the importance of gene-gene interactions for the etiology of neurodegenerative diseases.

Table 1 presents a summary of the mutations described in Colombia different from *PSEN1 E280A*, *PSEN1 I416T*, and *APOE3ch* ones.

CUBA

Alzheimer's disease

Presenilin 1 mutations

L174M

This variant was found in a family of 281 members over six generations, with the proband descending from a Spanish founder.[50] The mutation results from a C-to-A change detected in exon 6 of the *PSEN1* gene. Mean age of onset was 59 years. The patients had dyscalculia, attention difficulties, visuospatial disorientation, emotional apathy, anosognosia, and slowing speech. Nevertheless, the most relevant features were memory impairment and ischemic episodes. The *APOE* genotype varied: ε3/ε3, ε3/ε4, and ε4/ε4. The subjects with ischemic attack also had *APOE* ε4, an allele related to a possible increase in cerebrovascular risk. Brain examination confirmed amyloid pathology.

APOE genotype

The effects of ethnic identity, genetic admixture of *APOE* genotypes, and its association with dementia prevalence and incidence have been explored. In a 10/66 study report, Llibre-Rodriguez et al.[51] described the *APOE* status in 2520 participants, with genetic admixture in 235 dementia cases and 349 controls. They concluded that *APOE e*4 allele carriage is associated with an increased prevalence and incidence of dementia in populations characterized by African/European admixture. The associations of *APOE* ε4 allele carriage with prevalence were stronger than those with incidence. The explanation for this phenomenon could be a possible earlier age of onset for *APOE* ε4 carriers.

Table 1. Colombian mutations (besides Presenilin 1 *E280A*, Presenilin 1 *I416T*, and *APOE3ch*).

Mutation	State or department	Phenotype	Age of onset (years)
APP Gly708	Cundinamarca	Silent mutation, but the proband had sporadic Alzheimer's disease	71
PSEN1 Val94Met	Cundinamarca	Sporadic Alzheimer's disease	53
PSEN1 Ile143Thr	Cundinamarca	Autosomal dominant Alzheimer's disease	30
PSEN 1 Glu318Gly	Cundinamarca	Sporadic and familial cases (the mutation is a risk modifier)	65.8 (49–86)
PSEN1 Pro117Ala	Valle del Cauca	Autosomal dominant Alzheimer's disease	Fourth decade of life
PSEN2 Pro129	Cundinamarca	Silent mutation, but the proband had autosomal dominant Alzheimer's disease	62
PSEN2 Ser236	Cundinamarca	Silent mutation, but the probands had sporadic Alzheimer's disease	83.2 (78–88)
TREM2 Trp198X	Antioquia	PLOSL and early-onset dementia (autosomal recessive)	FTD-like syndrome, at 47

PSEN1: Presenilin 1; PSEN2: Presenilin 2; APP: amyloid precursor protein; PLOSL: polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy; TREM2: triggering receptor expressed on myeloid cells 2; FTD: frontotemporal dementia.

MEXICO

Alzheimer's disease

Presenilin 1 mutations

L171P

In 1998, Ramirez-Dueñas et al.[52] reported a new mutation in Mexican families with EOAD (36–40 y.o.), explained by a thymine to cytosine mismatch in exon 7 (nucleotide 760 of cDNA), which leads to the *Leu171Pro* mutation. This mutation was considered pathogenic.

A431E

Twelve unrelated families with EOAD from Jalisco, Mexico, were analyzed in 2005.[53] The *Ala431Glu* mutation in exon 12 of *PSEN1* was found in nine (75%) of these families, with an autosomal dominant inheritance. Also, 15 families were identified in Guadalajara (n=2), Chicago (n=1), and Southern California (n=12).[54]

The ages of onset ranged between 34 and 48 years (mean age of 40 years). A phenotypic variability characterized by spastic paraplegia, myoclonus, aphasia, and psychiatric symptoms (mostly depression and personality changes) was observed. Neuroimages (CT and MRI) showed cortical and subcortical atrophy, while pathology confirmed the diagnosis of AD.

APOE genotype and cognition

In 2008, Villalpando-Berumen et al.[55] conducted a cross-sectional analysis of a cohort study to determine the influence of *APOE* ε4 on the cognition of older multiracial Mexican adults. They found no increased risk for AD in *APOE* ε4 carriers, but its presence seems to be associated with worse performance in a long-term visual memory test among subjects with dementia. The authors concluded that *APOE* ε4 modifies the clinical expression of AD.

PUERTO RICO AND DOMINICAN REPUBLIC

Presenilin 1 G206A

A family case series and a cohort study were conducted in New York, Dominican Republic, and Puerto Rico.[56,57] The researchers identified a G-to-C nucleotide change that causes a glycine to alanine amino acid substitution at codon 206, exon 7 of *PSEN1*, defining a G206A mutation. These families have a possible common ancestor.

Besides cognitive impairment, the affected carriers presented depression, vascular dementia, and other FTD-like symptoms, such as psychosis, motor impairment, epilepsy, and ataxia.[57]

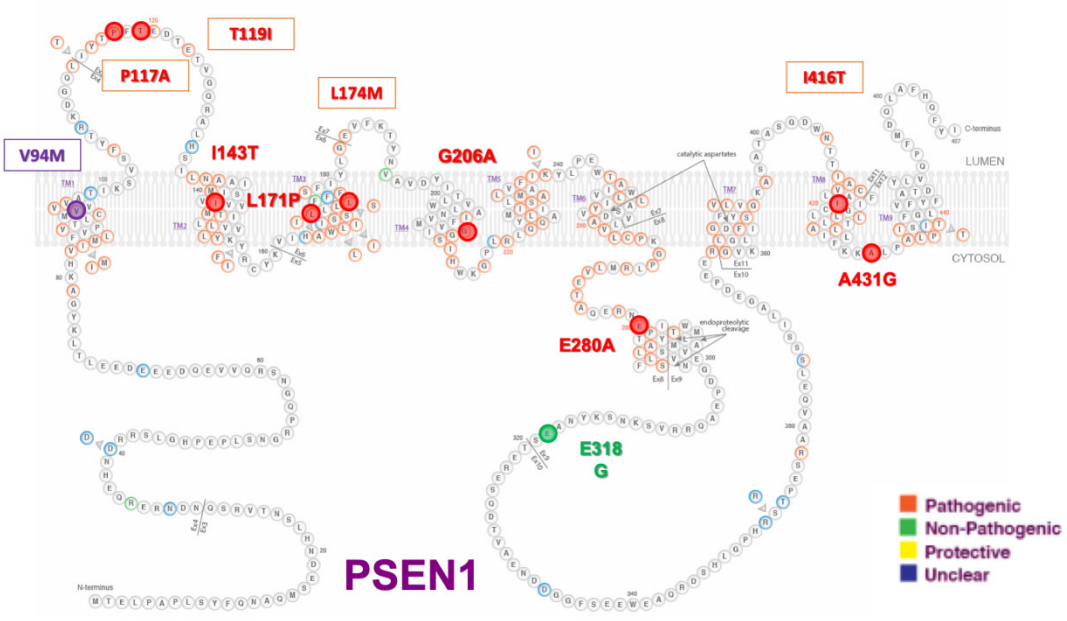
Age of onset slightly varied between the Caribbean countries: 54.7 (SD: 7.1) y.o. for Dominicans and 59.6 y.o. (range: 46–67, with an 81 y.o. outlier) for Puerto Ricans. *APOE* ε4 had no effect on the age of onset, while *SNX25*, a gene with a potential role in regulating membrane protein trafficking excess levels of amyloid-β in individuals with the *PSEN1 p.G206A* variant, may be a biologically relevant modifier of the age of onset.

URUGUAY

PRNP G114V

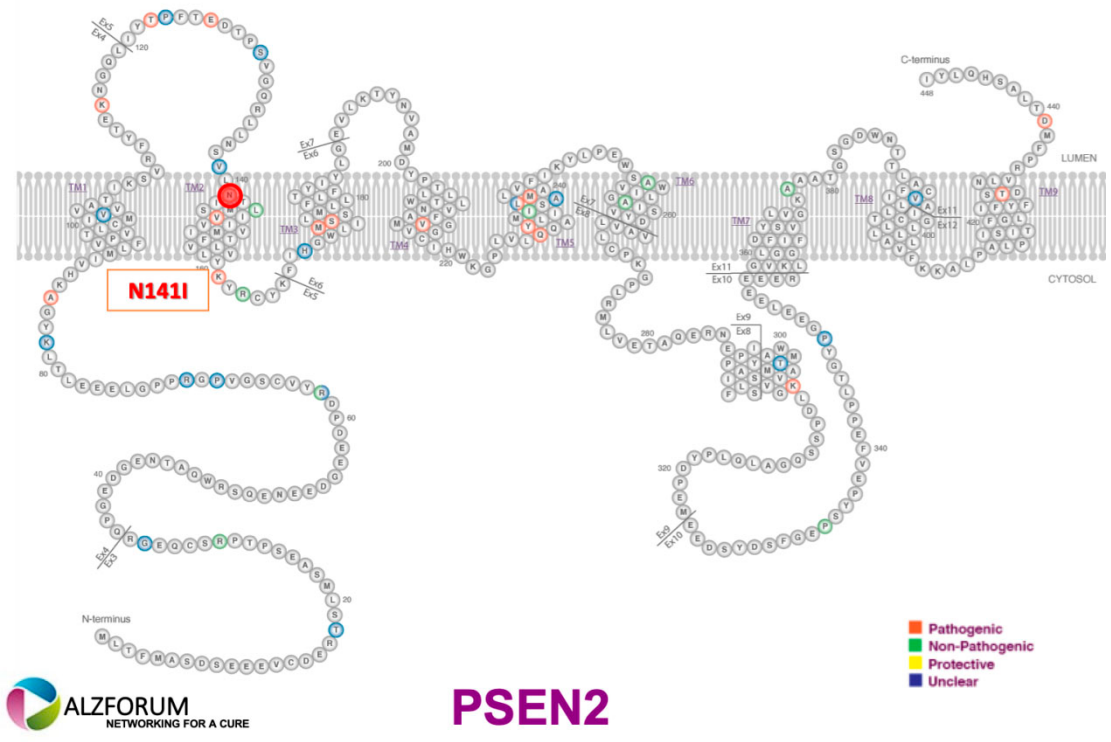
In 2005, Rodriguez et al.[58] described an Uruguayan family with a mutation in the *PRNP* gene, *Gly114Val* or *G114V*, related to bvFTD and motor neuron disease. The affected members had memory loss and neuropsychiatric symptoms, such as panic disorder, aggressiveness, visual hallucinations, grooming neglect, apathy, and stereotypic behavior, besides speech disorder, corticospinal syndrome, cerebellar signs, myoclonus, apraxia, and asomatognosia. This kind of dementia has a very early onset (second and third decade of life) and sometimes progresses rapidly. Electroencephalogram and brain MRI revealed diffuse brain damage. The frontal biopsy in one of the patients showed spongiosis, gliosis, and neuronal loss in the absence of amyloid deposition. Not all carriers developed the disease, which is suggestive of a mutation with incomplete penetrance.

Figures 1, 2, 3, and 4 present the Latin American mutations in *PSEN1*, *PSEN2*, *MAPT*, and *TREM2*, respectively. As described above, many lines of evidence point to a genetic basis for the development of AD, both in its early-onset forms and in the much more common late-onset form. The finding of different mutations in several genes related to AD and FTD provides a great opportunity for future studies based on primary and secondary prevention. Longitudinal follow-up studies of our own populations are necessary, as well as a continuous search for new cases of families with dementia in Latin America.



PSEN1: Presenilin 1.

Figure 1. Latin American Presenilin 1 mutations.



PSEN2: Presenilin 2.

Figure 2. Latin American Presenilin 2 mutations.

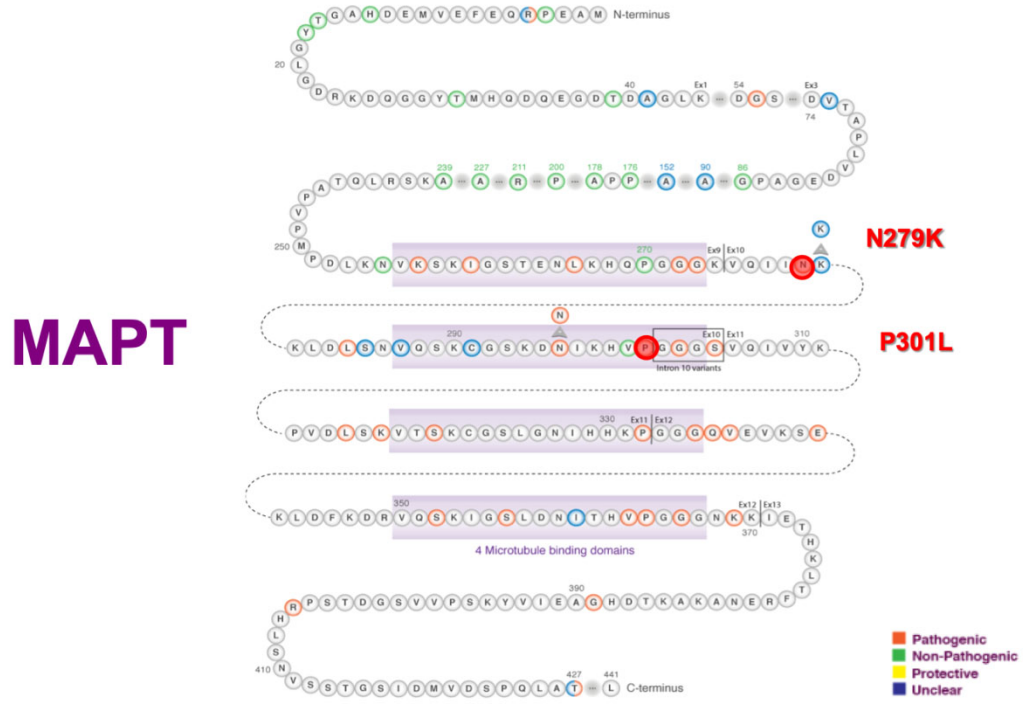
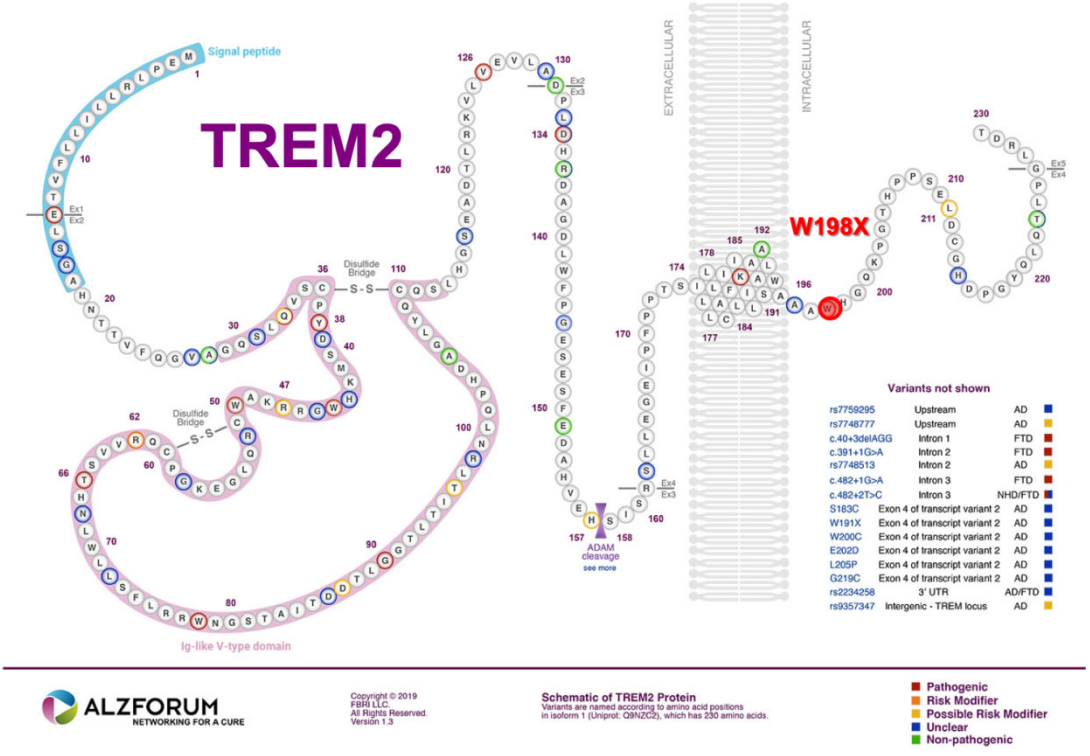


Figure 3. Latin American MAPT mutations.



TREM2: triggering receptor expressed on myeloid cells 2.

Figure 4. Latin American triggering receptor expressed on myeloid cells 2 mutations.

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5.2. Publicación No. 2: "A neurodegenerative disease landscape of rare mutations in Colombia due to founder effects"

Resumen

Antecedentes: La población colombiana, así como la de otras regiones de América Latina, surgió de una mezcla tricontinental reciente entre los nativos americanos, los invasores españoles y los africanos esclavizados, todos los cuales pasaron por un cuello de botella demográfico debido a enfermedades infecciosas generalizadas que dejaron pequeños asentamientos locales aislados. Como resultado, la población actual refleja múltiples efectos fundadores derivados de diversas ascendencias.

Métodos: Caracterizamos el papel de la mezcla y los efectos fundadores en el origen del paisaje mutacional que condujo a trastornos neurodegenerativos en estas circunstancias históricas. Se analizaron 900 genomas de individuos colombianos con enfermedad de Alzheimer (EA) [n= 376], espectro degeneración lobar frontotemporal - enfermedad motoneuronal (FTLD-MND) [n = 197], demencia de inicio temprano no especificada (EOD) [n = 73], y participantes sanos [n = 254]. Examinamos sus proporciones de ascendencia global y local y examinamos esta cohorte en busca de variantes patogénicas en los genes que causan enfermedades y confieren riesgos.

Resultados: Identificamos 21 variantes patogénicas en genes relacionados con AD-FTLD, y PSEN1 albergaba la mayoría (11 variantes patogénicas). Se identificaron variantes de las tres ascendencias continentales. Las variantes heterocigotas y homocigotas de TREM2 fueron las más comunes entre los genes de riesgo de EA (102 portadores), un punto de interés porque el riesgo de enfermedad conferido por estas variantes difería según la ascendencia. Algunas variantes genéticas que tienen una asociación conocida con MND en poblaciones europeas tenían fenotipos FTLD en un haplotipo nativo americano. De acuerdo con el efecto fundador, la identidad por descendencia entre portadores de la misma variante fue frecuente.

Conclusiones: La demografía colombiana con múltiples cuellos de botella probablemente mejoró la detección de efectos fundadores y dejó una frecuencia proporcionalmente mayor de variantes raras derivadas de las poblaciones ancestrales. Estos hallazgos demuestran el papel de la ascendencia definida genéticamente en la expresión fenotípica de la enfermedad, un espectro fenotípico de diferentes mutaciones raras en el mismo gen, y enfatizan aún más la importancia de la inclusión en los estudios genéticos.

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**Co-First authors.*

Material suplementario de interés:

Figura 3: imagen A. Mapa de Colombia representando el lugar de origen de familia

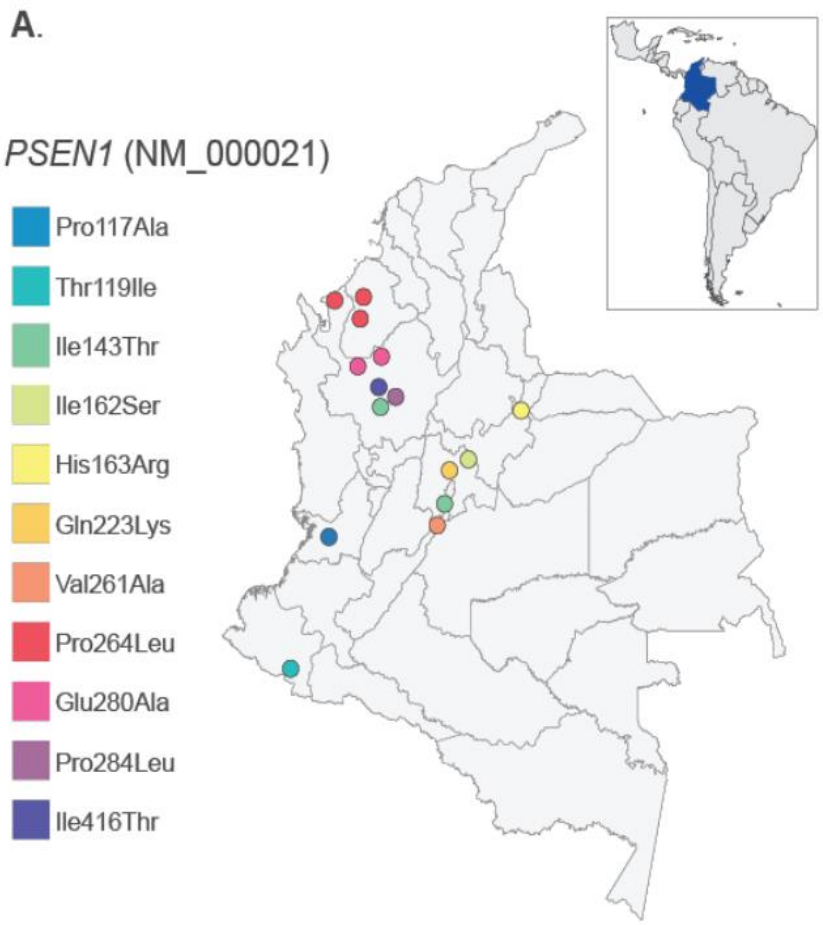

Tabla 1: Información fenotípica de portadores con variantes patogénicas en genes causantes de enfermedad. (*tabla modificada para mostrar solo las variantes relacionadas con EA*).

ALZHEIMER'S DISEASE GENES												
Gene	Coding Change	Proband Assesment					Family Assesment					
		Diagnosis	First Symptom	Age at First Symptom	AAO Dementia	APOE	Number of Symptomatic Subjects	Cognitive Symptoms	Psychiatric Symptoms	Myoclonus or seizures	Other Motor Symptoms	Atypical Symptoms
APP	g.(26253828_30011000)dup	Amnestic AD	Memory impairment	57	57	E3/E4	1	1/1	1/1	1/1	0/1	0/1
PSEN1	c.349C>G (p.Pro117Ala)	Amnestic AD	Memory impairment	32	34	E3/E3	3	3/3	1/3	2/3	0/3	0/3
	c.356C>T (p. Thr119Ile)	Amnestic AD	Memory impairment	57	62	E3/E3	4	4/4	3/4	0/4	0/4	0/4
	c.428T>C (p. Ile143Thr)	Amnestic AD	Memory impairment	33	36	E3/E4	2	2/2	1/2	1/2	0/2	0/4
	c.485T>G (p. Ile162Ser)	Amnestic AD	Memory impairment	48	53	E3/E3	2	2/2	2/2	0/2	0/2	0/2
	c.488A>G (p. His163Arg)	Amnestic AD	Memory impairment	45	45	E3/E3	2	2/2	2/2	2/2	0/2	0/2
	c.667C>A (p. Gln223Lys)	Amnestic AD	Memory impairment	40	40	E3/E4	2	2/2	2/2	0/2	0/2	0/2
	c.782C>T (p.Val261Ala)	Amnestic AD	Memory impairment	38	40	E3/E3	1	1/1	1/1	1/1	0/1	0/1
	c.791C>T (p. Pro264Leu)	Amnestic AD	Memory impairment	49	52	E3/E3	2	2/2	1/2	0/2	0/2	0/2
		Amnestic AD	Memory impairment	46	46	E3/E4	1	1/1	1/1	0/1	0/1	0/1
		Amnestic AD	Memory impairment	51	56	E3/E3	5	4/4	1/4	0/4	0/4	0/4
	c.851C>T (p.Pro284Leu)	Spastic paraparesis	Difficulty in walking	34	37	E3/E3	3	2/3	3/3	0/3	2/3	0/3
PSEN2	c.487C>T (p.Arg163Cys)	Amnestic AD	Memory impairment	48	50	E3/E4	1	1/1	1/1	1/1	0/1	0/1

Síntomas cognitivos: deterioro de la memoria, deterioro del lenguaje, desorientación, disfunción ejecutiva o visuoespacial.

Síntomas psiquiátricos: Depresión, ansiedad, irritabilidad, agresividad, alucinaciones, delirios, apatía o desinhibición.

Otros síntomas motores: inestabilidad postural, caídas frecuentes, signos cerebelosos, limitación de la mirada vertical, distonía, signos de degeneración de la neurona motora superior o inferior.

Síntomas atípicos: Hemineglígencia, hemiasomatognosia, agrafestesia, mano ajena o apraxia.

Genome Medicine

RESEARCH

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A neurodegenerative disease landscape of rare mutations in Colombia due to founder effects

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Abstract

Background: The Colombian population, as well as those in other Latin American regions, arose from a recent tri-continental admixture among Native Americans, Spanish invaders, and enslaved Africans, all of whom passed through a population bottleneck due to widespread infectious diseases that left small isolated local settlements. As a result, the current population reflects multiple founder effects derived from diverse ancestries.

Methods: We characterized the role of admixture and founder effects on the origination of the mutational landscape that led to neurodegenerative disorders under these historical circumstances. Genomes from 900 Colombian individuals with Alzheimer's disease (AD) [$n = 376$], frontotemporal lobar degeneration-motor neuron disease continuum (FTLD-MND) [$n = 197$], early-onset dementia not otherwise specified (EOD) [$n = 73$], and healthy participants [$n = 254$] were analyzed. We examined their global and local ancestry proportions and screened this cohort for deleterious variants in disease-causing and risk-conferring genes.

Results: We identified 21 pathogenic variants in AD-FTLD related genes, and *PSEN1* harbored the majority (11 pathogenic variants). Variants were identified from all three continental ancestries. *TREM2* heterozygous and homozygous variants were the most common among AD risk genes (102 carriers), a point of interest because the disease risk conferred by these variants differed according to ancestry. Several gene variants that have a known association with MND in European populations had FTLD phenotypes on a Native American haplotype. Consistent with founder effects, identity by descent among carriers of the same variant was frequent.

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Conclusions: Colombian demography with multiple mini-bottlenecks probably enhanced the detection of founder events and left a proportionally higher frequency of rare variants derived from the ancestral populations. These findings demonstrate the role of genomically defined ancestry in phenotypic disease expression, a phenotypic range of different rare mutations in the same gene, and further emphasize the importance of inclusiveness in genetic studies.

Keywords: Founder effect, Bottleneck, Admixture, Genetic drift, Selection, Demography, Neurodegeneration, Alzheimer's disease, Frontotemporal dementia, Motor neuron disease

Background

The circumstances related to Latin America's unique demographic history led to numerous genetic founders that expanded rare genetic variation. The regional populations of Colombia originated from varying proportions of a recent tri-continental admixture consisting of diverse indigenous peoples, Spanish invaders, and enslaved Africans, all of whom had been geographically separated for tens of thousands of years. During the Spanish conquest, these individuals suffered massive mortality from numerous infectious diseases, including smallpox, influenza, syphilis, hepatitis, measles, encephalitis, tuberculosis, diphtheria, cholera, typhus, scarlet fever, and meningitis, which created a narrow bottleneck with a minimum effective population size approximately 12 generations ago [1]. Survivors were geographically dispersed in a patchwork of relatively isolated small founder populations. Following the first decades of the Spanish invasion and European expansion throughout various territories, the second half of the sixteenth century saw a large and continuous growth of an admixed population, especially in the Andean region of the country (Additional file 1: Figure S1). The population growth amplified the effects of genetic drift confined to highly local settings that marked a fine-grained geographic map with a local genetic stamp [2].

Demographic history and local ancestry have gained significant interest in genomic studies aiming to understand the disease burden of underrepresented populations and transferability of risk scores from research done in European cohorts. However, most of these studies have focused on genome wide association studies (GWAS) and polygenic risk scores that usually rely on the sequencing of common genetic variants [3–5], while missing those rare alleles absent from European genomes [6]. Rare variants are likely to play a role in the problem of "missing heritability," have larger effect sizes [7], and are more susceptible to population dynamics and genetic drift.

Rare mutations contribute to the occurrence of neurodegenerative disease, which prompted a search for individuals with young onset familial dementia and related neurodegenerative disorders. We suspected that genetic drift stamped local populations with unique sets of rare variants. Numerous rare genetic conditions converge under this phenotypic label, and therefore as a population indicator of rare variation, dementia represents a readily identifiable trait with a great deal of genetic variation. Among the many genes in which disease mutations fit the phenotypic label are *PSEN1* [MIM: 104311], *PSEN2* [MIM: 600759], *APP* [MIM: 104760], *C9orf72* [MIM: 614260], *GRN* [MIM: 138945], *MAPT* [MIM: 157140], *TARDBP* [MIM: 605078], *FUS* [MIM: 137070], *VCP* [MIM: 601023], *CHMP2B* [MIM: 609512], and *TBK1* [MIM: 604834] [8]. Rare variants in these genes offer novel perspectives on the breadth of their associated clinical phenotypes and the underlying molecular pathways. Here, we describe a cohort of 900 Colombian individuals with neurodegenerative diseases and report the genetic variants associated with neurodegeneration in the context of their ancestral origins and admixture.

Methods

Subjects

Participants were recruited or referred to the "Grupo de Neurociencias de Antioquia," University of Antioquia, Colombia for "The Admixture and Neurodegeneration Genomic Landscape" (TANGL) study. The project was approved by the Institutional Review Board (IRB) of the Medical Research institute, School of Medicine, Universidad de Antioquia. Written informed consent following the guidelines of the Code of Ethics of the World Medical Association, Helsinki declaration, and Belmont Report was obtained from all participants or their legally authorized proxies. The recruitment targeted patients with early-onset dementia and families in which multiple first-degree relatives were affected. All the individuals were born in Colombia (Additional file 1: Figure S1). All subjects were evaluated following a standard protocol including physical and neurological examination, as well as population validated neuropsychological assessment [9, 10]. Family history was obtained from the patients and their relatives and was considered positive if at least one first or second degree relative presented dementia or motor neuron disease (MND). Families were classified as autosomal dominant if at least three first degree relatives suffered from dementia or MND in two consecutive generations. When patients had familial forms of dementia,

their relatives with neurological and psychiatric disorders were recruited along with healthy family members. Nine hundred individuals from 566 families with high quality genomes were used for analyses (genetic sequencing and quality control procedures are detailed in the Genome Sequencing methods).

Based on their clinical diagnosis, participants were divided in four cohorts:

- The Alzheimer's disease (AD) [MIM: 104300] cohort (n = 376) included individuals with early-onset AD (AAO ≤ 65 years) and individuals with autosomal dominant late onset AD. Patients with atypical presentations of AD, such as primary progressive aphasia–logopenic variant (lvPPA), posterior cortical atrophy, and spastic paraparesis associated with *PSEN1* pathogenic variants [MIM: 607822] were included in this cohort. AD was diagnosed according the NINCDS-ADRDA criteria [11].
- The frontotemporal lobar degeneration and motor neuron disease (FTLD-MND) spectrum cohort (n = 197) comprised patients with multiple presentations of frontotemporal lobar degeneration (FTLD) [MIM: 600274], which include behavioral variant of frontotemporal dementia (bvFTD), primary progressive aphasia-semantic variant (svPPA), primary progressive aphasia-non-fluent/agrammatic variant (navPPA), and FTLD with amyotrophic lateral sclerosis (FTLD-ALS). Diagnosis of FTLD variants was done according to Gorno-Tempini et al. 2011 [12] and Rascovsky et al. 2011 [13]. Patients with corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) [MIM: 601104] diagnosed according to The Movement Disorder Society Criteria [14], and with amyotrophic lateral sclerosis (ALS) [MIM: 105400], diagnosed according to Strong et al. 2017 [15], were included in this cohort.
- The early-onset dementia not otherwise specified (EOD) cohort (n = 73) included patients with early-onset dementia (AAO ≤ 65 years) that did not fully meet criteria for AD or FTLD at the time of evaluation and did not have secondary causes that explain their neurodegeneration. Some of these individuals were relatives of the patients from the other cohorts but presented with conditions such as Parkinson's disease [MIM: 168600], bipolar disorder [MIM: 125480], or Lewy body disease [MIM: 127750].
- The Healthy participant cohort (n = 254) included individuals related and unrelated to the patients. These subjects had a Clinical Dementia Rating (CDR) score of 0 in their last examination and no evidence of neurodegenerative dementia or motor neuron disease.

The complete demographic information of the 900 individuals can be found in Table 1, Additional file 2: Table S1 and Additional file 3: Table S2.

Genome sequencing

Peripheral blood from the participants was obtained by standard phlebotomy, and genomic DNA was isolated from leukocytes using the Gentra Puregene Blood Kit (Qiagen). Genome sequencing (WGS) was performed at the HudsonAlpha Institute for Biotechnology on either the Illumina HiSeq X platform, or the Illumina NovaSeq platform. A subset of individuals was sequenced at the Human Longevity Institute on the Illumina HiSeq X platform (119 samples). The combined dataset had a mean read depth of 34X and an average of 92% of bases covered at 20X. Sequencing libraries at HudsonAlpha were prepared by Covaris shearing, end repair, adapter ligation, and PCR using standard protocols. Library concentrations were normalized using KAPA qPCR prior to sequencing. Sequencing reads from both centers were

Table 1 Demographic information of the included cohorts

Cohort	*n*	AAO		Female		APOE genotype no. (%)											
						ϵ2/ϵ2		ϵ2/ϵ3		ϵ2/ϵ4		ϵ3/ϵ3		ϵ3/ϵ4		ϵ4/ϵ4	
		Mean	Range	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
AD	376	59	30-90	249	66.2	-	-	15	4	4	1.1	168	45	139	37.1	49	13.1
FTLD-MND	197	58.8	21-82	92	46.7	1	0.5	18	9.1	-	-	122	62	49	24.9	7	3.6
EOD	73	54.5	25-75	49	67.1	-	-	2	2.7	-	-	39	53	20	27.4	12	16.4
Healthy	254	60	18-100[a]	159	62.6	2	0.8	25	9.8	1	0.4	159	45	61	23.9	4	1.6
				549	60.7	3	0.3	60	6.7	5	0.6	488	54.2	269	29.9	72	8

AD Alzheimer's disease, *FTLD-MND* frontotemporal lobar degeneration and motor neuron disorder, *EOD* early-onset dementia not otherwise specified, *AAO* age at onset

[a] Age at evaluation. There were three Individuals with uncalled *APOE* genotype (one from AD cohort and two healthy individuals)

aligned to the hg19 reference genome with bwa-0.7.12 [16]. BAMs were sorted and duplicates were marked with Sambamba 0.5.4 [17]. Indels were realigned, bases were recalibrated, and gVCFs were generated with GATK 3.3 [18]. Variants were called across all samples in a single batch with GATK 3.8 using the -newQual flag to minimize false negative singleton calls. The recall rate for GATK against truth sets is between 93 and 99% for single nucleotide variants and 85 and 98% for small (less than 50 bp) indel events [19]. Genome annotation was performed using SnpEff 4.3 [20] after splitting multi-allelic sites with Vt [21]. The genome was annotated with the gene definitions from human genome build Ensembl GRCh37.75 [22]. All single nucleotide variants and indels were annotated with CADD v1.3 [23]. Population database frequency annotations included 1000 Genomes Phase 3 (1000GP) [24], TOPMed Bravo [25] (lifted over from hg38 to hg19 using CrossMap 0.2.7 [26]), and several population database sets annotated using WGSA 0.7 [27] including ExAC [28], gnomAD [29], ESP [30], and UK10K [31]. Variants were also annotated with dbSNP release 151 [32].

Calls were filtered with vcftools (v0.1.12b) [33] to retain sites with quality scores equal or greater than 20 and mean read depth scores equal or greater than 30. KING (v2.2.4) [34] was used to verify disclosed familiar relationships and pedigree structures, and individuals with unexplained relatedness were removed. For duplicate samples and monozygotic twin pairs, only one genome was kept. PLINK v.1.90 [35, 36] was used to identify and exclude individuals with discordant X-chromosome sex and those with more than 5% missing data [37]. Mendel errors were set to missing before removing autosomal variants with missingness > 5% obtaining a total of 41,123,431 variants and 900 individuals from 566 families available for analysis (Additional file 1: Figure S2).

To compare the TANGL genomes to previously identified carriers of *PSEN1* c.428T>C (p.Ile143Thr) [38] from Colombia and *PSEN1* c.356C>T (p.Thr119Ile) from Colombia and Argentina [39], we sequenced additional individuals using the Array-8+ v1.0 Kit + neuro booster array consortium (NBA) content, beadchip 20042459 Illumina Global Diversity (Catalog 20031816). Imputation was performed using the TOPMed Imputation Panel and Server (version 1.3.3) [40], which includes 97,256 references samples and 308,107,085 variants and uses Minimac4 for imputation. Pre-imputation scripts (version 4.3.0 from William Rayner at the University of Oxford) were run using default settings, which filtered out palindromic single nucleotide variants (SNVs) with minor allele frequency (MAF) > 0.4 or variants with > 0.2 MAF difference from the TOPMed reference panel [41]. The Colombian carriers of these *PSEN1* variants had been recruited and evaluated by the Grupo de Neurociencias de Antioquia (GNA). The Argentinian sample was provided by the Neurodegenerative illnesses' laboratory (Fleni-CONICET). The clinical assessment and sequencing of these individuals was done with written informed consent and approved by the IRB of the Medical Research Institute School of Medicine, Universidad de Antioquia, and the IRB from "Instituto de Investigaciones Neurológicas Raúl Carrea – FLENI."

To compare the TANGL genomes to previously identified carriers of *MAPT* c.1189C>T (p.Pro397Ser) from Spain, we obtained exome sequencing data from an individual previously sequenced by the Alzheimer's disease and other cognitive disorders unit at Hospital Clínic de Barcelona. The exome from the Spanish c.1189C>T (p.Pro397Ser) carrier [42] was processed from fastq to VCF using a standard clinical alignment pipeline from the HudsonAlpha Institute for Biotechnology Clinical Services Laboratory that uses Sentieon version 201808.07 (a computational wrapper for common tools such as bwa), including alignment with Sentieon-BWA (version 201808.07; identical to bwa mem 0.7.15-r1140) and variant calling with Illumina Strelka2 (version 2.9.10) [43]. The use of this sample was approved by the IRB from the "Hospital Clinic de Barcelona."

Population structure analysis

We implemented protocols similar to those previously developed for ancestry estimation in admixed populations [3, 44]. We merged the 900 genomes (TANGL cohort) with the 1000 Genomes Project (1000GP) Phase 3 genomes generating the TANGL.1000GP dataset ($n = 3404$). Then, we created a subset including only the TANGL cohort, the non-admixed African Populations (AFR), $N = 504$, and European populations (EUR), $N = 503$. We merged these genomes with Native American samples (NAT), $N = 43$ from Mao et al. [45] inferred to have > 0.99 Native Ancestry, and created the TANGL.AFR.EUR.NAT dataset. After removing monomorphic variants, triallelic sites that were not due to a strand flip in either dataset and those sites with missingness greater than or equal to 1%, we retained 845,950 autosomal variants and 1950 individuals for further analysis.

Global ancestry inference

A subset of unrelated samples from TANGL.AFR.EUR.NAT was selected by keeping only the proband of each family and, using KING (v2.2.4) [34] with "—related" and "--degree 3" settings to identify cryptic relatedness. Only sample pairs with kinship coefficient less than 0.044 were retained for TANGL, AFR and EUR. The NAT individuals showed significant relatedness between them, and the threshold for that population was set to "—degree 2"

to retain the most NAT samples with kinship less than 0.0884. The final TANGL.AFR.EUR.NAT -Unrelated dataset comprised 1611 unrelated individuals (TANGL $N = 566$, AFR $N = 501$, EUR $N = 503$, NAT = 41).

We calculated global ancestry using ADMIXTURE (v.1.3.0) [46] independently for the unrelated TANGL individuals ($n = 566$) and for the TANGL.AFR.EUR.NAT-Unrelated cohort. As recommended by ADMIXTURE, PLINK (v.1.9) [35, 36] was used to perform pair-phased linkage disequilibrium (LD) pruning; excluding variants with an r^2 value of greater than 0.2 with any other SNP within a 50-SNP sliding window, advancing by 10 SNPs each time (--indep-pairwise 50 10 0.2). The LD-pruned dataset contained 203,810 variants. We then performed an unsupervised analysis modeling from one to ten ancestral populations ($K = 1–10$) using the random seed option and replicating each calculation 20 times. We selected the run with the best Loglikehood value for each K and compared the cross validation (cv) error values to determine the model with the lowest cv value. Ancestral proportion statistics of mean and standard deviation were calculated using the statistical software R [47].

In addition, we determined mitochondrial and Y-chromosome haplogroups of the TANGL-unrelated cohort using HaploGrep 2 with Phylotree 17 [48], and yHaplo respectively [49].

Local ancestry inference

We phased the combined TANGL.AFR.EUR.NAT dataset with SHAPEIT (v.2.r900) [50] using the haplotype reference panel of the 1000GP. We used the parameters –duohmm and a window of 5 MB (-W 5), which takes advantage of the inclusion of families, pedigree structure, and the large amount of IBD shared by close relatives, leading to increased accuracy [51]. We used the PopPhased version of RFMix (v1.5.4) [52] to estimate the local ancestry using the following flags: -w 0.2, -e 1, -n 5, --use-reference-panels-in-EM, --forward-backward as recommended by Martin et al. [3] for estimating local ancestry in admixed populations. To determine the carrier haplotype and local ancestry of a rare variant of interest, we used PLINK (v.1.9) [35, 36]. We identified other single nucleotide variants (SNVs) in linkage disequilibrium with the variant of interest and used them as tags to identify the carrier haplotypes in the phased dataset, and then searched for the local ancestry of the specific locus in the RFMix output.

Principal component analysis (PCA)

For PCA, we used the subset of unrelated samples with LD-pruning of variants as described in the methods for "Global ancestry inference." We performed a PCA using the *smartpca* package from EIGENSOFT (v7.2.1) [53], with 3 outlier removal iterations (numoutlieriter: 3) and flag "altnormstyle: NO" to match EIGENSTRAT normalization formulas [53]. The PCA results were plotted using the PCAviz package [54] for R. For the PCA with the Ancestral populations, we retained variants with MAF >10%. For the PCA of the TANGL-unrelated cohort, we extracted a common variant set, retaining those with MAF > 10%, and then a lower frequency variant set, keeping only variants with MAF between 5 and 10%.

Genetic screening for disease causing variants

Each individual was initially screened for pathogenic variants in the most recognized genes associated with AD and FTLD according to AD/FTLD mutation databases (https://www.molgen.vib-ua.be/ADMutations, https://www.alzforum.org/mutations); *PSEN1*, *PSEN2*, *APP*, *MAPT*, *GRN VCP*, *FUS, CHMP2B*, *TARDBP*, and *TBK1* (the molgen.vib-ua.be/ADMutations database is not available as of July 2021). For the present study, the terms "pathogenic" and "likely pathogenic" refer to variants that are both predicted to be disruptive or damaging to the protein function and causative for a disease according ACMG criteria [55].

A secondary genetic analysis was done to identify pathogenic and likely pathogenic variants in other genes associated with similar or overlapping phenotypes. For the secondary screening, we chose the disease-causing genes reported in the following OMIM phenotypic series and phenotypes: frontotemporal dementia and/or amyotrophic lateral sclerosis [MIM: PS105550, PS167320, PS105400], Parkinson disease [MIM: PS168600], adult-onset leukoencephalopathies [MIM: PS125310, 221820], and ceroid lipofuscinoses [MIM: PS256730]. We retained variants with MAF of 0.001 or less in the ExAC database if the gene had autosomal dominant or X-linked inheritance, and 0.01 or less if the gene had autosomal recessive inheritance. The remaining variants were discarded if they were more prevalent in controls than cases or if they had a CADD Phred score less than 20. The selected protein altering variants defined as nonsynonymous single nucleotide variants, splicing altering variants, insertions, or deletions were manually curated by searching in the databases described before as well as ClinVar [56] and LitVar [57]. The previously unreported (novel) variants were classified according to the guidelines published by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [55]. Variants in *PSEN1* and *PSEN2* were also classified according the Guerreiro algorithm [58]. Additionally, subjects were screened for *C9ORF72* [MIM: 614260] hexanucleotide expansion using repeat-primer following the protocol described in DeJesus-Hernandez et al. [59] because, while *C9ORF72* expansions are possible to detect from

short-read PCR-free genomes [60], such events are not detectable from PCR positive genomes which were conducted here. We searched for large copy number variations using four callers: DELLY [61], ERDS [62], CNVnator [63], and BIC-seq2 [64]. Events called by multiple callers were inspected for validity using Integrative Genomics Viewer [65]. In contrast to GATK small variant calls, where recall rates against truth sets are known, there are not recall rates available for this employed combination of tools, though we note that there is a high false negative rate for all CNV callers from short read PCR-positive genome data; thus, the goal in CNV analysis was to have high confidence in those variants that were identifiable across all four callers at the expense of missing some true positives that may not pass these strict criteria. Better detection of expansions such as *C9ORF72* or heretofore unidentified similar events and/or better large indel detection will be aided by emerging use of long read sequencing which can help identify events that would be missed otherwise [66].

Neuropathologic assessment of *CSF1R* c.2068G>A (p.Gly690Ser) and *DNAJC5* c.347 T>G (p.Leu116Arg) carriers was performed at the Brain Bank of the Neuroscience Group of Antioquia following standardized protocols [67, 68]. Tissues were stained with hematoxylin-eosin, Luxol Fast blue, and periodic acid–Shiff (PAS). The brain donation and neuropathologic assessment were done with written informed consent and approved by the IRB of the Medical Research Institute School of Medicine, Universidad de Antioquia.

Genetic screening for risk associated variants

We used publications in the literature to identify genes in which rare variants were associated with increased risk for AD and/or FTLD-MND with an odds ratio higher than 2. *TREM2* [69, 70] [MIM: 605086], *ABCA7* [69, 71, 72] [MIM: 107741], and *SORL1* [69, 73] [MIM: 602005] were selected as intermediate effect risk genes. We retained variants that were known to be risk conferring, led to premature truncation of the protein (PTV), or that were classified as strictly damaging (SD) according to previous published criteria [69]. Strictly damaging variants had MAF ≤ 0.01 in the ExAC database and were unanimously classified as deleterious by three different in silico prediction algorithms; SIFT [74], Polyphen-2 (Hum Div.) [75], and MutationTaster [76]. In addition to this strategy, we included *ADAM10* [MIM: 602192] c.510G>T (p.Gln170His) and c.541A>T (p.Arg181Gly) variants as they have been reported to confer intermediate risk for AD [77, 78]. Variant nomenclature is according to the Human Genome Variation Society Recommendations [79]; the GenBank reference transcripts used for each disease causing and risk conferring variant can be found in Additional file 4: Table S3.

Identity by descent

If any of the disease-conferring or risk-associated variants were shared by two or more unrelated individuals, we used hap-IBD [80] v1.0 to search for identity by descent (IBD) around the locus. Because this software detects IBD of 2 cM and higher, we additionally performed an alignment of the haplotypes carrying the variants of interest to search for smaller IBD segments between the TANGL and 1000 Genomes Project (1000GP) carriers. Autozygosity (homozygosity by descent) was determined using the same methods. Code and scripts used for the population structure and identity by descent analyses are publicly available [81].

Results

Population analysis of the genomes from the neurodegeneration cohort

Nine hundred Colombian individuals with high-quality genome sequences were included in "The Admixture and Neurodegeneration Genomic Landscape" (TANGL) study. The individuals were divided into four different cohorts: Alzheimer's disease (AD), frontotemporal lobar degeneration and motor neuron disease (FTLD-MND), early-onset dementia not otherwise specified (EOD), and healthy participants (Table 1 and Additional file 2: Table S1). These 900 individuals represented 566 independent families, which were classified into the same four cohorts according to the diagnosis of the proband (Additional file 3: Table S2).

Because the sample set was highly selected, we first sought to determine the genomic similarity between the TANGL cohort and other Colombian individuals. We initially merged the TANGL and the 1000 Genomes Project (1000GP) phase 3 [82] datasets and performed a principal component analysis (PCA). The TANGL cohort had a similar distribution in the first three principal components (PC) to the "Colombians from Medellín" (CLM) of the 1000GP, allowing us to conclude that both populations are genetically similar (Additional file 1: Figure S3). To take a closer look into the ancestral origins of the TANGL cohort, we used the software ADMIXTURE to estimate the number of ancestral populations (K) from which the cohort arose. The lowest cross validation (cv) error was obtained when assuming the cohort was derived from three ancestral populations ($k = 3$), which agrees with the history of the tri-continental admixture after the Spanish conquest (Additional file 1: Figure S4). To analyze the global and local ancestry of the TANGL cohort, we merged the TANGL genomes with the European and African populations from the 1000GP

and Native American genomes from Mao et al. [45] and repeated the ADMIXTURE analysis. In this joint dataset, $K = 3$ accurately differentiated Native American, European and African cohorts, but the lowest CV error was obtained for $K = 6$ (Fig. 1 and Additional file 1: Figure S5). Modeling for six ancestral populations allowed the detection of substructure within the African and European cohorts and created an additional cluster described by Moreno-Estrada et al. [44] as a "Latino-specific European component." Consistent with previous studies [83], the ancestral population with the highest proportion in our cohort was European (mean of 64%, SD = 15%), followed by Native American (mean of 27%, SD = 11%), and African being the least represented (mean of 9%, SD = 11%) (Additional file 1: Figure S6). These individual admixture values (Q-values) at $K = 3$ correlated with the sum of local ancestries estimated by RFMix (Pearson's $r > 0.99$), allowing us to conclude that the local ancestry inferred for each individual matches the percentages of global ancestry obtained by an orthogonal method) (Additional file 1: Figure S7). However, the regional differences in the fine structure of the Colombian population make these global ancestry proportions highly region dependent. For example, the three individuals whose global ancestry was nearly 90% African were from the Pacific coast of the country where former enslaved Africans settled and most of the population self identifies as Afro-Colombian (Additional file 1: Figure S1).

After calculating the proportions of global ancestry, we evaluated the TANGL cohort for sex biased admixture,

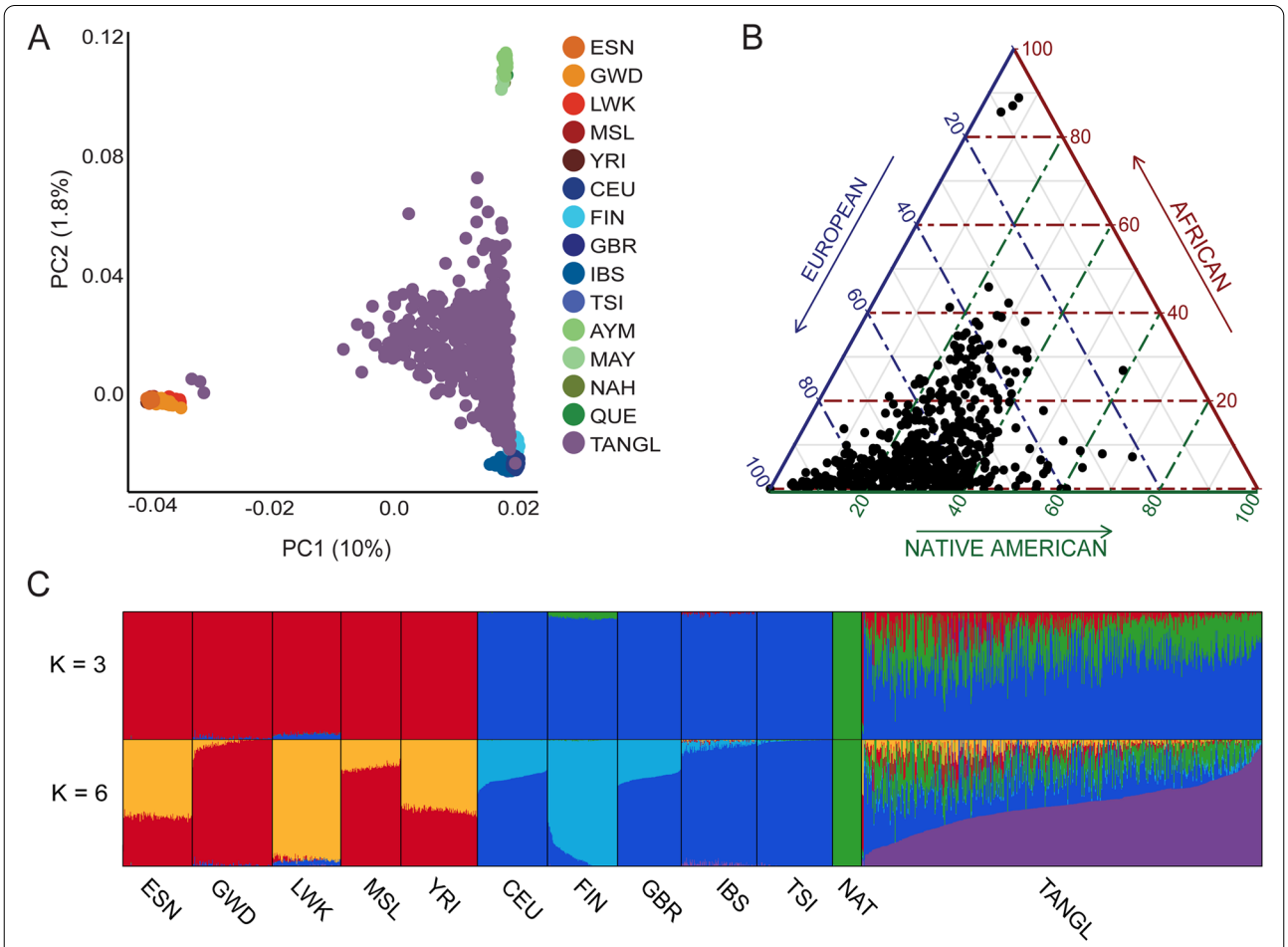

Fig. 1 Population structure and admixture analyses of the TANGL cohort. **A** PC1 vs PC2 of the PCA of the TANGL cohort (purple) with the European (blue) and African (orange) individuals from the 1000GP and 43 Native American genomes (green). **B** Ternary plot representing the global ancestry of each of the individuals in the TANGL cohort values according to sum of local ancestries calculated by RFMix. **C** Q plot of ADMIXTURE results assuming 3 and 6 ancestral populations (K). ESN: Esan in Nigeria. GWD: Gambian in Western Divisions in the Gambia. LWK: Luhya in Webuye, Kenya. MSL: Mende in Sierra Leone. YRI: Yoruba in Ibadan, Nigeria. CEU: Utah Residents (CEPH) with Northern and Western European Ancestry. FIN: Finnish in Finland. GBR: British in England and Scotland. IBS: Iberian Population in Spain. TSI: Toscani in Italia. AYM: Aymara. MAY: Mayan, NAH: Nahuatl. QUE: Quechua. NAT: Native American

a genetic trait previously described in the Colombian population [84, 85]. We used HaploGrep2 and yHaplo to determine mitochondrial and Y-chromosome haplogroups. The mitochondrial haplogroups of the probands ($n = 566$) were predominantly Native American (83.4%) while the Y-chromosome haplogroups ($n = 224$) were mostly of European and of Mediterranean origins (92.8%), thus supporting the conclusion than multiple cohorts of Colombian origin show sex-biased admixture with Native American maternal lineages and paternal lineages from Europe (Additional file 5: Table S4 and Additional file 6: Table S5). Overall, these analyses let us conclude that despite recruiting the TANGL cohort based upon neurodegenerative conditions from the Andes region of Colombia, it recapitulated the admixture patterns previously described in the country.

The TANGL cohort was distributed between the three ancestral populations in the PCA, clustering closer to Europeans and Native Americans. To determine if the clustering of the admixed individuals was driven by their percentages of global ancestry, we compared the values of the principal components (PC) with the percentage of global ancestry attributed to each of the three ancestral populations by ADMIXTURE. PC1 correlated with the percentage of African ancestry (Pearson's r2 of 1), and PC2 showed a correlation with the level of Native American ancestry (Pearson's r2 of 0.87) (Additional file 1: Figures S8, S9 and S10). To determine whether the Colombian population clustered according to their global ancestry without including the ancestral populations in the analyses, we retained the 566 unrelated probands from the TANGL cohort and performed two PCAs, one with common variants (MAF > 10%) and one with less frequent variants (MAF 5-10%). Both PCAs showed correlation of the PCs with the global admixture proportions, regardless of the inclusion of the ancestral population (Additional file 1: Figures S11, S12 and S13).

Neurodegenerative disease variants in the TANGL cohort

AD-associated genes

The 900 genomes were initially examined for variants in AD-associated genes (*PSEN1*, *PSEN2*, and *APP*), and the protein altering variants were curated according to the ACMG guidelines for the interpretation of genetic variants [55] and the algorithm proposed by Guerreiro et al. [58] to determine pathogenicity (Additional file 1: Figures S14, S15 and Additional file 7: Supplementary methods).

Eleven deleterious variants were identified in the *PSEN1* gene (Table 2 and Additional file 8: Table S6 and Additional file 9: Table S7). Three of these were novel; two classified as definite pathogenic, c.485 T>G (p.Ile162Ser) c.667C>A (p.Gln223Lys); and one as probably pathogenic according to the Guerreiro algorithm, c.782C>T (p.Val261Ala). Four of these *PSEN1* variants had been previously identified in the Colombian population c.349C>G (p.Pro117Ala), c.428T>C (p.Ile143Thr), c.839A>C (p.Glu280Ala), and c.1247 T>C (p.Ile416Thr) [38, 86–88], and four had been described in families outside Colombia with diverse ancestries c.356C>T (p.Thr119Ile) [39], c.488A>G (p.His163Arg) [89], c.791C>T (p.Pro264Leu) [89] and c.851C>T (p.Pro284Leu) [90]. *PSEN1* c.839A>C (p.Glu280Ala) [86], of European origin, is the largest family in the world with familial Alzheimer's disease and living nearby is a family with the *PSEN1* variant c.1247 T>C (p.Ile416Thr) [87] that originated in Africa.

PSEN1 c.782 T>C (p.Val261Ala) was identified in a singlet without confirmed paternity, and it was classified as likely pathogenic (ACMG criteria)/probably pathogenic (Guerreiro) despite the lack of family history due to the report of three different pathogenic mutations in the same codon c.780G>T (p.Val261Phe) [91], c.780G>A (p.Val261Ile) [92], andc.780G>C (p.Val261Leu) [93]. All the reported variants, except c.851C>T (p.Pro284Leu), presented as early-onset amnestic AD. The c.851C>T (p.Pro284Leu) carriers developed spastic paraparesis (SP), which is an atypical form of AD occasionally associated with certain *PSEN1* mutations [91, 94, 95]. All the families with pathogenic *PSEN1* mutations had autosomal dominant inheritance (Additional file 1: Figure S16); however, the singlet c.782 T>C (p.Val261Ala) was indeterminate. Among these *PSEN1* variants, six were of European origin, three were Native Americans, and one African (Table 2).

All the carriers of each variant, except c.791C>T (p.Pro264Leu), reported a known common ancestor (Additional file 1: Figure S16). Several families from the harbored the *PSEN1* c.791C>T (p.Pro264Leu) variant, but we could not connect them by family history. Therefore, to prove that c.791C>T (p.Pro264Leu) was the result of a founder effect, we used the hap-IBD software to identify identical by descent (IBD) segments between the variant carrying chromosomes. All the *PSEN1* c.791C>T (p.Pro264Leu) carrier haplotypes shared an IBD segment of 2.79 cM around the *PSEN1* locus, supporting the hypothesis of a common ancestor for all three families originating at about the same time (Additional file 1: Figure S17). *PSEN1* c.791C>T (p.Pro264Leu) has been described in multiple populations (France [89, 96–99], UK [100, 101], Turkey [102], and Japan [103]) suggesting that *PSEN1* c.791C>T (p.Pro264Leu) is a recurring mutation. While the European carriers of this variant often present SP [104], this phenotype was not observed in the Colombian carriers of the variant. To determine if this

Table 2 Pathogenic variants identified in disease causing genes

Alzheimer disease genes							
Gene	**Coding change**	**dbSNP/ClinVar**	**ExAC**	**SIFT**	**Polyphen**	**CADD**	**Local ancestry**
APP	g.(26253828_30011000)dup	SCV001751549	.	–	–	–	European
PSEN1	c.349C>G (p.Pro117Ala)	rs63750550	.	D	P	26.9	European
	c.356C>T (p.Thr119Ile)	rs1566630791	.	T	P	24.4	European
	c.428T>C (p.Ile143Thr)	rs63750004	.	D	D	26.8	European
	c.485T>G (p.Ile162Ser)	rs1898533739	.	D	D	32	Native American
	c.488A>G (p.His163Arg)	rs63750590	.	T	B	23.4	European
	c.667C>A (p.Gln223Lys)	rs1898776259	.	D	D	33	Native American
	c.782T>C (p.Val261Ala)	SCV001751539	.	D	P	25.9	Undetermined
	c.791C>T (p.Pro264Leu)	rs63750301	.	D	D	35	Native American
	c.839A>C (p.Glu280Ala)	rs63750231	.	D	D	29.3	European
	c.851C>T (p.Pro284Leu)	rs63750863	.	D	D	33	European
	c.1247T>C (p.Ile416Thr)	SCV001751540	.	D	P	25.9	African
PSEN2	c.487C>T (p.Arg163Cys)	rs200931244	.	D	D	35	African
FTLD genes							
Gene	**Coding change**	**dbSNP**	**ExAC**	**SIFT**	**Polyphen**	**CADD**	**Local ancestry**
C9ORF72	(GGGGCC)n Repeat Expansion	rs143561967		.	.	.	European
GRN	c.709-2A>G (p.Ala237fs)	rs63750548	.	.	.	23.1	European
MAPT	c.902C>T (p.Pro301Leu)	rs63751273	.	D	D	34	European
	c.1189C>T (p.Pro397Ser)	rs1295855402	.	D	D	25	European
TARDBP	c.881G>T (p.Gly294Val)	rs80356721	0.00000824	T	P	18.89	European
	c.1147A>G (p.Ile383Val)	rs80356740	0.00000865	T	B	0.308	European
TBK1	c.1257_1258del (p.Val421Cfs*26)	rs1392685429	.	.	.	.	European
	c.1717C>T (p.Arg573Cys)$^{+}$	rs772820487	0.00003329	T	D	29.6	European
ALS genes							
Gene	**Coding change**	**dbSNP**	**ExAC**	**SIFT**	**Polyphen**	**CADD**	**Local ancestry**
ANXA11	c.904C>T (p.Arg302Cys)	rs142183550	0.0000412	D	D	31	Native American
FIG4	c.122T>C (p.Ile41Thr) $^{+}$	rs121908287	0.001	D	D	26.5	European
HNRNPA2B1	c.965G>A (p.Gly322Glu)	SCV001751542	.	D	D	23.6	Native American
SOD1	c.63C>G (p.Phe21Leu)	rs1555836170	.	T	D	22.9	Native American
SQSTM1	c.1175C>T(p.Pro392Leu)	rs104893941	0.0009	D	B	34	European
TUBA4A	c.820C>G (p.Pro274Ala)	rs1241875438	.	.	D	23.8	Native American
TUBB4A	c.811G>A (p.Ala271Thr)	rs587777074	0.000003992	.	P	22.8	Native American
UBQLN2	c.724G>A (p.Ala242Thr)	SCV001751543	.	D	D	25.9	Undetermined
Other neurodegeneration associated genes							
Gene	**Coding change**	**dbSNP**	**ExAC**	**SIFT**	**Polyphen**	**CADD**	**Local ancestry**
CSF1R	c.2068G>A (p.Gly690Ser)	rs141866247	0.0000165	T	D	23.1	Native American
DNAJC5	c.347T>G (p.Leu116Arg)	SCV001751544	.	D	P	27.2	African
LRRK2	c.4334C>G (p.Ser1445Cys)	rs1945001552	.	T	P	24.3	European

ExAC ExAC database minor allelic frequency. SIFT scores are D, deleterious, and T, tolerated. PolyPhen-2 scores are D, probably damaging, P, possibly damaging, and B, benign. CADD corresponds to the Phred score. Variants with + were identified in homozygous states. GenBank transcripts for each gene can be found in Additional file 4: Table S3

phenotypic heterogeneity is related to the ancestral haplotype wherein the variant arose, we used RFMix to estimate the ancestry of the variant carrier haplotype (Table 2 and S6). In the TANGL cohort, *PSEN1* c.791C>T (p.Pro264Leu) resided on a Native American haplotype, which suggests that the haplotype of origin may play a role in the different expressivity and clinical manifestations between the variant carriers. Six of the other pathogenic *PSEN1* variants resided on European haplotypes, two variants were present in Native American and one in an African background. The multi-ancestral origins of the *PSEN1* variants suggest that the admixture process contributed to the introduction of pathogenic variants to a population.

Two of the *PSEN1* variants described in this cohort had been previously identified in other families in Colombia [c.428T>C (p.Ile143Thr) [38], c.356C>T (p.Thr119Ile)], and in Argentina [c.356C>T (p.Thr119Ile) [39]]. We performed additional array genotyping to test for IBD between the members of these families and those from the TANGL cohort. The Colombian carriers of c.428T>C (p.Ile143Thr) and c.356C>T (p.Thr119Ile) showed IBD overlapping the *PSEN1* locus (Additional file 1: Figures S18 and S19). Interestingly, the Colombian individuals who harbored c.356C>T (p.Thr119Ile) with whom no shared ancestor could be determined by history carried a small IBD segment shared with the Argentinian carrier of the same variant (Additional file 1: Figure S20). The geographical expanse over which these variants reside could reveal small population migratory streams from Europe or within the South American continent.

In addition to the eleven pathogenic variants, we identified four benign variants in *PSEN1.* c.1279A>G (p.Ile427Val) and c.114C>A (p.His38Gln) that did not segregate with the illness, while c.118G>A (p.Asp40Asn) and c.953A>G (p.Glu318Gly) have been reported in cases and controls without a clear disease association [105–107]. Thus, most of the *PSEN1* missense variants in this cohort are pathogenic and have an age-dependent phenotype of amnestic AD. In contrast, the majority of the variants observed in *PSEN2* were either benign or had been previously classified as risk factors for AD. Only the variant c.487C>T (p.Arg163Cys), which had been described in a Chinese patient with AD [108], was classified as likely pathogenic (Additional file 1: Figure S21). Interestingly, this variant resided on an African haplotype in the Colombian carrier. No pathogenic variants were observed in *APP*; but one individual with AD had copy number variation (CNV) spanning *APP* [104] (chromosome 21 g.(26253828_30011000)dup, Additional file 1: Figure S22). These results confirm *PSEN1* as the most prevalent gene associated with genetic AD in our cohort, mostly as the result of founder effects, and that the current genetic burden of the TANGL cohort is influenced by the genetic diversity of its founders.

Variants in FTLD-MND associated genes

We performed the same curation process for FTLD-MND associated genes (*MAPT*, *C9ORF72*, *GRN*, *VCP*, *FUS*, *CHMP2B*, *TBK1*, *TARDBP*). Most of the individuals with genetic forms of FTLD-MND in the TANGL cohort had deleterious variants in *MAPT* and *TARDBP* (Table 2 and Additional file 8: Table S6 and Additional file 9: Table S7). The *MAPT* c.1189C>T (p.Pro397Ser) variant was identified in three independent families from the same geographic region that shared IDB segment of 2.89 cM overlapping the locus (Additional file 1: Figures S23 and S24). This variant had been previously reported in five apparently unrelated Spanish families [42], and like the Spanish counterpart, the Colombian *MAPT* c.1189C>T (p.Pro397Ser) carriers had variable expressivity of the illness (Additional file 9: Table S7 and Additional file 10: Table S8). To elucidate whether the Colombian *MAPT* c.1189C>T (p.Pro397Ser) carriers were IBD with the Spanish families, we used exome sequencing data from a Spanish patient to search for similarities in the variant carrying haplotype. We identified a minimal shared haplotype of 2.65 cM including the *MAPT* locus, which suggests that the Colombian families share a common ancestor with the Spanish carriers of *MAPT* c.1189C>T (p.Pro397Ser) (Additional file 1: Figure S25).

Two siblings with FTLD-MND born of consanguineous parents were homozygous for the *TBK1* c.1717C>T (p.Arg573Cys) variant (Additional file 1: Figure S26). Haploinsufficiency of *TBK1* has been previously associated with familial ALS and FLTD and is a known mechanism of pathogenicity [109]. Homozygosity of nonsense *TBK1* variants has been proven to be lethal in mice [110]. A second variant in *TBK1* was c.1257_1258del (p.Val421Cfs*26), identified in two unrelated individuals that shared an IBD segment of 3.1 cM including the *TBK1* locus (Additional file 1: Figure S27). We identified two variants in *TARDBP* that had been previously reported in European populations with diagnosis of ALS [111, 112], and in contrast with these cohorts, Colombian *TARDBP* c.1147A>G (p.Ile383Val) carriers had significant intra-familial variability with heterogeneous FTLD-MND spectrum disorders (Additional file 1: Figure S28). Our study identified only one carrier of *C9ORF72* expansion, a single carrier of a pathogenic variant in *GRN* (Additional file 1: Figure S29), and no disease-causing variants in *CHMP2B*, *FUS*, or *VCP*. While the frequency of the identified mutations differs from those reported in European descent cohorts [59, 113], all the identified pathogenic variants in these FTLD-MND associated genes resided on European haplotypes.

Other genes associated with ALS in the cohort

To explore the phenotypic and genetic overlap between FTLD and ALS, we searched for deleterious variants in nineteen additional genes associated with ALS, with or without FTLD (Additional file 1: Figure S14, S15 and Additional file 7: Supplementary methods). The *SQSTM1* [MIM: 601530] c.1175C>T (p.Pro392Leu) variant was present in 11 unrelated cases and two controls of the TANGL cohort. These cases were unrelated and were clinically heterogeneous: six had diagnosis of AD, three of FTLD, one of CBD, and one PSP (Table 2 and Additional file 8: Table S6). Eight of the eleven cases had

family history of dementia or neurodegenerative disease, and none of them carried other pathogenic mutations in the explored disease-causing genes. This variant was initially reported in European individuals with familiar forms of FTLD, Paget's disease of the bone, and ALS [114–116]. Later studies identified this variant both in cases and controls, suggesting that it may be a risk factor rather than causal for illness [117, 118].

The *SQSTM1* c.1175C>T (p.Pro392Leu) is the result of founder effects in Belgian, Dutch, and Spanish individuals [119], and it was present in five individuals from the European cohort of the 1000GP. We used HAP-IBD to search for IBD between the Colombian and the 1000GP carriers of *SQSTM1* c.1175C>T (p.Pro392Leu). Ten carriers of the TANGL cohort shared IBD segments > 2 cM overlapping the variant, which resided in a European haplotype as well (Additional file 1: Figure S30). To determine IBD at a smaller scale, we did a manual alignment of all the variant-carrying haplotypes and detected an IBD segment of ~ 1 cM between all the TANGL cohort and 1000GP European *SQSTM1* c.1175C>T (p.Pro392Leu) carriers (Additional file 1: Figure S31). This observation suggests that *SQSTM1* c.1175C>T (p.Pro392Leu) shows the signature of a founder effect that pre-dates the Spanish invasion. Variants with higher allelic frequency also show IBD between the TANGL cohort and with other carriers outside of Colombia.

In contrast to the pathogenic variants in the FTLD-MND associated genes, five of the eight disease associated variants identified in the ALS panel were of Native American origin while only two were of European ancestry (Table 2). However, most of these individuals with pathogenic and likely pathogenic variants in Native American haplotypes presented with FTLD phenotypes (Additional file 8: Table S6 and Additional file 9: Table S7). For example, the *TUBA4A* [MIM: 191110] c.820C>G (p.Pro274Ala) variant was identified in two independent families with positive family histories of dementia and diagnosis of bvFTD and EOD without motor neuron disease (Additional file 1: Figure S32). As described previously for other variants, these families shared a long IBD haplotype of 15.54 cM overlapping the locus, suggesting a recent common ancestor (Additional file 1: Figure S33). The *SOD1* [MIM: 147450] c.63C>G (p.Phe21Leu) variant was identified in one patient with sporadic navPPA who did not have any motor or ALS-associated symptoms. This variant and others in this same amino acid [c.62 T>G (p.Phe21Cys)] had been previously reported in patients with ALS [120, 121]. Additional likely pathogenic variants in *ANXA11* [MIM: 602572] and *HNRNPA2B1* [MIM: 600124] residing in Native American haplotypes were identified in patients with svPPA and bvFTD. These results further intertwine ALS and FTLD with several genes previously associated exclusively with ALS that may also be responsible for a FTLD phenotype in a different ancestral context. The genetic and clinical heterogeneity of ALS associated genes had been previously described in European population [122], but the inclusion of diverse individuals expands the extent of genetic overlap between FTLD and ALS.

A patient with PSP was homozygous by descent for a European haplotype harboring the *FIG4* [MIM: 609390], c.122 T>C (p.Ile41Thr). Although this gene has been associated with autosomal dominant forms of ALS, this same specific variant has been reported in compound heterozygosity with nonsense variants in European individuals with autosomal recessive cases of Charcot-Marie-Tooth's disease [123] [MIM: 611228]. A family presenting with FTLD-ALS was shown to have a novel c.724G>A (p.Ala242Thr) variant in *UBQLN2* [MIM: 300264]. *UBQLN2*, found on the X-chromosome, is associated with ALS or FTLD-MND, with a lower penetrance in females [124]. The family with this mutation had late onset bvFTD presentation in the female carrier, while the male carrier had FTLD-MND (Additional file 1: Figure S34).

Other genes associated with neurodegenerative disorders

Several families with EOD were explained by variants in other non-AD-FTD-ALS genes (Additional file 1: Figures S14 and S15). A family with an unspecified autosomal dominant EOD had a novel mutation in *DNAJC5* [MIM: 611203] c.347 T>G (p.Leu116Arg) residing on an African haplotype. Their phenotype and postmortem brain tissue histopathology was compatible with adult-onset ceroid neuronal lipofuscinosis-4B (CNL4B) [MIM: 162350] (Additional file 1: Figure S35). A novel likely pathogenic variant in *LRRK2* [MIM: 609007] c.4334C>G (p.Ser1445Cys) was identified in a patient with a European background and non-motor symptoms in Parkinson's disease and dementia. One patient with a family history of cancer and dementia carried the *CSF1R* [MIM: 164770] c.2068G>A (p.Gly690Ser) variant in a Native American haplotype. *CSF1R* mutations have been associated with Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS) [125] [MIM: 221820] A postmortem brain tissue examination supported HDLS diagnosis for the *CSF1R* c.2068G>A (p.Gly690Ser) variant carrier (Additional file 1: Figure S36). These families provide novel insights on genetic-phenotypic relationships.

Despite an extensive evaluation of known genes previously reported for Mendelian forms of dementia, we were not able to identify a disease-causing variant in all families with autosomal dominant inheritance of the illness. Of the 566 families included in the present study,

59 had autosomal dominant inheritance defined as three or more affected individuals in two consecutive generations (Additional file 11: Table S9). For the 18 families in which all individuals had early onset of symptoms (< 65 years), we could identify disease causing variants in all but three, and 13 of them carried pathogenic *PSEN1* variants. In families with both early and late onset cases, we identified disease causing variants in seven of 33. No disease-causing variant was identified in the 12 individuals from the eight families where everyone had late onset, but 10 of them carried at least one *APOE* [MIM: 107741] ϵ4 allele (two were *APOE* ϵ3/ϵ3, six were ϵ3/ϵ4, and four ϵ4/ϵ4). In conclusion, a pathogenic or likely pathogenic variant was identifiable in the families with autosomal dominant inheritance in which most of the affected individuals had disease onset before 65 years.

Genetic variation associated with AD risk genes

Both rare and common variants can have a small effect size on AD risk [126]. To explore rare variants conferring intermediate risk for the illness, we selected three genes (*TREM2*, *SORL1*, and *ABCA7*) that have shown odds ratio (OR) higher than two (OR > 2) in disease association studies [69] Using the criteria suggested by Bellenguez et al. [69], we identified 14 protein truncating variants (PTV) and 16 strictly damaging (SD) variants in *TREM2*, *SORL1*, and *ABCA7* (Table 3 and Additional file 12: Table S10).

The most common risk-conferring variants in the TANGL cohort resided on *TREM2*, with over a hundred individuals carrying SD or PVT in this gene (Additional file 12: Table S10). The most prevalent variant was c.469C>T (p.His157Tyr), with 50 heterozygous and seven homozygous carriers. All the c.469C>T (p.His157Tyr) carriers were IBD for a Native American haplotype. Two out of three algorithms classified His157Tyr as definitely pathogenic, while a meta-analysis determined *TREM2* c.469C>T (p.His157Tyr) has an OR = 3.65 [127], and therefore, it qualified for the present study. Additionally, we identified 33 *TREM2* c.140G>A (p.Arg47His) carriers in our cohort; three of them were homozygous for this variant (Additional file 12: Table S10). All the *TREM2* c.140G>A (p.Arg47His) carriers from the TANGL cohort shared an IBD European haplotype overlapping the *TREM2* locus, and this same variant-carrying haplotype was present in five European individuals from the 1000GP who showed IBD with the Colombian carriers (Additional file 1: Figure S37). Besides risk conferring variants in Native American and European haplotypes, an African *TREM2* haplotype [GenBank: NM_001271821] carrying c.572G>A (p.Trp191*), c.632 T>C (p.Leu211Pro), and c.287C>A (p.Thr96Lys) was identified in 10 individuals. This haplotype was previously associated with an increased risk in African-American cohorts [128]. Unlike the previous cases of homozygosity, one individual with early-onset AD was a compound heterozygote with both the Thr96Lys/Trp191*/Leu211Pro haplotype and the c.469C>T (p.His157Tyr) variant, suggesting that genetic risk factors from different ancestral origins may coexist in admixed individuals and populations.

Rare variants in *TREM2* are population specific. For example, *TREM2* c.140G>A (p.Arg47His) is associated with increased risk for AD in European descent populations [129, 130] but not in African [128] or Asian [131, 132], while *TREM2* c.469C>T (p.His157Tyr) shows association with AD in Asian [127, 133] but not in European [134] or African [128] cohorts. Interestingly, the c.469C>T (p.His157Tyr) variant was found in Colombia on a Native American haplotype, raising the possibility that this allele arrived from Asia to the American continent close to the time when the Americas were first populated 15,000–20,000 years ago. To support this hypothesis, we searched for this variant in the Human Genome Dating database [135], which uses coalescent modeling to estimate the time to the most recent common ancestor (TMRCA) between the variant carriers and the age of the variant. The estimated age of the c.469C>T (p.His157Tyr) allele is 1265 generations (95% confidence interval of 1108.5–1430.9), which corresponds to 31,625 years by setting one generation equivalent to 25 years (https://human.genome.dating/snp/rs2234255). In contrast, the c.140G>A (p.Arg47His) variant emerged more recently, as it was estimated to be 425 generations old or 10,625 years (https://human.genome.dating/snp/rs75932628), dating to a time before gene flow from Europe to the Americas occurred. These results lead us to conclude that the disease burden in this population is not only affected by the recent admixture after the conquest of the Americas, but was also affected by migrations [136] during the original populating of the continent.

Risk-conferring variants in *ABCA7* and *SORL1* were less prevalent than those in *TREM2*. Most of the variants detected in *ABCA7* consisted in PTV and resided on African haplotypes (Additional file 1: Figure S37). The majority in *SORL1* were SD variants of European origin, two homozygous carriers of *ABCA7* variants c.2124_2130del (p.Glu709fs) and c.4886C>T (p.Ser1629Leu), and a compound heterozygote of risk variants from different ancestral origins. There were no compound heterozygous or homozygous variants for *SORL1*, and the c.6550G>A (p.Ala2184Thr) variant was only found in a healthy centenarian. Additionally, a search for risk associated variants in *ADAM10* [77, 78], identified c.510G>C (p.Gln170His) in ten individuals, including one homozygous patient. These reported variants in *TREM2*, *SORL1*, *ABCA7*, and *ADAM10* were IBD in carriers of the same

Table 3 Variants in risk-associated genes

Gene	Coding change	dbSNP/ClinVar	Classification	ExAC	1000G	CADD	Local ancestry
ABCA7	c.2T>C	rs1347920426	PTV (nonsense)	.	.	24.9	Native American
	c.236A>C (p.Asn79Thr)	rs377401443	SD	4.16E-05	.	24.5	African
	c.1180_1190del (p.Leu396fs)	rs567222111	PTV (frameshift)	0.0005	0.0022	.	African
	c.1531G>T (p.Glu511*)	rs374932832	PTV (nonsense)	7.60E-05	.	39	African
	c.1776G>T (p.Trp592Cys)	SCV001751545	SD	.	.	26	African
	c.2124_2130del (p.Glu709fs)+	rs547447016	PTV (frameshift)	0.0024	0.0006	.	European
	c.2194C>T (p.Gln732*)	rs1030634619	PTV (nonsense)	.	.	36	European
	c.2552+11_2552+58del	rs1178315251	PTV (splice)	.	.	.	African
	c.2611G>C (p.Asp871His)	rs139251928	SD	0.0004	0.0014	24.8	African
	c.3781delC (p.Pro1261fs)	SCV001751546	PTV (frameshift)			.	Native American
	c.4208delT (p.Leu1403fs)	rs538591288	PTV (frameshift)	0.0011	.	.	European
	c.4465C>T (p.Arg1489*)	rs753664323	PTV (nonsense)	6.66E-05	.	39	European
	c.4886C>T (p.Ser1629Leu)+	rs184590335	SD	0.0012	0.0006	35	Native American
	c.4895C>T (p.Pro1632Leu)	rs143083561	SD	0.0002	0.0006	34	African
	c.5302delC (p.Leu1768fs)	rs1348650979	PTV (frameshift)	.	.	.	Native American
	c.5463+2T>C	rs374611445	PTV (splice)	2.81E-05	.	23.7	European
	c.5794C>T (p.Arg1932C)	rs114787084	SD	0.0002	0.0006	34	African
SORL1	c.994C>T (p.Arg332Trp)	rs772110877	SD	5.77E-05	.	35	European
	c.1432G>C (p.Ala478Pro)	SCV001751547	SD	.	.	28.2	European
	c.1496C>T (p.Ser499Leu)	rs764032259	SD	8.24E-06	.	35	European
	c.2200G>A (p.Asp734Asn)	rs148430425	SD	0.0011	.	34	European
	c.2230C>T (p.Arg744*)	rs1050845490	PTV (nonsense)	.	.	39	European
	c.2710C>T (p.Arg904Trp)	rs148966249	SD	4.12E-05	2.00E-04	33	Native American
	c.3679G>T (p.Gly1227Cys)	rs1765488318	SD	.	.	34	European
	c.4520C>T (p.Pro1507Leu)	rs1308522330	SD	.	.	26.2	Undetermined
	c.6550G>A (p.Ala2184Thr)	rs369618646	SD	4.16E-05	.	34	African
TREM2	c.140G>A (p.Arg47His)+	rs75932628	SD	0.0021	0.002	33	European
	c.469C>T (p.His157Tyr)+	rs2234255	SD	0.0036	0.0028	23.1	Native American
	NM_001271821 c.287C>A (p.Thr96Lys) c.572G>A(p.Trp191*) c.632T>C (p.Leu211Pro)	rs2234253 rs2234258 rs2234256	PTV (nonsense)				African
	c.594G>A (p.Trp198*)	rs1765488318	PTV (nonsense)	.	.	39	Undetermined
ADAM10	c.510G>C (p.Gln170His)+	rs61751103	SD	0.0012	0.0012	19.17	European

PTV protein truncating variant, *SD* strictly damaging, *ExAC* ExAC database minor allelic frequency. CADD corresponds to the Phred score. Variants denoted with a + were identified in homozygous states. GenBank transcripts for each gene can be found in Additional file 4: Table S3

variant (Additional file 1: Figures S37, S38, S39 and S40). In summary, the characteristics we described for disease-causing variants such as IBD between carriers, multiple ancestral origins of deleterious variants within the same gene, and autozygosity were present in variants with higher allelic frequencies in risk-associated genes.

The high allelic frequency of some risk conferring variants in the TANGL cohort allowed the detection of individuals who were homozygous by descent and raised the hypothesis of consanguinity between their parents, as was the case for the two families with recessive dementias [*TBK1* c.1717C>T (p.Arg573Cys) and *FIG4* c.122 T>C (p.Ile41Thr)]. We used Hap-IBD and manual haplotype alignment to estimate the autozygosity of the homozygous individual for risk-associated variants in *ABCA7* [c.2124_2130del (p.Glu709fs) and c.4886C>T (p.Ser1629Leu)], *TREM2* [c.140G>A (p.Arg47His) and c.469C>T (p.His157Tyr)] and *ADAM10* [c.510G>C (p.Gln170His)]. Five individuals from three families who were the offspring of related parent had autozygous segments >30 cM overlapping the risk associated variant (Additional file 13: Table S11). The remaining individuals had smaller autozygous segments, suggesting background relatedness of the population due to a small effective population size or bottlenecks [137, 138].

Discussion

Genetic drift has been one of the main forces shaping human genomic variation [139, 140]. While populations that emerge from a bottleneck will harbor reduced genetic variation, over time, such a population can accumulate higher numbers of deleterious variants due to random fluctuations in allele frequencies [141]. Furthermore, deleterious allele frequencies decrease more slowly in smaller populations because natural selection acts on fitness differences and therefore requires genetic variation [141]. The Colombian tri-continental admixture among the Native Americans, Europeans, and Africans combined a portion of the genetic disease burden that was previously limited to each of these ancestral populations. Within the backdrop of an admixed population, numerous infectious diseases extracted a very steep mortality. As a consequence, the small isolated settlements that survived the bottleneck rapidly expanded locally during the colonial period [1]. These multiple isolated bottlenecks each with their own rare variants added to the diversity over the entire population. The TANGL cohort recapitulated the admixture patterns previously described in the Colombian population, suggesting that the country´s demographic history is likely to underlie the modern clustering of familial neurodegenerative diseases arising from multi-ancestral rare disease-associated alleles.

In this cohort, most familial early-onset AD cases were caused by variation in the *PSEN1* gene. We identified eleven different pathogenic *PSEN1* variants from multiple ancestral origins, nearly all attributed to founder effects. The *PSEN1* mutations emerged from a small effective population in each of the early settlements that constituted a patchwork of bottlenecks dispersed throughout the country. Because people tended to remain geographically isolated, the rare variants represent a local genetic footprint. Survivors who emerged from the bottleneck had escaped the large number of infectious diseases responsible for decimating the population. During the historical period of colonization, populations in these settlements grew rapidly as the incidence of diseases diminished, which favored the segregation of potentially damaging variants at higher rates. The question arises as to whether the *PSEN1* mutations could be under positive selection or are the mutations completely explained by drift. Because *PSEN1* mutant phenotypes do not appear until after the age of child-bearing, it is unnecessary to invoke trade-off effects for maintaining the mutation in the population. Positive selection for Alzheimer risk in the context of infectious burden has been previously attributed to the *APOE* ϵ4 risk allele [142]. *PSEN1* mutations cause the production of excess amyloid-beta, which may function as an anti-microbial peptide (AMP) [143]. In this manner, *PSEN1* mutations may have been positively selected as protection against the enormous mortality of infectious diseases. AMPs function as an ancient component of the innate immune system that target bacteria, mycobacteria, enveloped viruses, fungi, and protozoans [144]. Amyloid beta is active against at least eight common and clinically relevant microorganisms, and several anti-amyloid-beta clinical trials have reported increased rate of infections among the participants [143, 145]. However, given the short ~500-year interval since the selective pressure occurred and the ~100-year pulse-like nature of the selection, the possibility of positive selection must remain speculative. Without a sufficient time interval for the mutation to spread widely through the population, the only indirect support for positive selection might consider the collective fitness conferred by all of the *PSEN1* mutations due to their shared phenotypic effect of increasing amyloid beta as an AMP. Whether these mutations represent a statistical excess will require further study, but given the population size at the time to which the mutations can be historically traced (see ancestry data for each mutation), it is likely that the mutations derived from a small effective population, thus supporting their possible over-representation. A comparison comes from large catchment groups for clinics with an interest in familial dementias—one in Alabama had no *PSEN1* cases in their series [146] and another in San Francisco had six *PSEN1* cases (personal communication, Jennifer Yokoyama, University of California San Francisco). In one study that sought early-onset Alzheimer patients from 28 university hospitals across France spanning the dates 1993 to 2016, 17 sporadic cases carried a *PSEN1* mutation [104]. However, any comparison with our cases is problematic because ten of these arose de novo, which was not the case in the TANGL cohort, and some were of unknown pathogenicity.

In addition to the *PSEN1* variants, we identified multiple rare variants causing autosomal dominant early-onset dementia. Variants were usually found in one locality and likely derived from a common ancestor (Additional file 1: Figure S41). Previous studies had reported disease causing variants for other neurological disorders with the signature of founder effects; among these are four different cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [MIM: 125310] associated variants in *NOTCH3* [MIM: 600276, c.307C>T(p.Arg103Cys), c.421C>T (p.Arg141Cys), c.484T>A (p.Cys162Ser), c.1363T>C (p.Cys455Arg)] [147, 148], a familial episodic pain syndrome [MIM: 615040] with a variant in *TRPA1* [MIM: 604775, c.2564A>G (p.Asn855Ser)] [149], Huntington's disease [150] [MIM: 143100], a Parkinson disease variant in *LRRK2* [c.6055G>A (p.Gly2019Ser)]

[151], blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) [MIM: 110100] type 1 with a *FOXL2* [MIM: 605597, c.157C>T (p.Gln53*)] variant and BPES type 2 with *FOXL2* in-frame 30 bp duplication (c. 909–938dup) [152], a complex ataxia due to a *KIF1A* variant [MIM: 601255, variant c.304G>C (p.Gly102Arg)], generalized epilepsy with febrile seizures plus (GEFS+) [MIM: 604403] with *SCN1A* [MIM: 182389 c.5225A>G (p.Asp1742Gly)] variant [153], and non-syndromic hearing loss [MIM: 220290] due to a *GJB2* variant [MIM: 121011 c.35delG (p.Gly12Valfs∗] [154] . Founder effects can also be detected in other non-neurologic conditions: *BRCA1/2* variants [MIM: 113705, 600185] among Colombian women with breast and ovary cancer increased the prevalence of these variants in the studied population [155]. Most of these mutations map to small distinct locales that when, taken together, demonstrate the remarkable overlap of the genetic and geographic maps.

This study underscores the numerous genetic insights that can emerge from Latin American populations. Another example is the putative modifier gene—homozygosity of the Christchurch variant in ApoE3—that may strongly delay the onset of Alzheimer's disease [156]. This gene variant and many of the rare large effect size mutations reported here arose due to the unique genetic history of the region. Ongoing interest in Latin American genetic studies, akin to all genetic studies in underrepresented populations, must consider the ethical implications of the research. Over the many years these were obtained, the research was conducted with the full involvement of the community and extensive interactions with and informed consent from the contributing families.

Conclusions

Demographic history plays a significant role in shaping a population's genetic risk for disease. The genetic complexity of the dementias offers a phenotypic heading for a search to uncover genetic variation for the familial dementias. In the Colombian population, founder effects led to a large number of ancestral disease-causing alleles from each of three admixed continents. We also observed a confluence of rare variants arising from different ancestral origins in dementia risk-conferring genes. Variants of different ancestries combined to create a heterogeneous landscape for the genetic risk of dementia. In addition to the significant role of admixture and drift, we raise the question of whether positive selection of *PSEN1* mutations could contribute to the large number of these in a relatively small effective population size. *PSEN1* variants lead to excess of amyloid-beta, which may function as anti-microbial protein and may have protected against the massive mortality due to infectious diseases during the conquest and colonization of the Americas. This work reinforces the need to include diverse populations for gene-trait association studies including populations that underwent bottlenecks as a source for gene discovery.

Abbreviations

1000GP: 1000 Genomes Project; ACMG: American College of Medical Genetics; AD: Alzheimer's disease; AFR: African; ALS: Amyotrophic lateral sclerosis; AMP: Anti-microbial peptide; BPES: Blepharophimosis-ptosis-epicanthus inversus syndrome; bvFTD: Behavioral variant of frontotemporal dementia; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CBD: Cortico-basal degeneration; CDR: Clinical Dementia Rating; CLM: Colombians from Medellín; CNL4B: Ceroid neuronal lipofuscinosis-4B; CNV: Copy number variation; CV: Cross validation; DNA: Deoxyribonucleic acid; EOD: Early-onset dementia not otherwise specified; EUR: European; FTLD: Frontotemporal lobar degeneration; GEFS+: Generalized epilepsy with febrile seizures plus; GWAS: Genome wide association studies; HDLS : Hereditary diffuse leukoencephalopathy with spheroids; IBD: Identity by descent; LD: Linkage disequilibrium; lvPPA: Logopenic variant of primary progressive aphasia; MAF: Minor allele frequency; MND: Motor neuron disease; NAT: Native American; navPPA: Non-fluent/agrammatic variant of primary progressive aphasia; OMIM: Online Mendelian Inheritance in Men database; OR: Odds ratio; PC: Principal component; PCA: Principal component analysis; PSP: Progressive supranuclear palsy; PTV: Protein truncating variants; SD: Strictly damaging; SNVs: Single nucleotide variants; SP: Spastic paraparesis; svPPA: Semantic variant of primary progressive aphasia; TANGL: The Admixture and Neurodegeneration Genomic Landscape; TMRCA: Time to the most recent common ancestor; WGS: Whole genome sequencing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13073-022-01035-9.

Additional file 1: Figure S1. Demographic information of the TANGL cohort and the Colombian population. **Figure S2.** Pipeline for whole genome sequence data quality control (QC). **Figure S3.** Principal Component Analysis of whole genomes from 1000 Genomes project and the TANGL cohort. **Figure S4.** Cross validation error for unsupervised ADMIXTURE clustering analysis of the TANGL cohort probands. **Figure S5.** Cross Validation Error for unsupervised ADMIXTURE clustering of the multi-ancestral dataset (TANGL genomes with the European and African populations from the 1000GP and Native American genomes from Mao et al. **Figure S6.** Global ancestry proportions of the TANGL cohort calculated by ADMIXTURE and sum of RFMix local ancestry estimation. **Figure S7.** Correlation of global ancestry proportions calculated for each individual by two different software, RFMix sum of local ancestries vs ADMIXTURE. **Figure S8.** Principal component analyses of the African and European cohorts of the 1000GP, along with 43 Native American genomes and the TANGL cohort. **Figure S9.** Principal component analyses of the African and European cohorts of the 1000GP, along with 43 Native American genomes and the TANGL cohort colored according to their proportions of global ancestry. **Figure S10.** Correlation of the principal component 1 and 2 values and the global ancestry proportions. For the TANGL.AFR.EUR.NAT cohort. **Figure S11.** Principal component analyses of the TANGL cohort colored according to their proportions of global ancestry. **Figure S12.** Correlation of the principal component 1 and 2 values and the global ancestry proportions for the TANGL cohort using common variants (MAF >10%). **Figure S13.** Correlation of the principal component 1 and 2 values and the global ancestry proportions for the TANGL cohort using common variants (MAF 5-10%). **Figure S14**. Pipeline of the curation of disease-causing variants in the TANGL cohort. **Figure S15.** Variant filtering of disease-causing variants in the TANGL cohort. **Figure S16.** Pedigrees of the families with pathogenic variants in *PSEN1* (NM_000021). **Figure S17.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor the *PSEN1* NM_000021 c.791C>T (p. Pro264Leu) variant. **Figure S18.**

Pairwise identity by Descent (IBD) segments in the chromosomes that harbor the *PSEN1* NM_000021 c.428T>C (p.Ile143Thr) variant. **Figure S19.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor the *PSEN1* NM_000021 c.356C>T (p.Thr119Ile) variant in Colombian individuals. **Figure S20.** Pairwise identity by Descent (IBD) segments carrying the *PSEN1* NM_000021 c.356C>T (p.Thr119Ile) variant in Colombian and Argentinian individuals. **Figure S21.** Pedigrees of the family with a pathogenic variant in *PSEN2* (NM_000447). **Figure S22.** Depth and allele balance indicate a duplication including *APP*. **Figure S23.** Pedigrees of the families with pathogenic variants in *MAPT* (NM_005910). **Figure S24.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor the *MAPT* NM_005910 c.1189C>T (p.Pro397Ser) variant. **Figure S25.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor the *MAPT* NM_005910 c.1189C>T (p.Pro397Ser) variant from Colombian and Spanish families. **Figure S26.** Pedigrees of the families with pathogenic variants in *TBK1* (NM_013254). **Figure S27.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor *TBK1* NM_013254 c.1257_1258del (p.Val421Cfs) variant. **Figure S28.** Pedigree of the family with a pathogenic variant in *TARDBP* (NM_007375). **Figure S29.** Pedigree of the family with a pathogenic variant in *GRN* (NM_002087). **Figure S30.** Pairwise identity by Descent (IBD) segments in the chromosomes that harbor *SQSTM1* NM_003900 c.1175C>T (p.Pro392Leu) variant in the TANGL cohort. **Figure S31.** Alignment of the haplotypes that harbor *SQSTM1* NM_003900 c.1175C>T (p.Pro392Leu) variant in the TANGL and the 1000GP cohort. **Figure S32.** Pedigrees of the families with pathogenic variants in *TUBA4A* (NM_006000). **Figure S33**. Pairwise identity by Descent (IBD) segments in the chromosomes that harbor *TUBA4A* NM_006000 c.820C>G (p.Pro274Ala) variant. **Figure S34.** Pedigrees of the families with pathogenic variants in *UBQLN2* (NM_0013444) identified by the present study. **Figure S35.** Histological characterization of ceroid neuronal lipofuscinosis-4B (CNL4B) and Pedigree of the family. **Figure S36.** Histological characterization of hereditary diffuse leukoencephalopathy with spheroids (HDLS). Bottom row and Pedigree of the family. **Figure S37.** Alignment of the haplotypes that carry Strictly Damaging and Protein Truncating Variants in *TREM2* present in more than 1 individual. **Figure S38.** Alignment of the haplotypes that carry Strictly Damaging and Protein Truncating Variants in *ABCA7* present in more than 1 individual. **Figure S39.** Alignment of the haplotypes that carry Strictly Damaging and Protein Truncating Variants in *SORL1* present in more than 1 individual. **Figure S40.** Alignment of the haplotypes that carry Strictly Damaging and Protein Truncating Variants in *ADAM10* present in more than 1 individual. **Figure S41.** Maps of Colombia representing the place of origin of the families with disease causing variants.

Additional file 2: Table S1. Demographic information of the included cohorts and their respective sub-cohorts.

Additional file 3: Table S2. Demographic information of the probands from included cohorts and their respective sub-cohorts.

Additional file 4: Table S3. GenBank accession numbers for the genes reported in the present study.

Additional file 5: Table S4. Mitochondrial haplogroups of the probands.

Additional file 6: Table S5. Y chromosome haplogroups of the male probands.

Additional file 7:. Supplementary methods.

Additional file 8: Table S6. Pathogenic variants identified in disease causing genes with additional information of the carriers.

Additional file 9: Table S7. Phenotypic information of the carriers of pathogenic variants in disease causing genes.

Additional file 10: Table S8. Neuropsychological battery performance in *MAPT* c.1189C>T (p.Pro397Ser) carriers vs non-carriers according to their age groups and clinical diagnosis.

Additional file 11: Table S9. Family history of dementia and or motor neuron disease from the 566 probands.

Additional file 12: Table S10. Additional information of the carriers of Protein Truncating Variants (PVT) and Strictly Damaging variants (SD) in risk conferring genes.

Additional file 13: Table S11. Homozygosity by descent (HBD) in carriers of disease causing and risk conferring variants.

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Authors' contributions
J.A-U, D.A., J.N.C., F.L., and K.S.K. conceived and designed the project with some discussion from EMR. J.A-U, D.A., M.G., D.A., L.V., S.M., L.H., L.M., D.V., J.M.S., D.M., and F.L. performed the clinical evaluations of the participants in Colombia. H.E.L provided the sociodemographic data from the Colombian participants. L.M., A.S., and F.P. gathered the pedigree information of the participants and collected samples. G.P.G. was in charge of the DNA extraction. E.I.S., T.I., and R.A. performed the clinical evaluation and provided the DNA sample from the participant from Argentina. R.S-V. performed the clinical evaluation and provided the DNA sample from the participant from Spain. J.N.C and R.M.M. performed the genomic sequencing. J.A-U. and B.W.K. did the variant curation process. J.A-U and S.L. performed Sanger sequencing of pathogenic and likely pathogenic variants. J.N.C. performed the copy number variation study. J.A-U, B.W.K, R.S., and N.P. performed the population structure, ancestry and identity by descent analyses with the guidance of S.R.B. A.V-L, and C.L.W. III performed the neuropathology assessments. J.A-U, J.N.C., and K.S.K. wrote the manuscript. S.R.B., F.L., and K.S.K. supervised the data generation and analyses. All authors read and approved the final manuscript.

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Availability of data and materials
The genetic data obtained from the TANGL cohort (Raw data and BAM and VCF files aligned to hg19) have been deposited in the Grupo de Neurociencias de Antioquia (GNA) genetic data repository, Institutional repository of the Universidad de Antioquia (doi:10.5062/F4N58JNW) [157]. The Institutional Review Board (IRB) of the Medical Research Institute at the School of Medicine Universidad de Antioquia has restricted the deposition of the TANGL dataset to an institutional repository within the University of Antioquia. The TANGL dataset can be accessed and used by qualified researchers in collaborative projects involving the GNA. The application form for data access can be downloaded from the DOI link and should be emailed to juliana.acosta@gna.org.co. Applications are evaluated by GNA Neurogenetics Data Access Committee and response if given within 15 calendar days from application reception date. Novel "disease causing" and "risk conferring" variants that were not present in dbSNP and/or ClinVar databases were submitted to the National Center for Biotechnology Information ClinVar database [56]; https://www.ncbi.nlm.nih.gov/clinvar/ (accession numbers SCV001751539, SCV001751540, SCV001751542, SCV001751543, SCV001751544, SCV001751545, SCV001751546, SCV001751547, SCV001751549). The code used for the data

analyses and plotting can be found at: https://github.com/acostauribe/TANGL (doi:10.5281/zenodo.5809622) [81].

Declarations

Ethics approval and consent to participate

Written informed consent following the guidelines of the Code of Ethics of the World Medical Association, Helsinki Declaration and Belmont Report was obtained from all participants or their legally authorized proxies. For the Colombian participants, the project was approved and overseen by the Institutional Review Board (IRB) of the Medical Research Institute, School of Medicine, Universidad de Antioquia (IORG0010323, FWA00028864). The IRB from "Instituto de Investigaciones Neurológicas Raúl Carrea – FLENI" (IORG0002360, FWA00022436) and "Hospital Clinic de Barcelona" (IORG0000975, FWA00000738) approved the use of the samples from Argentina and Spain. This research project conformed to the principles of the Helsinki Declaration and Belmont report. The brain donation and neuropathologic assessment were done with written informed consent and approved by the IRB of the Medical Research Institute, School of Medicine, Universidad de Antioquia.

Consent for publication

Not applicable

Competing interests

FL and EMR are the principal investigator of Alzheimer's prevention trials supported by NIH, philanthropy, and Genentech/Roche. EMR is also the principal investigator of Alzheimer's prevention trials supported by Eli Lilly, scientific advisor to Alzheon, Aural Analytics, Denali, Green Valley, Retromer Therapeutics & Vaxxinity, a co-founder and share-holder of ALZPath, and co-inventor of a pending patent and inventor of existing patents related to Alzheimer's drug treatment discovery and the accelerated evaluation of Alzheimer's prevention therapies. The remaining authors declare that they have no competing interests.

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Publisher's Note

5.3. Publicación No. 3: "Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer 's disease."

Resumen

Introducción: Tau fosforilada en treonina 217 (p-tau217) medida en plasma es un potencial biomarcador no invasivo de la enfermedad de Alzheimer (EA). Investigamos si el p-tau217 en plasma predice el rendimiento cognitivo posterior y los marcadores de patología en la tomografía por emisión de positrones (PET) en EA autosómica dominante.

Métodos: Analizamos los niveles basales de p-tau217 en plasma y sus asociaciones con PET amiloide, PET tau y el recuerdo diferido de la lista de palabras del CERAD medido 7,61 años más tarde en portadores asintomáticos con variante PSEN1-E280A (n = 24) emparejados por edad y escolaridad con familiares no portadores (n = 20).

Resultados: Los portadores tenían niveles plasmáticos de p-tau217 más altos que los no portadores. La p-tau217 plasmática inicial se asoció con los niveles de patología PET amiloide y tau subsecuentes y cambios en la función cognitiva.

Discusión: Nuestros hallazgos sugieren que los niveles plasmáticos de p-tau217 predice la carga patológica cerebral posterior y el rendimiento de la memoria en los portadores de PSEN1-E280A. Estos resultados respaldan a p-tau217 plasmática como un biomarcador de diagnóstico y pronóstico mínimamente invasivo para la EA, con utilidad potencial en la práctica clínica y los ensayos clínicos.

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RESEARCH ARTICLE

Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease

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Abstract

Introduction: Plasma-measured tau phosphorylated at threonine 217 (p-tau217) is a potential non-invasive biomarker of Alzheimer's disease (AD). We investigated whether plasma p-tau217 predicts subsequent cognition and positron emission tomography (PET) markers of pathology in autosomal dominant AD.

Methods: We analyzed baseline levels of plasma p-tau217 and its associations with amyloid PET, tau PET, and word list delayed recall measured 7.61 years later in non-demented age- and education-matched presenilin-1 E280A carriers (n = 24) and non-carrier (n = 20) family members.

David Aguillon and Stephanie Langella are co-first authors.

Results: Carriers had higher plasma p-tau217 levels than non-carriers. Baseline plasma p-tau217 was associated with subsequent amyloid and tau PET pathology levels and cognitive function.

Discussion: Our findings suggest that plasma p-tau217 predicts subsequent brain pathological burden and memory performance in presenilin-1 E280A carriers. These results provide support for plasma p-tau217 as a minimally invasive diagnostic and prognostic biomarker for AD, with potential utility in clinical practice and trials.

KEYWORDS
autosomal dominant Alzheimer's disease, blood biomarkers, dementia, presenilin-1, tau pathology

Highlights

- Non-demented presenilin-1 E280A carriers have higher plasma tau phosphorylated at threonine 217 (p-tau217) than do age-matched non-carriers.
- Higher baseline p-tau217 is associated with greater future amyloid positron emission tomography (PET) pathology burden.
- Higher baseline p-tau217 is associated with greater future tau PET pathology burden.
- Higher baseline p-tau217 is associated with worse future memory performance.

1 | BACKGROUND

In vivo imaging of tau neurofibrillary tangle accumulation via positron emission tomography (PET) has improved the study, diagnosis, and monitoring of early Alzheimer's disease (AD).[1] Measuring tau via cerebrospinal fluid (CSF) samples has similarly shown utility as an early and specific measure of AD pathology.[2] However, there is a critical need for sensitive, cost effective, and minimally invasive biomarkers of AD. Plasma-based measures of phosphorylated tau (p-tau), which are less costly and invasive compared to PET or CSF, increase early in the disease process and reliably discriminate between AD and other neurodegenerative diseases.[3] Further research is needed to determine the utility of plasma p-tau as a preclinical biomarker.

Plasma-measured tau phosphorylated at site threonine 217 (p-tau217) has emerged as a particularly promising and specific AD biomarker.[3–6] Growing evidence shows elevated plasma p-tau217 across preclinical to clinical disease stages,[5,7–9] particularly in adults with high brain amyloid beta (Aβ) load.[5,10–12] Further, p-tau217 may have better diagnostic ability than other plasma biomarkers in early stages (e.g., p-tau181, neurofilament light [NfL], Aβ40, Aβ42).[5,7,13,14] We previously showed in a kindred with autosomal dominant Alzheimer's disease (ADAD) due to a mutation on the presenilin-1 (*PSEN1*) gene that increased levels of plasma p-tau217 were able to distinguish carriers from age-matched non-carriers 20 years prior to their estimated age of symptom onset.[7]

The association between tau measured through plasma and PET is important to characterize, as tau PET remains the gold standard for in vivo quantification of tau pathology for research and clinical purposes. Plasma p-tau217 is correlated with concurrent tau PET in individuals with high Aβ, mild cognitive impairment (MCI), and AD.[5,15–17] Notably, a recent study found increased plasma p-tau217 in cognitively unimpaired individuals with positive Aβ PET imaging and negative tau PET, suggesting that plasma p-tau217 levels become abnormal before accumulation is detectable via tau PET.[15]

Less is known, however, about the association between plasma p-tau217 and subsequent tau PET accumulation. In sporadic AD (e.g., older adults with high Aβ), one study reported an association between plasma p-tau217 and increasing tau PET in the entorhinal cortex on average 1.6 years later.[15] A second study, similarly examining measurements 1 to 2 years from baseline, reported an association with increasing medial temporal lobe tau PET.[18] Further research into this association is critical to determine whether p-tau217 may serve as an early marker of AD pathology and aid in early detection. If plasma p-tau217 can predict future tau PET at a longer interval, clinical trials may be able to enroll individuals at an earlier stage.

In this study, we leveraged a cohort of carriers of the *PSEN1* E280A mutation for ADAD to examine whether baseline levels of plasma p-tau217 are associated with subsequent PET-based markers of AD pathology in the brain, measured on average 7.61 years after plasma collection. Secondarily, we examined the association between plasma

p-tau217 and subsequent cognition. These findings would inform the use of plasma p-tau217 as a biomarker for the selection, monitoring, and evaluation in clinical trials and other investigations.

2 | METHODS

2.1 | Study design and participants

This cohort study included 24 *PSEN1* E280A mutation carriers (23 Aβ-pathology positive) and 20 age- and education-matched non-carriers from the same kindred, enrolled in the Massachusetts General Hospital (MGH) COLBOS (Colombia–Boston) longitudinal biomarker study. Participants were recruited from the Alzheimer's Prevention Initiative (API) registry of familial AD, which currently includes more than 6,000 living members of the kindred and approximately 1,200 mutation carriers.[19] Characteristics of this kindred have been well characterized.[20–22] Notably, the onset of clinical impairment occurs in mid-life, with the median age of onset of MCI at 44 years old and dementia at 49 years old.[21]

Participants with a diagnosis of dementia at the time of blood sample collection or with a significant medical, psychiatric, or neurological disorder (e.g., stroke, seizures, substance abuse, and other disorders that affect motor, visuospatial or cognitive abilities) were excluded. Neither the participants nor raters were informed of the genetic status of the individuals. This study was approved by the institutional ethics review boards of the University of Antioquia in Medellin, Colombia, and the MGH in Boston, Massachusetts, USA. All participants provided written informed consent before inclusion in the study.

Blood sampling was performed at baseline. Neuroimaging and cognitive memory assessment were completed at follow-up (mean = 7.61 ± 4.05 years). All participants were cognitively unimpaired at baseline. At follow-up, all non-carriers and 18 carriers were cognitively unimpaired, and 6 carriers progressed to MCI. Participants were considered cognitively unimpaired if they had a Mini-Mental State Examination (MMSE)[23] score ≥26 and a Functional Assessment Staging Test (FAST)[24] score of 1 or 2. Impaired carriers were defined as having a FAST score of 3.

2.2 | Plasma p-tau217 assay

Plasma was collected in the morning (without fasting) at the University of Antioquia in aliquots of 1 mL. Samples were stored at −80°C. Concentrations of plasma p-tau217 were measured using immunoassays at Lilly Research Laboratories, using the MSD (Meso Scale Discovery) platform as previously described.[7] Biotinylated-IBA493 was used as a capture antibody and SULFO-TAG-4G10-E2 (anti-Tau) as the detector. Additional details of the plasma p-tau217 analysis are described in Palmqvist et al. Supplemental Material.[7]

RESEARCH IN CONTEXT

- **Systematic Review**: We used PubMed to review the literature on plasma tau phosphorylated at threonine 217 (p-tau217) in Alzheimer's disease (AD). Recent studies have reported converging results indicating plasma p-tau217 as a promising and specific biomarker for AD; however, the relationship between plasma p-tau217 and future positron emission tomography (PET) pathology has not been widely studied. Relevant citations are appropriately noted in the article.
- **Interpretation**: Our results demonstrate an association between baseline plasma p-tau217 and subsequent measures of in vivo brain pathology and cognition. These findings add to the growing literature supporting the utility of plasma p-tau217 as a minimally invasive diagnostic and prognostic marker of AD.
- **Future Directions**: Future studies should investigate the longitudinal relationships between plasma p-tau217 and tau PET pathology in both autosomal dominant and sporadic AD.

2.3 | Clinical and cognitive assessments

Clinical assessments were performed at the University of Antioquia. Participants underwent a clinical interview and were administered the MMSE, FAST, and a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list, which has been adapted for this Colombian population.[25] Other cognitive tests were performed in these participants as part of a Spanish neuropsychological test battery used by the Grupo de Neurociencias de Antioquia–Colombia[26] (data not shown in this article). Cognitive measures were administered in Spanish by a neuropsychologist, or a psychologist trained in neuropsychological assessment. Neurological examinations were performed by a neurologist or by a general practitioner trained in assessing neurodegenerative disorders.

2.4 | Image acquisition and processing

All participants in this study traveled from Colombia to Boston (USA) for PET at the MGH. PET data were acquired on a Siemens ECAT HR+ (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; 2.4 mm slice interval).

11C-Pittsburgh compound B (11C-PiB) PET was acquired with an 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12 × 15 seconds, 57 × 60 seconds). 11C-PiB PET data were quantified as the distribution volume ratio

(DVR) with cerebellar gray as a reference region; regional time-activity curves were used to compute regional DVRs for each region of interest (ROI) using the Logan graphical method applied to data obtained between 40 and 60 minutes after injection.[27] 11C-PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal, and retrosplenial cortices as described previously.[28]

[F18] Flortaucipir (FTP) was acquired between 80 and 100 minutes after a 9.0 to 11.0 mCi bolus injection in four separate 5-minute frames. [F18] FTP-specific binding was expressed in FreeSurfer ROIs as the standardized uptake value ratio (SUVR) to the cerebellum. The spatially transformed SUVR PET data were smoothed with an 8 mm Gaussian kernel to account for individual anatomic differences.[29] SUVR values were represented graphically on vertices at the pial surface. A priori ROIs were inferior temporal cortex, entorhinal cortex, and precuneus.[30,31]

Partial volume correction was applied using the extended Muller–Gartner method implemented in FreeSurfer for both PiB and FTP.[32]

2.5 | Genotyping

Genomic DNA was extracted from the blood by standard protocols, and *PSEN1* E280A characterization was done at the University of Antioquia using methods previously described.[33] Genomic DNA was amplified with the primers PSEN1-S 5′ AACAGCTCAGGAGAGGAATG 3′ and PSEN1-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme *Bsm*I for restriction fragment length polymorphism analysis. Each participant was classified as a *PSEN1* E280A carrier or non-carrier.

2.6 | Statistical analysis

Analyses and visualizations were performed in R (version 4.0.3) and used a significance threshold of two-tailed $P < .05$. Group differences in normally distributed continuous variables were compared using independent two-sample *t* tests (Levene's test was used for examining equality of variances). Group differences in non-normally distributed continuous variables were compared using Mann–Whitney U tests. Chi-square tests were used for categorical variables. Spearman correlation was used to test associations between continuous variables in the whole sample (reported in the main text), with and without covariates (age, sex, time between PET and blood measures). Correlations were additionally conducted within each group and are presented in the supporting information. One potential outlying value was identified (mutation carrier who converted to MCI at follow-up), and correlation analyses were repeated excluding this carrier, with consistent results (see Table S1 in supporting information).

Pearson correlation was used in exploratory analyses of plasma p-tau217 and vertex-wise Aβ and tau PET within carriers. PET images were normalized to standard (Montreal Neurological Institute [MNI]) space and projected onto the average surface, and vertex-wise values were sampled at the midpoint of the gray matter. Partial volume correction was applied using the extended Muller–Gartner method implemented in FreeSurfer.[32] Results were displayed as −log10(p), significant at cluster-wise $P < .05$ (minimum cluster extent = 100 mm^2) after false discovery rate (FDR) correction for multiple comparisons. Clustering and multiple comparisons corrections were performed using FreeSurfer tools.

3 | RESULTS

3.1 | Baseline sample characteristics and plasma p-tau217 levels

A total of 24 *PSEN1* E280A carriers and 20 non-carriers were included in analyses (Table 1). Carriers and non-carriers did not differ in age at baseline ($t[42] = 1.71$, $P = .094$), years of education ($t[42] = 1.41$, $P = .167$), or sex ($\chi^2 = 0.78$, $P = .378$). Carriers had higher plasma p-tau217 levels than non-carriers ($W = 122$, $P = .005$). Neuroimaging occurred on average 7.61 years after plasma sample collection (median = 6.00 years), with a statistically significant longer interval for non-carriers than for carriers ($t[42] = 2.07$, $P = .044$).

3.2 | Group differences in biomarkers at follow-up assessment

Of the 24 carriers, 18 remained cognitively unimpaired and 6 converted to MCI at follow-up. Carriers exhibited elevated neuroimaging biomarkers at follow-up (Table 2), namely higher cortical Aβ DVR ($W = 11$, $P < .001$) and regional tau PET SUVR in the entorhinal cortex ($W = 51$, $P < .001$), inferior temporal cortex ($W = 141$, $P = .019$), and precuneus ($W = 86$, $P < .001$). CERAD word list delayed recall ($W = 357.5$, $P = .005$) and MMSE scores ($W = 366$, $P = .002$) were lower in carriers than non-carriers.

3.3 | Associations between plasma p-tau217 levels and age, cortical Aβ, regional tau, and cognition

To assess the utility of plasma p-tau217 as an early AD biomarker, we examined its associations with various concurrent and subsequent markers of AD in the whole sample. Older age at baseline was associated with higher levels of plasma p-tau217, $r = 0.41$, $P = .006$, 95% confidence interval (CI) [0.13, 0.63] (Figure 1A). Higher baseline plasma p-tau217 was associated with lower MMSE ($r = -0.57$, $P < .001$, CI [−0.74, −0.33]; Figure 1B) and delayed recall ($r = -0.52$, $P < .001$, CI [−0.71, −0.26]; Figure 1C) scores at follow-up. Higher baseline plasma p-tau217 was also associated with higher subsequent PET measures of cortical Aβ ($r = 0.55$, $P < .001$, CI [0.30, 0.73]; Figure 2A) and tau in all ROIs: entorhinal cortex ($r = 0.47$, $P = .001$, CI [0.20, 0.67]; Figure 2B), inferior temporal cortex ($r = 0.44$, $P = .003$, CI [0.16, 0.65]; Figure 2C), and precuneus ($r = 0.53$, $P < .001$, CI [0.28, 0.72]; Figure 2D). We additionally examined these relationships separately for carriers and

TABLE 1 Baseline demographic and plasma p-tau217 data

	Non-carriers ($n = 20$)	Carriers ($n = 24$)	Test statistic	*P*-value	95% CI
Age at baseline (years)	27.6 ± 6.98	31.1 ± 6.81	$t[42] = 1.71$	.094	[−7.78, 0.63]
Education (years)	11.3 ± 4.10	9.38 ± 4.63	$t[42] = 1.41$	.167	[−0.81, 4.56]
Sex (male/female)	11/9	10/14	$X^2(1) = 0.78$	.378	
p-tau217 (pg/mL)	2.53 ± 1.39	5.27 ± 4.69	$W = 122$	.005	[−3.07, −0.42]
Time between blood samples and PET scans (years)	8.95 ± 4.19	6.50 ± 3.65	$t[42] = 2.07$	.044	[−4.83, −0.07]

Note: Means and standard deviations given for age, education, p-tau217, and follow-up time. Group differences were assessed using *t* tests for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables.
Abbreviations: CI, confidence interval; PET, positron emission tomography; p-tau217, tau phosphorylated at threonine 217.

TABLE 2 Follow-up neuroimaging and cognitive data

	Non-carriers ($n = 20$)	Carriers ($n = 24$)	Test statistic	*P*-value	95% CI
11C PiB-PET (DVR)	1.11 ± 0.04	1.69 ± 0.39	$W = 11$	<.001	[−0.69, −0.37]
Entorhinal cortex FTP (SUVR)	1.02 ± 0.12	1.52 ± 0.45	$W = 51$	<.001	[−0.58, −0.26]
Inferior temporal FTP (SUVR)	1.21 ± 0.13	1.56 ± 0.68	$W = 141$	.019	[−0.29, −0.01]
Precuneus FTP (SUVR)	1.05 ± 0.13	1.72 ± 1.02	$W = 86$	< .001	[−0.59, −0.11]
Mini-Mental State Examination	29.0 ± 0.97	26.7 ± 3.50	$W = 366$	.002	[< 0.01, 2.00]
CERAD delayed recall	7.85 ± 1.18	5.17 ± 3.21	$W = 357.5$	.005	[1.00, 4.00]

Note: Means and standard deviations given. Group differences were assessed using *t* tests for normally distributed variables and Wilcoxon rank sum test for non-normally distributed variables.
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's; CI, confidence interval; DVR, distribution volume ratio; FTP, flortaucipir; PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio.

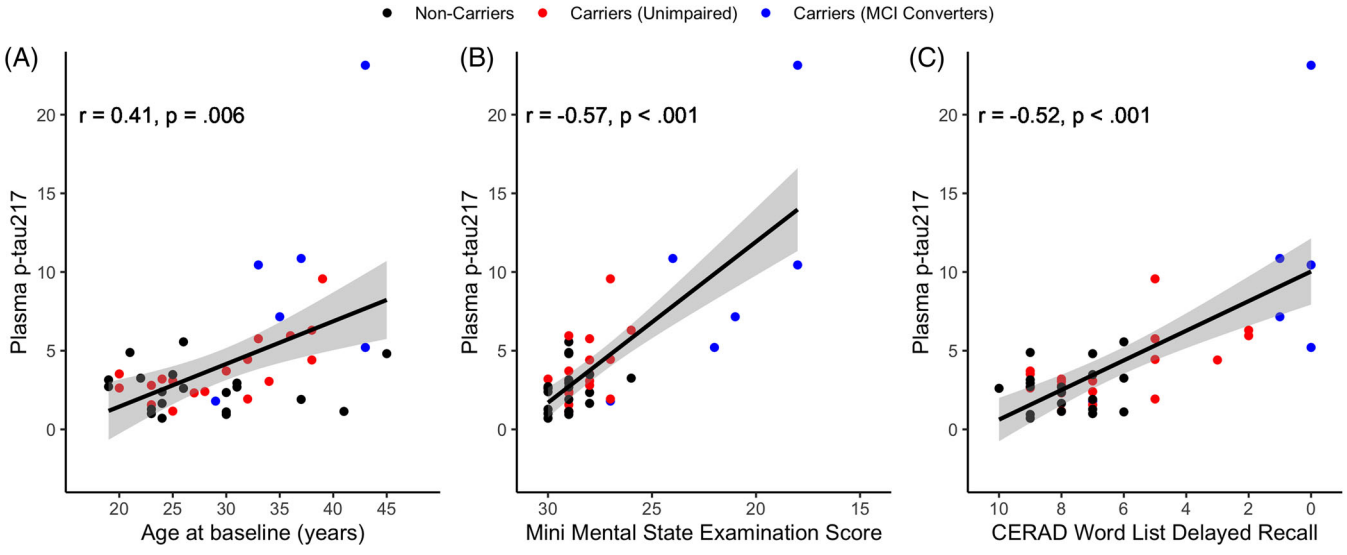

FIGURE 1 Plasma tau phosphorylated at threonine 217 (p-tau217) associations with age and cognition in the whole sample. Scatterplots with simple regression line and standard error showing the association between plasma p-tau217 (picograms per milliliter) and (A) age at baseline, (B) Mini Mental State Examination Score, and (**C**) Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list delayed recall. Black circles: non-carriers; red circles: carriers (unimpaired), blue circles: carriers (mild cognitive impairment [MCI] converters)

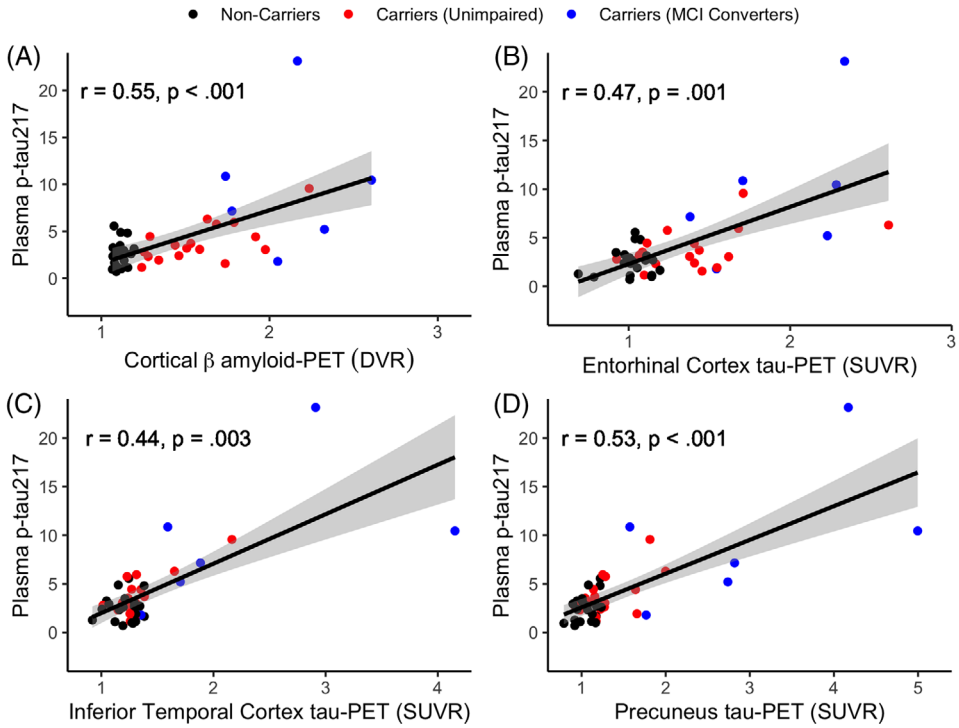

FIGURE 2 Plasma tau phosphorylated at threonine 217 (p-tau217) associations with positron emission tomography (PET)-based pathology in the whole sample. Scatterplots with simple regression line and standard error showing the association between plasma p-tau217 (picograms per milliliter) and (A) mean cortical amyloid beta (β amyloid) PET, (B) entorhinal cortex tau PET, (C) inferior temporal cortex tau PET, and (D) precuneus tau PET. Black circles: non-carriers; red circles: carriers (unimpaired), blue circles: carriers (mild cognitive impairment [MCI] converters). DVR, distribution volume ratio; SUVR, standardized uptake value ratio

non-carriers, finding that associations between p-tau217 and age, PET pathology, and cognition were only significant for carriers (Table S2 in supporting information).

Consistent results were observed in the whole group after controlling for age, sex, and time between measurements: MMSE $r = -0.42$, $P = .006$, CI [−0.65, −0.13]; delayed recall $r = -0.30$, $P = .056$, CI [−0.56, 0.01]; cortical Aβ PET $r = 0.49$, $P = .001$, CI [0.22, 0.69]; entorhinal cortex tau PET $r = 0.39$, $P = .012$, CI [0.09, 0.62]; inferior temporal cortex tau PET $r = 0.31$, $P = .043$, CI [0.01, 0.57]; and precuneus tau PET $r = 0.48$, $P = .001$, CI [0.21, 0.69]. Within-group correlations were not significant after controlling for these covariates (Table S3 in supporting information). There was no significant relationship between p-tau217 and tau PET ROIs when including Aβ as a covariate, but the negative associations with cognition remained significant (Table S4 in supporting information). Further, cortical Aβ was a significant partial mediator of the relationship between plasma p-tau217 and tau PET (Table S5 in supporting information).

3.4 | Associations between plasma p-tau217 and whole-brain Aβ- and tau PET in *PSEN1* carriers

We assessed the relationship between plasma p-tau217 and vertex-wise PET pathology in mutation carriers. Plasma p-tau217 was positively correlated with Aβ burden in frontal, lateral temporal, parietal, and retrosplenial cortices. Correlations with tau PET were strongest in temporal and parietal regions, consistent with the known anatomy of early tau accumulation in mutation carriers, as well as involvement of frontal regions (Figure 3A). Limiting analyses to cognitively unimpaired carriers only (Figure 3B), Aβ and tau PET correlations with plasma p-tau217 were observed to a smaller extent, primarily in the left lateral temporal cortices.

Results were attenuated when adjusting for age, sex, and time between measurements in the carrier group, but the regional associations between p-tau217 and tau PET were similar to unadjusted results (Figure S1A in supporting information). Limiting analyses to unimpaired carriers only, the age-, sex-, and time-adjusted associations did not survive FDR correction. Similarly, including cortical Aβ as a covariate attenuated the associations in all carriers, and the associations did not remain significant when limiting to unimpaired carriers only (Figure S1B). As a supplementary analysis, we also examined the associations between p-tau217 and cortical thickness. Associations with cortical thickness were weaker than those with tau- and amyloid PET, and none of the thickness results survived multiple comparisons correction with FDR (Figure S2 in supporting information).

4 | DISCUSSION

The primary aim of this study was to examine whether plasma p-tau217 is associated with subsequent PET-based markers of AD pathology in the brain and cognitive performance. We examined this association

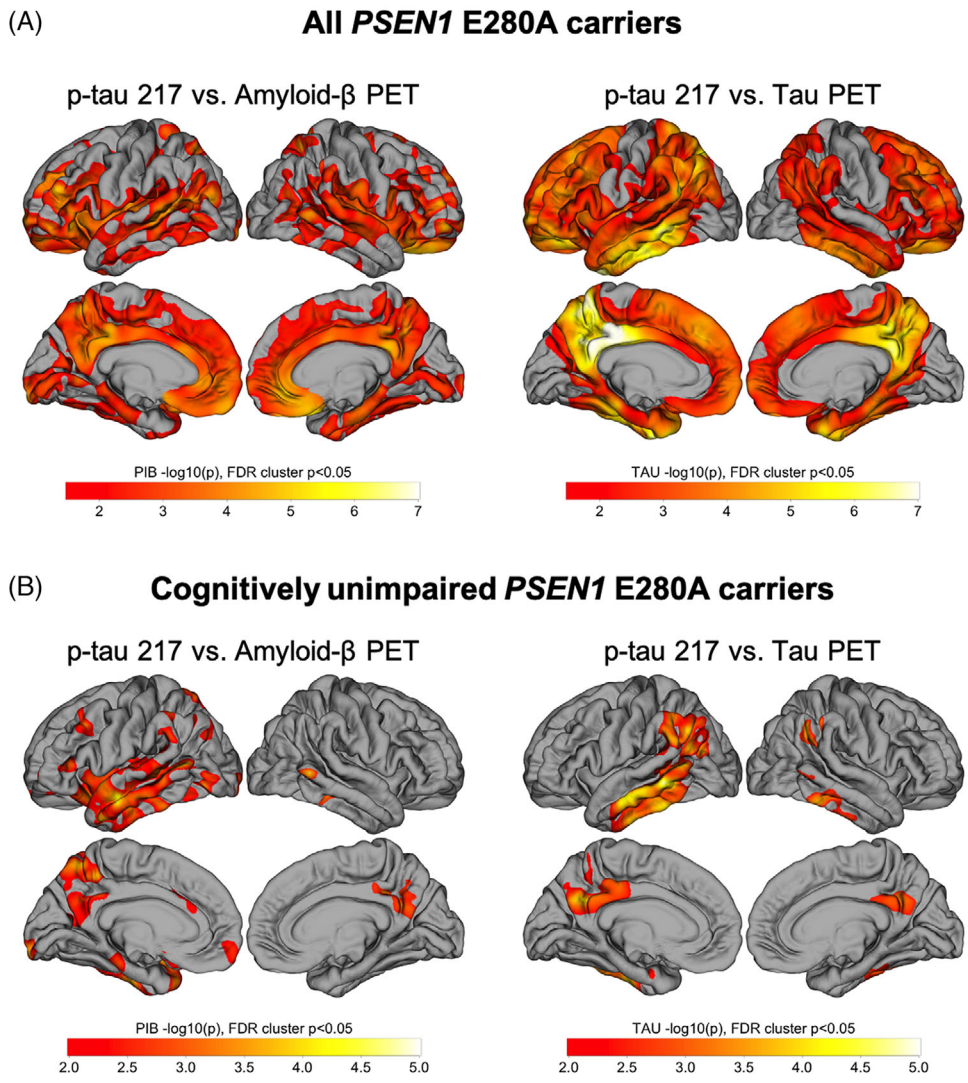

FIGURE 3 Whole-cortex analysis of amyloid beta (Aβ) and tau positron emission tomography (PET) versus plasma tau phosphorylated at threonine 217 (p-tau217). Pearson correlations were performed between p-tau217 concentrations and Aβ (left) and tau (right) PET. Results are displayed as −log10(p), significant at cluster $P < .05$ after false discovery rate (FDR) correction. Correlations performed in (A) all presenilin-1 (*PSEN1*) E280A carriers ($n = 24$) and (B) cognitively unimpaired *PSEN1* E280A carriers ($n = 18$)

in a cohort of *PSEN1* E280A carriers, who will develop dementia by mid-life, and non-carrier family members, using plasma p-tau217 and neuroimaging markers collected on average 7.61 years apart. Consistent with our hypotheses, plasma p-tau217 was elevated in cognitively unimpaired *PSEN1* carriers compared to non-carrier family members. Critically, baseline p-tau217 levels were associated with subsequent Aβ and tau PET deposits and lower memory performance. Together, our results suggest that plasma p-tau217 is a promising biomarker for early AD detection and progression.

In our sample, carriers had higher plasma levels of p-tau217 than non-carriers prior to the onset of cognitive impairment, and, within carriers, higher p-tau217 was associated with older age. The median age of onset of MCI in this kindred is 44 years,[21] more than a decade older than the average age of carriers in this sample at the time of plasma collection. Although these data are not longitudinal, due to the well-characterized clinical trajectory of the mutation carriers and near complete penetrance of the mutation, age serves as a proxy for time until clinical onset and provides a model for disease progression. As such, these associations provide evidence that plasma p-tau217 may be an early marker of preclinical AD and related to disease progression, potentially increasing as clinical onset approaches. Consistent results have been previously reported from this kindred[7] and from studies of sporadic AD, using comparisons of unimpaired older adults with high- versus low-Aβ.[15,34] However, longitudinal studies are required to describe the trajectory of plasma p-tau217 across disease stage.

Although converging findings indicate this early change in plasma p-tau217, little has been reported about its associations with subsequent PET-based pathology, the current gold standard in measuring in vivo AD pathology. Prior findings in older adults at risk for sporadic AD found an association between plasma p-tau217 and concurrent Aβ PET[17] and tau PET imaging;[5,16,17,35] however, only two studies, to our knowledge, have examined the relationship with future tau PET.

These prior studies, with measurements conducted approximately 1 to 2 years apart, found a relationship between plasma p-tau217 and subsequent medial temporal lobe tau PET.[15,18] Our study expands on these results by showing an association with widespread Aβ and tau pathology 7.61 years after plasma collection. Regional analyses revealed an association with mean cortical Aβ and regional tau PET in three key anatomical regions: interior temporal cortex, entorhinal cortex, and precuneus. Our findings in inferior temporal cortex and entorhinal cortex are consistent with prior findings in plasma PET investigations,[5,15,18,35] and we additionally show this association with precuneus, a region previously shown to be early impacted by AD pathology in this kindred.[31,36] Further, our study is the first to conduct whole-brain analyses, revealing the correlations between plasma and tau PET mirror the known progression of early tau pathology accumulation.[30,31] As expected early in the course of the disease, the correlations were limited to the temporal cortices in the cognitively unimpaired carriers. In contrast, when including the carriers with MCI, the spatial extent was much greater, including parietal and frontal cortices.

To note, the associations between p-tau217 and regional tau PET were no longer significant when controlling for cortical Aβ, which was shown to be a partial mediator of the plasma–tau PET relationship, and the voxel-wise associations were attenuated when controlling for cortical Aβ. Other findings have shown an association between p-tau217 and Aβ PET[15,37] and p-tau217 has been shown to do particularly well at discriminating between AD and other neurodegenerative diseases.[11,13] Together, these findings suggest that p-tau217 may be reflecting both Aβ- and tau-related processes, though more work is needed to determine the exact pathology that is indicated by p-tau217.

Other plasmatic biomarkers, such as p-tau181, have been associated with markers of neurodegeneration in AD-related areas through magnetic resonance imaging, fluorodeoxyglucose PET, amyloid PET, and tau PET,[38,39] and have been able to differentiate AD from other neurodegenerative diseases.[40] P-tau181 has also been found to predict tau pathology 6 years later in temporoparietal regions that are associated with AD.[41] However, in several studies, p-tau217 has shown superiority and greater diagnostic accuracy than other biomarkers in plasma and CSF, such as p-tau181.[5,7,13,14]

In addition to pathological markers, elevated plasma p-tau217 was associated with lower subsequent delayed recall and global cognition. Tau PET burden has been consistently associated with worse cognition in this kindred,[31,36,42] though only one prior study has reported an association between plasma p-tau217 and cognition in this kindred.[7] In sporadic AD, longitudinal increases in plasma p-tau217 were associated with worse cognition.[12] However, another study found that tau PET had a stronger association with cognition than did plasma p-tau217.[35] More work is needed to clarify the association between plasma p-tau217 and cognition and the extent to which it can predict declines in various cognitive domains and global cognitive changes.

This study has several strengths and limitations. A primary strength of this study is the kindred with a single variant mutation for autosomal dominant AD, whose clinical trajectory is well characterized.[20,21] Due to the early median age of onset for MCI in this kindred, typical age-related confounds prevalent in studies of older adults are mitigated in this sample. This is particularly important for studies of tau pathology, which can accumulate with age in the absence of other AD pathology.[42] Another strength is the 7.61-year interval between plasma collection, at which time all participants were cognitively unimpaired, and neuroimaging measures, at which time only six participants converted to MCI, thereby highlighting the utility of early plasma p-tau217 for predicting pathology prior to conversion to dementia. Despite the advantages provided by studying this kindred, our sample size is relatively small for a biomarker study, and the extent to which these findings can be generalized to sporadic AD is unknown. Recent findings indicate similar in vivo pathology in sporadic and autosomal dominant AD, including CSF measures of p-tau.[43] However, future studies in additional autosomal dominant and sporadic AD populations are needed to investigate plasma biomarkers' generalizability. Additionally, analysis of blood samples was not available at follow-up in our sample. Future studies would benefit from longitudinal collection of both plasma p-tau217 and tau PET to assess the trajectory of each biomarker, as well as investigate potential differences in the plasma–PET association at varying follow-up intervals.

In sum, our results show that baseline levels of plasma p-tau217 predict subsequent levels of amyloid and tau burden and worse future memory performance in *PSEN1* E280A carriers. These findings add to the growing literature suggesting that plasma p-tau217 is an early marker for AD by demonstrating an association between plasma and PET measures of pathology. Our results provide support for plasma p-tau217 as a potential minimally invasive diagnostic and prognostic biomarker of AD pathology and cognition, with promising utility in clinical practice and trials.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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5.4. Manuscrito en proceso de sometimiento para publicación No. 4: "Longitudinal analysis of qEEG in subjects with autosomal dominant Alzheimer's disease due to PSEN1-E280A variant"

RESUMEN

Introducción: La enfermedad de Alzheimer (EA) es la principal causa de demencia en el mundo. La disfunción sináptica es un evento fisiopatológico que altera las conexiones neuronales a múltiples escalas: molecular, celular, redes cerebrales, corteza cerebral, entre otras. Existen diferentes mecanismos que interactúan para desencadenar alteraciones en la homeostasis de la función sináptica, entre ellos los más destacados son amiloidosis, taupatía e inflamación. El EEG se ha utilizado en los últimos años como una alternativa económica, portátil y no invasiva para el estudio de biomarcadores en la enfermedad de Alzheimer.

Metodología: Todos los participantes eran miembros de familias con la variante genética PSEN1-E280A y controles sanos reclutados voluntariamente. Se planificó un seguimiento longitudinal, este estudio recoge datos desde la visita inicial y en el primer año de seguimiento. En cada visita se realizó una evaluación neurológica y neuropsicológica y un electroencefalograma. Se analizaron las bandas de potencia espectral del EEG en estado de reposo y el índice de reactividad Alfa/Theta.

Resultados: Las bandas de frecuencia Alfa1 y Alfa2 no presentaron cambios significativos en el año de seguimiento, en la banda de frecuencia Beta3 en el componente 20 y Beta2 en el componente 22 se encontraron diferencias estadísticamente significativas. Sin embargo, la distribución de los datos en los gráficos de distribución por deciles para la banda de frecuencia Beta presenta pendientes con pobre inclinación, lo que indica un tamaño del efecto modesto y una precisión baja.

Conclusiones: La banda de frecuencia Beta es un potencial marcador neurofisiológico que en estadios preclínicos de ADAD muestra diferencias estadísticamente significativas entre portadores asintomáticos y no portadores. Esta señal se relaciona con componentes cuyo origen se estima en regiones posteriores, lo que resalta la importancia de los hallazgos previos en la precuña. Sin embargo, los tamaños del efecto fueron modestos y con baja precisión. Se recomendarían muestras más amplias y un seguimiento más prolongado en futuras investigaciones.

Longitudinal analysis of qEEG in subjects with autosomal dominant Alzheimer's disease due to PSEN1-E280A variant.

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ABSTRACT

Introduction: Alzheimer's disease (AD) is the leading cause of dementia in the world. Synaptic dysfunction is a pathophysiological event that alters neuronal connections at multiple scales: molecular, cellular, brain networks, cerebral cortex, among others. There are different mechanisms that interact to trigger alterations in the homeostasis of synaptic function, among them the most prominent are amyloidosis, tauopathy and inflammation. EEG has been used in recent years as a cost-effective, portable, and noninvasive alternative for the study of biomarkers in Alzheimer's disease.

Methodology: All participants were members of families with PSEN1-E280A genetic variant and healthy controls recruited voluntarily. A longitudinal follow-up was planned, this study collects data from the initial visit and in the first year of follow-up. At each visit, neurological and neuropsychological evaluation and electroencephalogram were performed. We analyzed the resting state EEG spectral power bands and the Alpha/Theta reactivity index.

Results: Alpha1 and Alpha2 frequency bands did not have significant changes in the follow-up year, in the Beta3 frequency band in component 20 and Beta2 in component 22 statistically significant differences were found. However, the distribution of the data in the shift graphs for the Beta frequency band presents some slopes, which indicates a modest effect sizes and low precision.

Conclusion: The Beta frequency band is a potential neurophysiological marker that in preclinical stages of ADAD show statistically significant differences between asymptomatic carriers and non-carriers. This signal is related to components whose origin is estimated in posterior regions, which highlights the importance of previous findings in the precuneus. However, the effect sizes were modest and with low precision. It would recommend larger samples and longer following in future research.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia in the world, it is characterized by the abnormal accumulation of beta-amyloid (Aβ) protein and hyperphosphorylated tau protein (1). About 5-10% of cases with early-onset Alzheimer's disease (EOAD) are of familial origin (FAD) by autosomal dominant inheritance; pathology explained by pathogenic genetic variants of complete penetrance in the amyloid precursor protein (APP) genes (<1%), presenilin 1 (PSEN1) gene (6%) and presenilin 2 (PSEN2) gene (1%). Pathological genetic variants in PSEN1 are the most common cause of FAD (2). The Neurosciences Group of Antioquia has characterized for 30 years an extended family with the genetic variant PSEN1-E280A, with a penetrance of almost 100%, with an amnestic presentation and age of onset of MCI at 44 years and dementia at 49 years. Synaptic dysfunction is a pathophysiological event that alters neuronal connections at multiple scales: molecular, cellular, brain networks, cerebral cortex, among others (1). It is possible that the cognitive alterations in the early stages of the disease are a product of the loss of synapses rather than the loss of neurons. There are different mechanisms that interact to trigger alterations in the homeostasis of synaptic function, among them the most prominent are amyloidosis, tauopathy and inflammation (3). Different biomarkers have been reported in this population in amyloid PET, Tau PET, CSF, and cognitive markers that have allowed to know the different stages of the pathophysiological process in preclinical stages, however, they do not allow to trace phenomena as early as the presence of Aβ oligomers and the process of synaptic dysfunction. EEG has been used in recent years as a cost-effective, portable, and noninvasive alternative for the study of biomarkers in Alzheimer's disease(4,5). EEG has been most widely used in late sporadic AD population at different clinical stages of the disease (6). In the current study we want to perform a longitudinal analysis with resting EEG in asymptomatic population carriers and non-carriers of the PSEN1-E280A genetic variant; also, we want to evaluate some neurophysiological markers proposed in previous EEG studies such as Alpha/Theta reactivity in this population (7).

METHODOLOGY

Subjects

All participants were members of families with PSEN1-E280A genetic variant and healthy controls recruited voluntarily. Asymptomatic subjects between the ages of 20 and 45 years were included: 32 carrier (G1) and 37 non-carrier subjects (G2). Nineteen subjects with MCI and 8 with dementia carriers of this genetic variant were included (SIN), all of them older than 40 years. Finally, 30 community controls recruited voluntarily were included (CTR). Subjects with psychiatric, neurological, or systemic disorders that could affect EEG or cognitive test performance, history of TBI, stroke, use of anticonvulsant drugs or abuse of psychoactive substances were excluded. Participants and evaluators were blinded to genetic status. Groups were matched for age, sex, and schooling as best as possible; however, given the particularities of the population, exact matching is not possible. Participants were evaluated by medical and neuropsychological experts. The inclusion criteria were to perform genotyping for the PSEN1-E280A variant, verify cognitive status according to the protocol of the Neurosciences Group of Antioquia. All subjects signed an informed consent approved by the Ethics Committee Board of the Faculty of Medicine - University of Antioquia.

A longitudinal follow-up was planned with biannual visits for a period of 2 years; this study collects data from the initial visit and in the first year of follow-up. At each visit, neurological and neuropsychological evaluation and electroencephalogram were performed.

At the baseline visit 126 subjects were recruited, for the follow-up visit in the first year there was a loss to follow-up of 11.1%, registering 112 subjects at this visit with the following distribution: 30 asymptomatic carriers (G1), 33 asymptomatic non-carriers (G2), 18 with MCI and 8 with dementia due to AD carrying the PSEN1-E280A variant (SIN), 23 community controls matched for sex and schooling (CTR). Longitudinal analyses were performed with this sample because the participants had neurophysiological recordings at the initial visit and at one-year follow-up. (See table 1).

EEG acquisition

EEG signals were acquired in the resting state for 5 minutes with eyes closed (EC) and with eyes open (EO). EEG data were recorded with a Neuroscan amplifier (Neuroscan Medical System, Neurosoft Inc. Sterling, VA, USA) and a 58 tin-channel cap with electrodes placed according to the international 10-10 system. Signals were recorded at a sampling rate of 1000 Hz, in addition the data were filtered in-line with a band pass filter (0.05 to 200 Hz), and a band reject filter (60 Hz) to remove power supply noise. The reference electrode was located on the right earlobe, and an electrode located at Fz was used as ground. Channel impedance calibration was performed, where the contact impedances of the EEG electrodes were kept below 1 KΩ. The recordings were performed in a Faraday cage, a cabinet isolated from audio and external electromagnetic signals.

EEG data pre-processing and normalization

The EEG data preprocessing was based on the pipeline proposed by Suarez et al (8) and the protocol of the Neuropsychology and Behavior research group (GRUNECO). The processing flow applied to the signals was implemented using Python programming language.

Initially, signal detrending and robust average referencing were performed, where bad channels are excluded and interpolated after referencing, based on the standardized early-stage EEG processing (PREP) pipeline(9). Then, a high-pass FIR filter at 1 Hz with Hamming window, order 3300 and transition bandwidth of 1 Hz was applied, subsequently applied and FastICA algorithm from Scikit-learn library to identify artifactual and neural components (10). Next, epoch segmentation was performed, taking 5-second epochs; to smooth eye blink artifacts, wICA (11) was applied. Afterwards, a low-pass FIR filter of 50 Hz with Hamming window, order of 264 and transition bandwidth of 12.5 Hz was applied, and the remaining noisy epochs were detected and removed, according to the criteria: abnormal linear trends, extreme signal amplitudes, statistically atypical activity, extreme kurtosis values, power spectrum anomaly (12).

Finally, signal normalization was performed according to the methodology proposed by Nima et al. (13), which calculates the record-specific constant by applying a 20 Hz low-pass filter to the recordings and then finding the Huber mean of these, normalization is performed by dividing the data for each channel by the constant found. This approach was considered mainly to reduce channel dispersion, because in EEG there is usually variability in the channels induced by artifacts in the signals (13). The above preprocessing and normalization flow is shown in Figure 1.

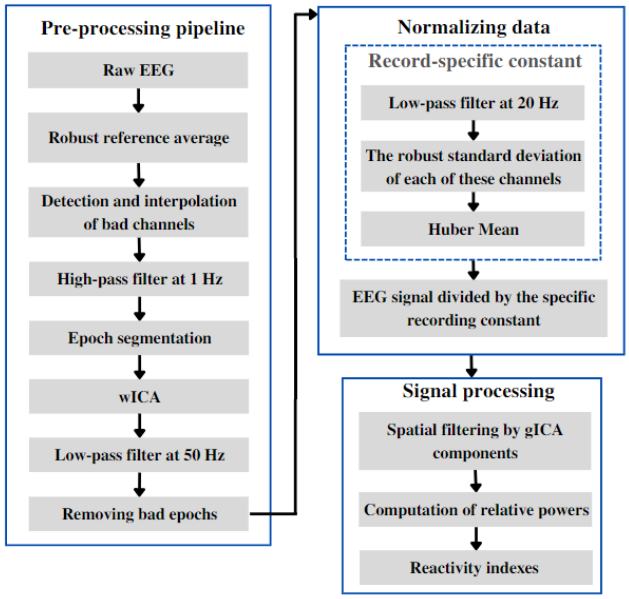


Figure 1. Processing pipeline.

EEG data processing

After normalization of all the signals, the neural independent components (IC) were extracted and calculated using a 58x25 spatial filter based on the study performed by Garcia et al (11). In that study, the group independent component analysis (gICA) was performed, and a classification was made using ICLabel, to find the neural independent components, 8 of the 25 components calculated were selected as neural, and these were the ones that were selected in the present study to be analyzed. Figure 2 shows the topographic head maps corresponding to the neural activity of the selected components.

This approach was taken into account because gICA allows the sources obtained by the decomposition to be comparable between subjects, due to the fact that concatenation of data from different subjects is used for the decomposition, which implies a common mixture matrix and, subsequently, common comparable sources (14).

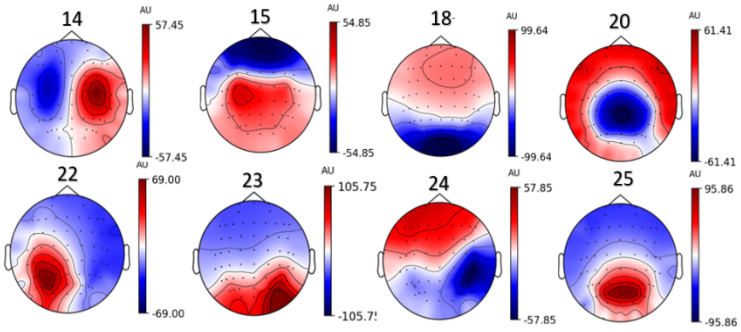


Figure 2. A) Scalp maps projections of the gICA components selected as neural.

The power spectral density was calculated for each neuronal component of the EEG signals, from which the relative power densities were calculated by taking the ratio of the absolute amplitude/power density in a given frequency band to the mean of the amplitude/power density in all frequency bands of the components' spectrum (15). The mean of the following frequency bands was taken: delta (1.5-6 Hz), theta (6-8.5 Hz), alpha 1 (8.5-10.5 Hz), alpha 2 (10.5-12.5 Hz), beta 1 (12.5-18.5 Hz), beta 2 (18.5-21 Hz), beta 3 (21 -30 Hz) and gamma (30-45 Hz) (15).

Having the relative power densities, it was possible to evaluate the alpha theta reactivity in each of the neural components, two formulas were evaluated in this study, where the way to calculate the alpha and theta reactivity indices varies, taking into account the eyes open (EO) and eyes closed (EC) resting state (7). Formula 1 was based on equation 1, with alpha and theta indices according to equations 2 and 3, respectively. Formula 2 was based on equation 1, with alpha and theta indices taken from equations 4 and 5, respectively. For each formula evaluated, 3 results were obtained: alpha 1/theta, alpha 2/theta, and alpha/theta, where alpha corresponded to the average between alpha 1 and 2.

$$I.R\ \alpha/\Theta = \frac{I.R.\alpha}{I.R.\Theta} \quad (1)$$

$$I.R.\alpha = \frac{Power\ \alpha\ (EC - EO)}{Power\ \alpha\ (EC)} \quad (2)$$

$$I.R.\Theta = \frac{Power\ \Theta\ (EC - EO)}{Power\ \Theta\ (EC)} \quad (3)$$

$$I.R.\alpha = \frac{Power\ \alpha\ (EO)}{Power\ \alpha\ (EC)} \quad (4)$$

$$I.R.\Theta = \frac{Power\ \Theta\ (EO)}{Power\ \Theta\ (EC)} \quad (5)$$

Data analysis

Power measurements were evaluated by components and by wave, divided into alpha-1, alpha-2, beta-1, beta-2, beta-3, theta, gamma, delta. The following clinical and sociodemographic variables were included: age, sex, schooling, neuropsychological variables detailed in Table 1. Each participant was included in one of 5 groups according to their initial status, as follows: healthy carriers (G1), healthy non-carriers (G2), MCI and dementia (SIN), healthy controls (CTR).

For the descriptive analysis, qualitative data were presented in tables with absolute and relative frequency measures; and for quantitative data, measures of central tendency and dispersion, mean and standard deviation, or median and range were used, depending on whether the variable has a normal or nonparametric distribution. For the longitudinal analysis, the records of the initial visit and the one-year follow-up visit were taken. Statistical comparison between power by waves and by components was performed using the Kruskal-Wallis test for comparison of multiple variables and the Mann-Whitney test for comparison between pairs of unpaired variables with nonparametric distribution. To compare between quantitative data, the chi-square test or Fisher's test was used when the expected cases in one of the variable values was less than 5. Also, the Mann-Whitney-Wilcoxon test for paired data was used for power comparisons between the two visits.

All these statistical comparisons were run with an alpha of 0.05 in RStudio software (R version 4.1.1).

Alpha theta reactivity indices were analyzed graphically and by means of a statistical test, where the following groups were compared: G1-G2, G1-SIN, CTR-SIN, CTR-G2.

According to G. A. Rousselet (16), to make the most of neuroscience datasets and compare groups, it is important to use graphical methods that allow a more complete visualization of the data for analysis and to better describe how the distributions differ, as well as to implement robust estimators to construct confidence intervals. For this reason, the shift function was implemented to understand and quantify how two distributions differ, and it is both a graphical and an inferential method. Specifically, the shift function describes how one distribution should be rescaled to match another (16). The following were evaluated from these graphs when comparing two groups: differences in deciles, difference in central tendency, slope of the graph, and 95% Brootstrap confidence Interval.

Likewise, the Mann-Whitney U statistical test was performed, a nonparametric test, in which the null hypothesis states that the underlying distribution sample x is the same as the underlying distribution sample y (17), with the aim of finding statistically significant differences between the groups evaluated in a non-graphical way. This test was performed using Python's pingouin library and the significance level considered was 0.05.

RESULTS

- **Sociodemographic and cognitive data**

Table 1 shows sociodemographic and cognitive characteristics of the groups among initial visit (V0) and the first-year follow-up visit (V2). Mean age at V0 was 30.4 years (SD 5.57) in asymptomatic carriers, 31.3 years (SD 6.12) in non-carriers, 46.9 (SD 5.81) in MCI group, 48.9 years (SD 5.44) in the dementia group and 50.1 years (SD 7.72) in controls. Regarding sex, most of the individuals were female except in the MCI (50% male and 50% female) and dementia groups (37.5% female and 62.5% male). Mean years of education in the asymptomatic carriers group was 10.9 years, 13.3 years in non-carriers, 7.33 years in the MCI group, 8.75 years in the dementia group and 8.61 years in healthy controls.

About to cognition, no statistical significance was found in any of the groups between V0 and V2 in MMSE and MoCA scores. Median FAST score was 1.00 (min 1.00, max 2.00) in asymptomatic carriers, non-carriers, and controls, in both V0 and V2. In contrast, the MCI group had a median FAST score of 3.00 (min 3.00, max 5.00) at V0 and 4.00 (min 3.00, max 6.00) at V2; the group of individuals with dementia showed a median score of 4.00 (min 4.00, max 5.00) at V0 and 4.50 (min 4.00, max 9.00) at V2. As with MMSE and MoCA scores, no statistical differences are reported in the FAST scale nor in the rest of the cognitive items.

- **Power spectral density – Transversal Analysis**

We had previously reported findings in spectral power in subjects of the same population with statistically significant differences in Beta and Theta bands, especially in electrodes located in parietal regions to discriminate asymptomatic carriers from non-carriers (11). In this analysis of cross-sectional data from the initial visit (V0), we can evidence findings consistent with the literature regarding the decrease in high frequency bands such as Alpha and Beta and increase in low frequency bands such as delta and theta in subjects with MCI and dementia compared to controls (data no shown). Regarding discrimination between asymptomatic carriers and noncarriers, we observed that the C14 component is the component with a tendency to discriminate in the Alpha1, Alpha2 and Beta3 frequency bands. In the remaining components (C18, C20, C22) highlights the Beta3 frequency band tends to discriminate asymptomatic carriers from noncarriers. However, the slopes the slopes have a poor degree of steepness, and the confidence intervals are wide, in some cases crossing 0, indicating that there are no differences between the two comparison groups. (See figure 3).

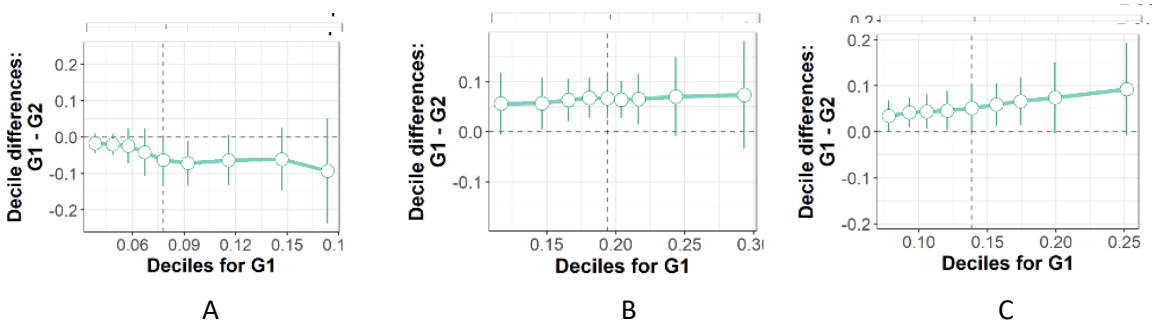


Figure 3. Plots obtained with the shift function, compare groups G1 vs G2: a) C14 component with Alpha2, b) C14 component with Beta3, c) C18 component with Beta3.

Table 1: Sociodemographic and cognitive data.

	Asymptomatic Carriers			Non-Carriers			MCI (Symptomatic carriers)			Dementia (Symptomatic carriers)			Community Control		
	V0	V2		V0	V2		V0	V2		V0	V2		V0	V2	
	(N=30)	(N=30)	p-value	(N=33)	(N=33)	p-value	(N=18)	(N=18)	p-value	(N=8)	(N=8)	p-value	(N=23)	(N=23)	p-value
Age															
Mean (SD)	30.4 (5.57)	31.5 (5.51)	0,515	31.3 (6.12)	32.4 (6.16)	0,489	46.9 (5.81)	48.0 (5.82)	0,794	48.9 (5.44)	50.0 (5.26)	0,752	50.1 (7.72)	51.2 (7.69)	0,272
Median [Min, Max]	29.5 [22.0, 43.0]	31.0 [23.0, 44.0]		30.0 [20.0, 45.0]	31.0 [21.0, 46.0]		46.5 [38.0, 63.0]	47.5 [39.0, 64.0]		49.0 [42.0, 56.0]	50.0 [44.0, 57.0]		49.0 [38.0, 63.0]	50.0 [39.0, 64.0]	
Sex															
Femenino	18 (60.0%)	18 (60.0%)	1,000	21 (63.6%)	21 (63.6%)	1,000	9 (50.0%)	9 (50.0%)	1,000	3 (37.5%)	3 (37.5%)	1,000	12 (52.2%)	12 (52.2%)	1,000
Masculino	12 (40.0%)	12 (40.0%)		12 (36.4%)	12 (36.4%)		9 (50.0%)	9 (50.0%)		5 (62.5%)	5 (62.5%)		11 (47.8%)	11 (47.8%)	
Education															
Mean (SD)	10.9 (3.14)	10.9 (3.14)	0,834	13.3 (2.63)	13.3 (2.63)	0,973	7.33 (5.44)	7.33 (5.44)	0,962	8.75 (3.92)	8.75 (3.92)	1,000	8.61 (4.30)	8.61 (4.30)	0,962
Median [Min, Max]	11.0 [5.00, 18.0]	11.0 [5.00, 18.0]		13.0 [5.00, 17.0]	13.0 [5.00, 17.0]		5.50 [1.00, 18.0]	5.50 [1.00, 18.0]		11.0 [3.00, 13.0]	11.0 [3.00, 13.0]		9.00 [2.00, 16.0]	9.00 [2.00, 16.0]	
MMSE															
Mean (SD)	29.4 (0.932)	29.4 (0.850)	0,772	29.7 (0.816)	29.6 (0.708)	0,540	25.2 (3.79)	23.6 (4.68)	0,200	21.3 (5.82)	15.5 (7.58)	0,233	28.9 (1.20)	28.3 (1.64)	0,201
Median [Min, Max]	30.0 [27.0, 30.0]	30.0 [27.0, 30.0]		30.0 [27.0, 30.0]	30.0 [28.0, 30.0]		25.5 [13.0, 29.0]	24.5 [9.00, 29.0]		23.5 [10.0, 27.0]	19.5 [3.00, 21.0]		29.0 [26.0, 30.0]	29.0 [25.0, 30.0]	
Verbal Fluency															
Mean (SD)	21.7 (3.97)	21.8 (4.01)	0,725	23.0 (3.96)	23.9 (5.13)	0,421	15.5 (4.08)	13.8 (4.95)	0,354	11.8 (4.77)	9.57 (5.50)	0,469	17.0 (3.87)	18.0 (3.24)	0,349
Median [Min, Max]	21.5 [14.0, 29.0]	22.5 [13.0, 28.0]		23.0 [17.0, 32.0]	24.0 [14.0, 32.0]		15.5 [8.00, 22.0]	13.0 [4.00, 22.0]		12.5 [4.00, 19.0]	10.0 [3.00, 20.0]		17.0 [12.0, 26.0]	18.0 [13.0, 24.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
Boston test															
Mean (SD)	12.3 (3.06)	13.3 (1.17)	0,384	13.7 (1.02)	13.8 (0.795)	0,460	12.3 (1.84)	11.4 (2.28)	0,294	11.6 (2.50)	10.6 (3.36)	0,586	12.3 (1.64)	12.6 (2.02)	0,741
Median [Min, Max]	13.0 [0, 15.0]	13.5 [10.0, 15.0]		14.0 [11.0, 15.0]	14.0 [12.0, 15.0]		12.0 [9.00, 15.0]	12.0 [7.00, 15.0]		12.0 [7.00, 14.0]	11.0 [5.00, 14.0]		13.0 [9.00, 15.0]	12.0 [9.00, 15.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
word memory list recall															
Mean (SD)	21.0 (2.86)	21.7 (3.28)	0,466	23.0 (2.55)	23.0 (2.51)	0,905	10.4 (4.27)	9.67 (3.73)	0,736	7.63 (3.89)	6.50 (5.13)	0,624	17.9 (3.18)	19.3 (2.77)	0,130
Median [Min, Max]	21.0 [14.0, 26.0]	21.5 [16.0, 27.0]		23.0 [17.0, 28.0]	23.0 [18.0, 28.0]		10.5 [3.00, 18.0]	10.0 [1.00, 17.0]		7.50 [2.00, 14.0]	6.50 [0, 16.0]		18.0 [11.0, 24.0]	19.0 [14.0, 24.0]	
Intrusions word memory list															
Mean (SD)	0.667 (0.994)	0.600 (1.19)	0,665	0.758 (0.969)	0.818 (1.10)	0,778	6.11 (3.14)	4.83 (3.29)	0,076	4.88 (5.03)	5.67 (4.23)	0,674	1.52 (1.59)	2.43 (2.54)	0,136
Median [Min, Max]	0 [0, 4.00]	0 [0, 6.00]		0 [0, 3.00]	0 [0, 4.00]		6.00 [1.00, 14.0]	4.00 [0, 13.0]		4.50 [0, 15.0]	5.50 [0, 13.0]		1.00 [0, 5.00]	2.00 [0, 9.00]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	2 (25.0%)		0 (0%)	0 (0%)	
Total recognition word memory list															
Mean (SD)	9.80 (0.484)	9.80 (0.484)	1,000	10.0 (0)	9.91 (0.292)	0,149	6.33 (2.33)	5.89 (2.52)	0,739	3.75 (3.11)	2.88 (2.47)	0,445	9.52 (0.790)	9.78 (0.518)	0,212
Median [Min, Max]	10.0 [8.00, 10.0]	10.0 [8.00, 10.0]		10.0 [10.0, 10.0]	10.0 [9.00, 10.0]		7.00 [1.00, 10.0]	6.50 [0, 10.0]		4.00 [0, 9.00]	4.00 [0, 6.00]		10.0 [7.00, 10.0]	10.0 [8.00, 10.0]	
constructional praxis recall															
Mean (SD)	9.03 (1.79)	9.33 (1.95)	0,368	9.67 (1.81)	9.91 (1.16)	0,902	1.89 (2.14)	2.11 (2.27)	0,696	0.750 (1.04)	1.43 (1.13)	0,236	7.52 (3.26)	8.00 (2.50)	0,422
Median [Min, Max]	9.50 [4.00, 11.0]	10.0 [4.00, 11.0]		10.0 [4.00, 11.0]	10.0 [7.00, 11.0]		1.00 [0, 7.00]	2.00 [0, 8.00]		0 [0, 2.00]	2.00 [0, 3.00]		7.00 [1.00, 11.0]	8.00 [2.00, 11.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (12.5%)		0 (0%)	0 (0%)	
MCT free recall															
Mean (SD)	22.8 (5.44)	21.0 (5.39)	0,093	24.1 (3.54)	24.6 (3.98)	0,630	5.12 (4.86)	4.87 (5.67)	0,753	2.80 (2.77)	1.33 (1.37)	0,461	18.5 (4.79)	19.5 (5.11)	0,425
Median [Min, Max]	22.5 [8.00, 32.0]	21.5 [7.00, 30.0]		23.0 [15.0, 30.0]	25.0 [15.0, 30.0]		5.00 [0, 18.0]	4.00 [0, 24.0]		2.00 [0, 7.00]	1.00 [0, 3.00]		19.0 [5.00, 27.0]	19.0 [7.00, 28.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		3 (37.5%)	2 (25.0%)		0 (0%)	0 (0%)	

Familiar complaints															
Mean (SD)	4.17 (5.27)	3.40 (4.17)	0,557	4.15 (5.75)	1.73 (2.90)	0,069	15.9 (10.8)	23.0 (12.4)	0,084	25.8 (13.2)	23.9 (14.9)	0,461	4.64 (6.08)	6.52 (6.01)	0,176
Median [Min, Max]	1.50 [0, 19.0]	2.00 [0, 15.0]		1.00 [0, 21.0]	0 [0, 10.0]		15.5 [0, 36.0]	25.5 [0, 38.0]		28.5 [0, 45.0]	22.5 [0, 45.0]		0.500 [0, 19.0]	6.00 [0, 22.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (4.3%)	0 (0%)	
Personal complaints															
Mean (SD)	10.6 (6.39)	10.9 (7.04)	0,990	8.58 (5.55)	7.73 (5.57)	0,536	18.9 (7.77)	20.1 (12.1)	0,813	12.6 (12.9)	16.8 (15.5)	0,933	10.8 (5.83)	12.3 (7.19)	0,807
Median [Min, Max]	9.50 [2.00, 28.0]	9.50 [1.00, 32.0]		8.00 [1.00, 21.0]	6.00 [1.00, 20.0]		17.0 [8.00, 34.0]	18.5 [0, 39.0]		11.0 [0, 39.0]	12.0 [0, 41.0]		10.0 [1.00, 22.0]	12.0 [2.00, 28.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (4.3%)	0 (0%)	
INECO															
Mean (SD)	19.9 (3.06)	20.6 (3.24)	0,412	20.7 (3.27)	21.5 (2.73)	0,268	14.0 (3.24)	12.7 (4.83)	0,398	10.7 (4.23)	7.25 (2.82)	0,416	18.5 (3.74)	18.4 (3.44)	1,000
Median [Min, Max]	20.0 [14.0, 28.5]	21.3 [14.0, 26.0]		21.0 [12.5, 26.0]	22.0 [15.0, 26.0]		13.0 [9.00, 20.0]	11.0 [5.00, 21.0]		12.5 [4.00, 15.0]	7.50 [4.00, 10.5]		18.5 [9.50, 26.0]	18.0 [13.5, 23.5]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		2 (11.1%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	
FAST															
Mean (SD)	1.13 (0.346)	1.13 (0.346)	1,000	1.06 (0.242)	1.03 (0.174)	0,773	3.39 (0.608)	3.94 (0.998)	0,066	4.13 (0.354)	5.25 (1.83)	0,098	1.09 (0.288)	1.26 (0.449)	0,129
Median [Min, Max]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]		1.00 [1.00, 2.00]	1.00 [1.00, 2.00]		3.00 [3.00, 5.00]	4.00 [3.00, 6.00]		4.00 [4.00, 5.00]	4.50 [4.00, 9.00]		1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	
MoCA															
Mean (SD)	24.2 (2.58)	24.6 (3.09)	0,657	25.9 (2.55)	25.5 (2.50)	0,708	14.4 (4.50)	14.1 (4.02)	0,392	11.5 (5.32)	9.50 (4.09)	0,625	20.6 (4.53)	21.6 (3.96)	0,393
Median [Min, Max]	24.5 [19.0, 28.0]	25.0 [18.0, 30.0]		26.0 [20.0, 29.0]	25.0 [20.0, 30.0]		15.0 [5.00, 20.0]	14.0 [6.00, 19.0]		12.5 [3.00, 18.0]	9.50 [5.00, 15.0]		19.0 [11.0, 29.0]	21.0 [13.0, 29.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	
MoCA: adjusted for schooling															
Mean (SD)	24.6 (2.49)	24.5 (5.32)	0,485	25.9 (2.55)	25.8 (2.37)	0,922	15.1 (4.41)	14.9 (3.84)	0,468	12.3 (5.09)	10.3 (3.83)	0,625	21.4 (4.35)	22.3 (3.80)	0,374
Median [Min, Max]	25.0 [19.0, 28.0]	25.0 [1.00, 30.0]		27.0 [20.0, 29.0]	26.0 [20.0, 30.0]		16.0 [6.00, 21.0]	15.0 [7.00, 20.0]		13.5 [4.00, 18.0]	10.5 [6.00, 15.0]		20.0 [12.0, 30.0]	22.0 [14.0, 30.0]	
Missing	0 (0%)	0 (0%)		0 (0%)	0 (0%)		1 (5.6%)	3 (16.7%)		2 (25.0%)	2 (25.0%)		0 (0%)	0 (0%)	

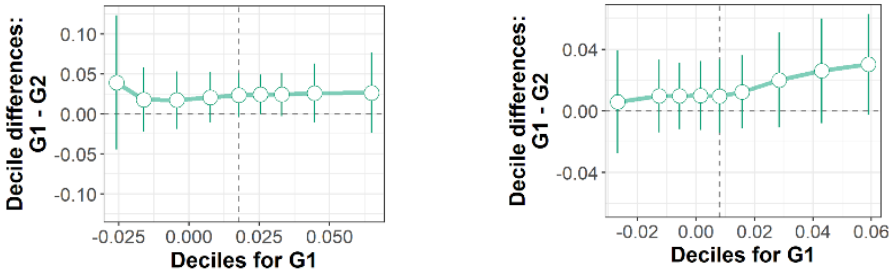
*p-value obtained by McNemar test for qualitative variables and Mann-Whitney-Wilcoxon test for dependent samples for quantitative variables.

- **Power spectral density – Longitudinal Analysis**

To analyzing all groups together comparing the mean of each spectral power band at the initial visit vs. the first-year follow-up visit, we observed statistically significant changes in the Delta, Alpha1, Alpha2, and Beta2 frequency bands. This difference is more prevalent in the components evaluated in the Delta frequency band (Supplementary Table 1). When performing a sub-analysis with the asymptomatic carriers group (G1), we observed statistically significant changes in the Delta and Beta2 frequency bands, being more frequent in Delta frequency band. (See Table 2).

When comparing the changes in the frequency bands in groups G1 (asymptomatic carriers) vs G2 (non-carriers) in a 1-year longitudinal follow-up, we see in shift graphs that in most of neuronal components no differences were found, we observed most of the deciles around zero, with non-linear slopes that showed greater difference towards the deciles located at the extremes (decile 8 and 9), with wide confidence interval. When analyzing the statistically significant findings shown in Table 2, the shift graphs for the Delta band showed nonlinear slopes in the evaluated components; in Beta1 frequency band in C22 component, a slope with a linear tendency with a poor degree of inclination was found, indicating non strong differences between the groups, Finally, frequency band Beta3 in component C20 showed a linear slope especially in the last deciles but with wide intervals that crossed 0, so the differences were not significant in the frequency sense (See Figure 4).

Figure 4. Plots obtained with the shift function: a) C22 component with Beta1. b) C20 component with Beta3.



A B

Table 2: Differences in spectral power bands in components with neuronal origin in asymptomatic carriers. Initial visit (V0) and 1-year follow-up visit (V2).

	DELTA			THETA		
	V0 (N=25)	V2 (N=25)	p-value	V0 (N=25)	V2 (N=25)	p-value
C14						
Mean (SD)	0.120 (0.0603)	0.167 (0.0880)	**0,011**	0.0662 (0.0297)	0.0731 (0.0293)	0,134
Median [Min, Max]	0.115 [0.0284, 0.230]	0.157 [0.0531, 0.422]		0.0589 [0.0220, 0.129]	0.0670 [0.0416, 0.172]	
C15						
Mean (SD)	0.222 (0.108)	0.240 (0.0872)	0,325	0.111 (0.0489)	0.110 (0.0400)	0,979
Median [Min, Max]	0.225 [0.0762, 0.438]	0.249 [0.115, 0.457]		0.112 [0.0389, 0.266]	0.100 [0.0638, 0.202]	
C18						
Mean (SD)	0.168 (0.0761)	0.205 (0.0723)	**0,007**	0.0907 (0.0353)	0.101 (0.0411)	0,230
Median [Min, Max]	0.180 [0.0633, 0.346]	0.213 [0.0800, 0.328]		0.0860 [0.0382, 0.185]	0.0963 [0.0493, 0.257]	
C20						
Mean (SD)	0.141 (0.0688)	0.186 (0.110)	0,075	0.0807 (0.0394)	0.0920 (0.0605)	0,367
Median [Min, Max]	0.129 [0.0293, 0.303]	0.152 [0.0456, 0.441]		0.0794 [0.0274, 0.173]	0.0848 [0.0371, 0.335]	
C22						
Mean (SD)	0.107 (0.0416)	0.161 (0.0893)	**0,002**	0.0757 (0.0356)	0.0869 (0.0427)	0,107
Median [Min, Max]	0.0988 [0.0427, 0.198]	0.144 [0.0546, 0.429]		0.0653 [0.0316, 0.171]	0.0783 [0.0445, 0.222]	
C23						
Mean (SD)	0.129 (0.0655)	0.178 (0.0935)	**0,009**	0.0904 (0.0409)	0.102 (0.0460)	0,101
Median [Min, Max]	0.117 [0.0395, 0.307]	0.162 [0.0590, 0.422]		0.0790 [0.0252, 0.199]	0.0897 [0.0414, 0.204]	
C24						
Mean (SD)	0.0845 (0.0478)	0.159 (0.0866)	**0,000**	0.0775 (0.0528)	0.0916 (0.0471)	**0,037**
Median [Min, Max]	0.0657 [0.0211, 0.216]	0.139 [0.0573, 0.430]		0.0592 [0.0123, 0.242]	0.0902 [0.0317, 0.190]	
C25						
Mean (SD)	0.128 (0.0570)	0.180 (0.0999)	**0,005**	0.0827 (0.0312)	0.0986 (0.0488)	0,241
Median [Min, Max]	0.122 [0.0564, 0.290]	0.161 [0.0611, 0.440]		0.0707 [0.0404, 0.153]	0.0816 [0.0473, 0.189]	
	ALPHA-1			ALPHA-2		
	V0 (N=25)	V2 (N=25)	p-value	V0 (N=25)	V2 (N=25)	p-value
C14						
Mean (SD)	0.0950 (0.0495)	0.0904 (0.0445)	0,895	0.0972 (0.0727)	0.0933 (0.0676)	0,833
Median [Min, Max]	0.0796 [0.0368, 0.203]	0.0745 [0.0488, 0.243]		0.0778 [0.0340, 0.371]	0.0747 [0.0404, 0.374]	
C15						
Mean (SD)	0.0902 (0.0474)	0.0910 (0.0484)	0,672	0.0652 (0.0427)	0.0645 (0.0385)	0,979
Median [Min, Max]	0.0699 [0.0292, 0.213]	0.0769 [0.0451, 0.238]		0.0525 [0.0235, 0.239]	0.0523 [0.0316, 0.215]	
C18						
Mean (SD)	0.150 (0.0801)	0.145 (0.0743)	0,560	0.108 (0.0481)	0.110 (0.0546)	0,833
Median [Min, Max]	0.142 [0.0531, 0.389]	0.118 [0.0669, 0.390]		0.0973 [0.0456, 0.239]	0.0940 [0.0484, 0.290]	
C20						
Mean (SD)	0.141 (0.0693)	0.141 (0.0790)	1,000	0.104 (0.0446)	0.115 (0.0735)	0,791
Median [Min, Max]	0.125 [0.0369, 0.239]	0.111 [0.0417, 0.369]		0.104 [0.0347, 0.215]	0.0875 [0.0390, 0.330]	
C22						
Mean (SD)	0.186 (0.0885)	0.187 (0.0994)	0,958	0.159 (0.0601)	0.151 (0.0769)	0,381
Median [Min, Max]	0.178 [0.0428, 0.329]	0.173 [0.0542, 0.368]		0.153 [0.0444, 0.252]	0.138 [0.0439, 0.294]	
C23						
Mean (SD)	0.248 (0.128)	0.216 (0.120)	0,096	0.139 (0.0506)	0.132 (0.0575)	0,560
Median [Min, Max]	0.246 [0.0621, 0.482]	0.172 [0.0808, 0.505]		0.127 [0.0464, 0.239]	0.124 [0.0348, 0.229]	
C24						
Mean (SD)	0.316 (0.175)	0.266 (0.151)	0,052	0.180 (0.0887)	0.161 (0.0843)	0,252
Median [Min, Max]	0.301 [0.0330, 0.592]	0.246 [0.0690, 0.583]		0.185 [0.0384, 0.449]	0.145 [0.0250, 0.333]	
C25						
Mean (SD)	0.239 (0.136)	0.218 (0.128)	0,200	0.179 (0.0701)	0.172 (0.0930)	0,596
Median [Min, Max]	0.215 [0.0513, 0.482]	0.177 [0.0712, 0.450]		0.188 [0.0676, 0.315]	0.148 [0.0303, 0.373]	

	BETA-1			BETA-2		
	V0	V2	p-value	V0	V2	p-value
	(N=25)	(N=25)		(N=25)	(N=25)	
C14						
Mean (SD)	0.183 (0.0535)	0.186 (0.0523)	0,751	0.0834 (0.0299)	0.0761 (0.0313)	**0,042**
Median [Min, Max]	0.174 [0.123, 0.325]	0.177 [0.110, 0.335]		0.0819 [0.0475, 0.173]	0.0660 [0.0390, 0.169]	
C15						
Mean (SD)	0.130 (0.0447)	0.140 (0.0495)	0,134	0.0591 (0.0188)	0.0601 (0.0191)	0,615
Median [Min, Max]	0.112 [0.0831, 0.264]	0.131 [0.0824, 0.285]		0.0544 [0.0252, 0.113]	0.0571 [0.0288, 0.0918]	
C18						
Mean (SD)	0.171 (0.0536)	0.168 (0.0492)	0,711	0.0680 (0.0241)	0.0615 (0.0245)	0,096
Median [Min, Max]	0.148 [0.103, 0.296]	0.159 [0.0924, 0.298]		0.0646 [0.0291, 0.124]	0.0639 [0.0225, 0.145]	
C20						
Mean (SD)	0.168 (0.0399)	0.162 (0.0393)	0,542	0.0630 (0.0163)	0.0603 (0.0233)	0,525
Median [Min, Max]	0.162 [0.101, 0.279]	0.157 [0.0724, 0.245]		0.0633 [0.0380, 0.109]	0.0582 [0.0170, 0.116]	
C22						
Mean (SD)	0.203 (0.0651)	0.186 (0.0633)	**0,034**	0.0675 (0.0254)	0.0618 (0.0364)	**0,024**
Median [Min, Max]	0.201 [0.112, 0.361]	0.170 [0.106, 0.303]		0.0651 [0.0352, 0.151]	0.0505 [0.0250, 0.179]	
C23						
Mean (SD)	0.169 (0.0707)	0.158 (0.0709)	0,210	0.0444 (0.0169)	0.0421 (0.0160)	0,411
Median [Min, Max]	0.162 [0.0660, 0.354]	0.151 [0.0558, 0.411]		0.0436 [0.0205, 0.0791]	0.0386 [0.0202, 0.0774]	
C24						
Mean (SD)	0.152 (0.0797)	0.142 (0.0600)	0,252	0.0420 (0.0209)	0.0406 (0.0220)	0,525
Median [Min, Max]	0.146 [0.0369, 0.349]	0.127 [0.0581, 0.255]		0.0373 [0.0132, 0.0909]	0.0320 [0.0147, 0.107]	
C25						
Mean (SD)	0.182 (0.0836)	0.163 (0.0681)	0,059	0.0491 (0.0185)	0.0439 (0.0259)	**0,034**
Median [Min, Max]	0.179 [0.0787, 0.472]	0.161 [0.0800, 0.366]		0.0428 [0.0161, 0.0933]	0.0365 [0.0138, 0.129]	

	BETA-3			GAMMA		
	V0	V2	p-value	V0	V2	p-value
	(N=25)	(N=25)		(N=25)	(N=25)	
C14						
Mean (SD)	0.193 (0.0527)	0.177 (0.0555)	0,101	0.162 (0.112)	0.137 (0.0769)	0,101
Median [Min, Max]	0.197 [0.101, 0.316]	0.156 [0.104, 0.308]		0.132 [0.0321, 0.455]	0.124 [0.0427, 0.315]	
C15						
Mean (SD)	0.172 (0.0616)	0.165 (0.0528)	0,634	0.150 (0.101)	0.129 (0.0606)	0,325
Median [Min, Max]	0.159 [0.0898, 0.299]	0.145 [0.0957, 0.272]		0.122 [0.0404, 0.431]	0.124 [0.0341, 0.261]	
C18						
Mean (SD)	0.143 (0.0562)	0.124 (0.0427)	0,075	0.102 (0.0630)	0.0863 (0.0381)	0,275
Median [Min, Max]	0.138 [0.0525, 0.287]	0.131 [0.0362, 0.203]		0.0769 [0.0233, 0.269]	0.0926 [0.0160, 0.162]	
C20						
Mean (SD)	0.140 (0.0463)	0.120 (0.0434)	**0,032**	0.162 (0.114)	0.124 (0.0891)	0,052
Median [Min, Max]	0.141 [0.0586, 0.239]	0.125 [0.0331, 0.231]		0.157 [0.0244, 0.485]	0.0935 [0.0210, 0.348]	
C22						
Mean (SD)	0.112 (0.0421)	0.0983 (0.0439)	0,101	0.0897 (0.0786)	0.0673 (0.0555)	0,055
Median [Min, Max]	0.0975 [0.0469, 0.212]	0.0832 [0.0397, 0.214]		0.0675 [0.0170, 0.357]	0.0524 [0.0168, 0.299]	
C23						
Mean (SD)	0.0843 (0.0401)	0.0818 (0.0426)	0,711	0.0970 (0.0728)	0.0901 (0.0718)	0,458
Median [Min, Max]	0.0736 [0.0218, 0.193]	0.0670 [0.0299, 0.184]		0.0697 [0.0117, 0.317]	0.0776 [0.0143, 0.311]	
C24						
Mean (SD)	0.0699 (0.0492)	0.0693 (0.0378)	0,895	0.0782 (0.0866)	0.0703 (0.0614)	1,000
Median [Min, Max]	0.0560 [0.0143, 0.221]	0.0609 [0.0187, 0.155]		0.0428 [0.00788, 0.375]	0.0499 [0.0134, 0.234]	
C25						
Mean (SD)	0.0789 (0.0366)	0.0719 (0.0342)	0,164	0.0611 (0.0533)	0.0533 (0.0439)	0,381
Median [Min, Max]	0.0747 [0.0215, 0.163]	0.0736 [0.0185, 0.156]		0.0395 [0.0111, 0.244]	0.0406 [0.00954, 0.177]	

- **Alpha/Theta Reactivity**

When analyzing the shift graphs obtained with formulas 1 and 2, it was observed that in most of the neural components no differences were found between the reactivity indices of the groups compared, presenting differences around 0 in most of the deciles, mainly in the central tendency and in the neighboring deciles; the extreme deciles (decile 1 and decile 9) were the ones that mainly showed greater differences, but also wider confidence intervals. Likewise, when evaluating the slope of the graphs obtained with formula 1, in all cases it was non-linear, and although with formula 2 most of the slopes were non-linear, in some cases slopes with low steepness were shown. The non-linear slopes indicate differences in skewness between distributions of the groups with respect to the reactivity indices, while the slopes indicate differences in the spread between

distributions of the reactivity indices, and slopes with low steepness indicate that the differences are not strong. On the other hand, in both formulas evaluated, most of the confidence intervals of the deciles crossed 0, so that the differences were not significant in the frequentist sense (16).

In formula 1, group differences were observed between G1 and G2 in components C23 (in alpha/theta), C20 and C23 (in alpha1/theta), as well as differences between CTR and G2 in components C18 (in alpha/theta, alpha1/theta and alpha2/theta) and C25 (in alpha/theta). In these results, all group differences in reactivity indices were positive, with higher reactivity indices in G1 compared to G2, as well as higher values of CTR indices compared to G2; likewise, the slopes generated between the deciles were non-linear. The graphs that show in a representative way what has been described above for differences and non-differences between groups with formula 1 are shown in Figure 5. It is important to note that there are group differences in Figure 5c, but the differences in the deciles appear to be very close to zero due to the wide confidence intervals; the differences in the different deciles are around 2.5.

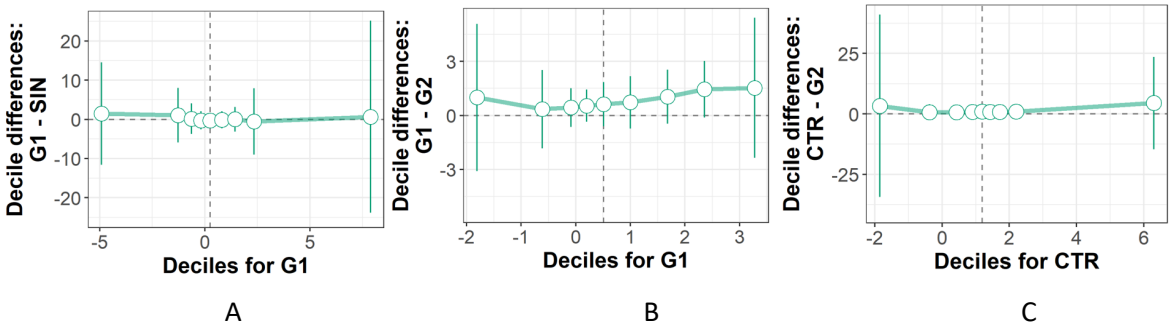


Figure 5. Plots obtained with the shift function: a) C24 component with alpha/theta, no group differences between G1 and SIN, b) C23 component with alpha/theta, group differences between G1 and G2, c) C18 component with alpha1/theta, group differences between CTR and G2.

In formula 2, group differences were observed between G1 and G2 in component C24 in alpha/theta, between G1 and SIN in component C18 in alpha/theta and C24 in alpha1/theta. Also, between CTR and SIN with alpha/theta in components C18, C20, C22, C24 and C25, in alpha1/theta in components C14, C15, C18, C22, C23 and C25. Finally, between CTR and G2, with alpha/theta in components C20, C23, C24 and C25, with alpha1/theta in components C14, C18, C20, C22, C23 and C25, and with alpha2/theta in component C25. As could be seen from the graphs obtained with this formula, negative differences, non-linear behavior of the deciles and slopes with low gradients between the different deciles predominated. In general, there were higher values of G2 indices with respect to G1, higher values of G2 with respect to CTR and SIN with respect to CTR; likewise, G1 and SIN show differences in the distribution due to the positive slope with low inclination. Figure 6 shows some graphs that are representative of the behavior described above for differences and non-differences between groups with formula 2.

All the results that showed differences when performing the Mann-Whitney U test also showed differences in the graphs when using the shift function, however, not all the results that showed differences graphically gave group differences in the statistical test, this is due to the assumptions made by the statistical tests that can affect the final result of the test, while the implemented graphical method allowed observing the differences along the distribution in a better way, as it is a more robust method for analyzing group differences (16).

Considering these results, formula 2, both graphical and statistical, resulted in a greater number of results showing group differences.

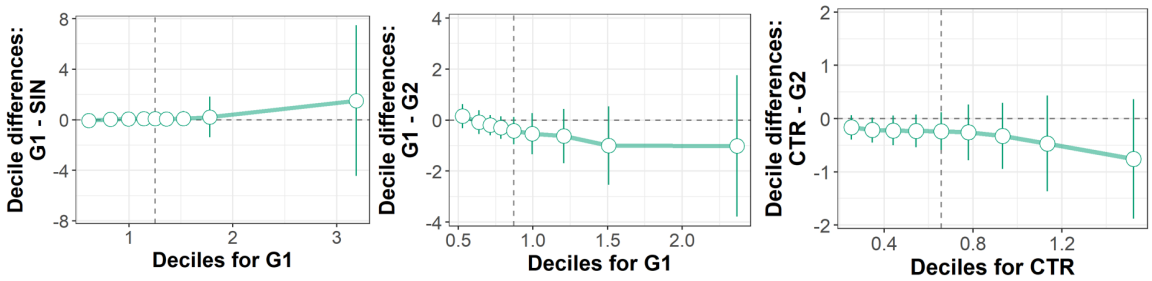


Figure 6. Plots obtained with the shift function: a) C23 component with alpha2/theta, no group differences between G1 and SIN, b) C24 component with alpha/theta, group differences between G1 and G2, c) C25 component with alpha1/theta, group differences between CTR and G2.

Tables 3 and 4 show the results that showed statistically significant differences with the Mann-Whitney U test, using formulas 1 and 2. These tables show the reactivity index, the component, the groups evaluated (A and B), and the U and p values of the test.

Table 3. Mann-Whitney U test results showing differences using formula 1.

Test				MWU	
Reactivity index	**Component**	**A**	**B**	**U-val**	**p-val**
alpha-theta	**C18**	**CTR**	**G2**	834.00	0.02
alpha1-theta	**C18**	**CTR**	**G2**	859.00	0.01
alpha2-theta	**C18**	**CTR**	**G2**	879.00	0.00

Table 4. Mann-Whitney U test results showing differences using formula 2.

Test				MWU	
Reactivity index	**Component**	**A**	**B**	**U-val**	**p-val**
alpha-theta	**C18**	**CTR**	**SIN**	193.00	0.01
		G1	**SIN**	177.00	0.03
	C20	**CTR**	**G2**	434.00	0.02
	C22	**CTR**	**SIN**	235.00	0.05
	C23	**CTR**	**G2**	424.00	0.02
	C24	**CTR**	**G2**	455.00	0.04
		G1	**G2**	357.00	0.05
	C25	**CTR**	**G2**	445.00	0.03
alpha1-theta	**C14**	**CTR**	**G2**	453.00	0.04
			SIN	215.00	0.02
	C18	**CTR**	**G2**	438.00	0.03
			SIN	170.00	0.00
	C20	**CTR**	**G2**	404.00	0.01
	C22	**CTR**	**G2**	439.00	0.03
			SIN	178.00	0.00
	C23	**CTR**	**G2**	420.00	0.02

			SIN	234.00	0.04
	C24	**G1**	**SIN**	184.00	0.05
	C25	**CTR**	**G2**	427.00	0.02
			SIN	212.00	0.02

- **Neuropsychological data**

A boxplot of the MMSE results of each of the evaluated groups is presented (G1 and G2 are presented as healthy "SAN") (See Figure 7). Subsequently, a correlation was made between the MMSE result and the spectral power data of each of the frequency bands in the components with neuronal origin. A negative correlation coefficient with statistical significance ($p<0.05$) was found for the Beta3 frequency band in components C18, C20, C22, C23, C24 and C25. In these same components, a positive correlation coefficient with statistical significance was found for the Alpha1 and Alpha2 frequency bands. No statistically significant findings were found for the other frequency bands (See figure 8).

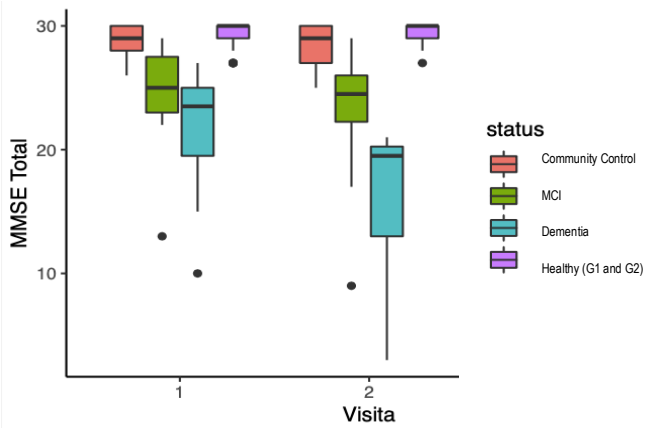


Figure 7: boxplot MMSE in all groups: Community control, MCI (Mild cognitive impairment), Dementia, Healthy (G1 and G2 groups).

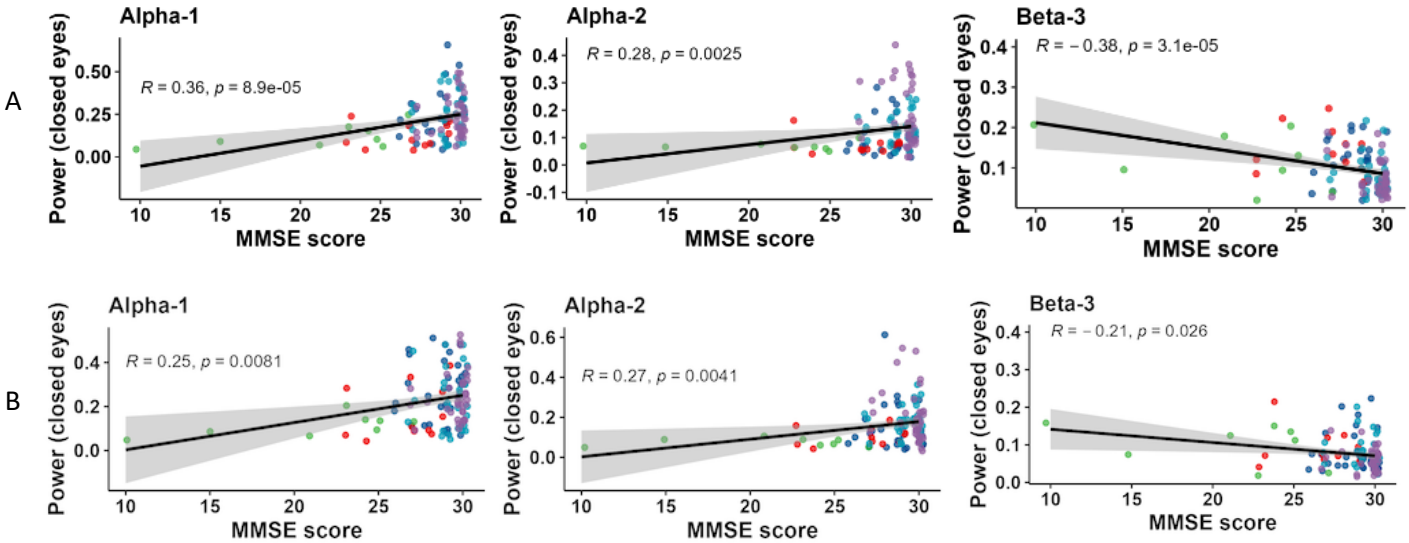


Figure 8: Pearson's correlation of total MMSE vs spectral frequency bands Alpha1, Alpha2 and Beta3 in components C23 (A) and C25 (B).

Discussion

Currently, the diagnosis of AD in the research context is based on the use of biomarkers that track pathophysiological phenomena such as amyloidosis, tauopathy and neurodegeneration in pre-clinical stages and clinical stages of the disease (18). Most of the instruments used to identify these biomarkers require high-tech equipment, are expensive and their availability is limited in middle-to low-income countries as is the case in Colombia (19). It is necessary to advance in the search for low-cost and accessible biomarkers that can be used in the clinical context with the objective of identifying population that may be susceptible to intervention. EEG is a noninvasive, cost-effective, available, and reproducible technique that could be postulated as an alternative in the search for early biomarkers in AD (18). This study is the first longitudinal study in an asymptomatic population carrying the PSEN1-E280A genetic variant by means of resting EEG and its objective was to evaluate possible neurophysiological markers that can track disease progression.

Previously, differences have been described in people with AD (symptomatic and pre-symptomatic) and controls by means of resting state EEG recording. In clinical stages, an increase in slow frequency bands (Delta and Theta) and an increase in fast frequency bands (Alpha, Beta and Gamma) have been described (4). On the contrary, in pre-clinical stages of the disease, an opposite phenomenon has been described, decrease of spectral density in slow frequency bands and increase in fast frequency bands (20). This relationship between the spectral power of slow and fast bands explains the need to use ratios in the search for biomarkers that amplify the differences between control groups and patients.

In our analysis of spectral power in the resting state, taking as reference the components with a neural origin, in a cross-sectional study we found a tendency to differentiate the groups of asymptomatic carriers vs. non-carriers with the Alpha1, Alpha2 and Beta3 frequency bands; finding a lower power in asymptomatic carriers vs. non-carriers in the Alpha frequency bands and a higher power in the Beta frequency bands. When performing the same analysis in the longitudinal follow-up, the Alpha1 and Alpha2 frequency bands did not have significant changes in the follow-up year, but the Beta3 frequency band in component 20 and Beta2 in component 22 statistically significant differences were found, but with low accuracy. Finally, the Delta frequency band presented statistically significant differences in several components between the initial visit and the follow-up visit, however, the distribution of the data in the shift graphs for the Beta frequency band presents slopes with poor slope, which indicates a poor strength in the difference between both groups with wide confidence intervals; and in the case of the Delta frequency band, it presents nonlinear slopes.

In other longitudinal studies with population with subjective cognitive impairment and positive amyloid, they found a higher theta power in those subjects who progressed (mean 0.13 [SD 0.05]) vs subjects who did not progress (mean 0.10 [SD 0.03]; $p < 0.01$) (21); another study with adults under 65 years of age with positive amyloid, found a higher relative theta power that was related to the clinical progression of these individuals (22). When analyzing the ranges used for the frequency bands in these two studies (delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10. 5-13 Hz), beta 1 (13-20 Hz), beta 2 (20-30 Hz), and gamma (30-40 Hz)), we found differences with the recommendations given by the International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup in 2020 (15), where they give recommendations on frequency and topography for resting EEG analysis and record the following ranges in frequency bands: delta (1. 5-6 Hz), theta (6-8.5 Hz), alpha 1 (8.5-10.5 Hz), alpha 2 (10.5-12.5 Hz), beta 1 (12.5-18.5 Hz), beta 2 (18.5-21 Hz), beta 3 (21 -30 Hz) and gamma (30-45 Hz) (15). In this sense, incipient findings such as the significant changes reported in the Delta frequency band in the group of asymptomatic carriers take relevance and would be congruent with those reported in the literature.

Using EEG, several cross-sectional studies have reported differences in carriers of the PSEN1-E280A genetic variant when compared with non-carriers in clinical and pre-clinical stages (20,23,24). In these studies, a decrease in the Theta frequency band and an increase in Alpha2 were found in carriers of this genetic variant (25). Other studies in relation to the precuneus region have been performed finding less deactivation in PSEN1-E280A carriers in memory tasks using fMRI (26,27), hypometabolism using FDG PET, decreased cortical thickness measured by MRI (28) and increased connectivity in visual processing tasks using EEG (29). In conclusion, hindbrain

regions have been proposed as one of the areas that are pathologically and functionally affected in preclinical stages of AD (30). These data are congruent with the results obtained in this study in components such as C22 and C25, related to the precuneus region and superior parietal lobe.

In a previous study with the same population as this study, Garcia et al, were able to classify with up to 83% accuracy preclinical AD in asymptomatic carriers (G1) compared to non-carriers (G2), using spectral features on gICA components, suggesting the importance of Beta banding over regions such as the Precuneus, Superior Parietal Lobe and Medial Frontal Gyrus in the development of early familial AD (11). These findings are congruent with longitudinal analyses, where the Beta frequency band presents statistically significant differences over time and retains discrimination ability between both comparison groups (G1 vs G2).

In summary, Beta frequency band is a potential neurophysiological marker that in preclinical stages of ADAD show statistically significant differences between asymptomatic carriers and non-carriers. Additionally, this signal is related to components whose origin is estimated in posterior regions, which highlights the importance of previous findings in the precuneus. Future research is required with a larger sample and with longer follow-ups to evaluate changes in the progression of the disease and compare results with available screening instruments for dementia. This study has some limitations. One of them is that our results should be taken cautiously because they would apply to this sample of asymptomatic individuals with the PSEN1 E280A variant for ADAD. Also, 11% of the individuals were unable to continue with the follow-up because of the pandemic, thus accuracy got affected by reduced sample size.

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Supplementary Table 1: Differences in spectral power bands in components with neuronal origin in all subjetcs. Initial visit (V0) and 1-year follow-up visit (V2).

	DELTA			THETA		
	V0 (N=93)	V2 (N=93)	p-value	V0 (N=93)	V2 (N=93)	p-value
C14						
Mean (SD)	0.122 (0.0692)	0.142 (0.0848)	**0,018**	0.0736 (0.0457)	0.0728 (0.0391)	0,368
Median [Min, Max]	0.106 [0.00266, 0.370]	0.134 [0.00300, 0.428]		0.0652 [0.00721, 0.234]	0.0670 [0.00282, 0.202]	
C15						
Mean (SD)	0.218 (0.109)	0.225 (0.120)	0,500	0.106 (0.0551)	0.101 (0.0489)	0,157
Median [Min, Max]	0.206 [0.0155, 0.529]	0.208 [0.00643, 0.671]		0.104 [0.0173, 0.317]	0.0919 [0.00391, 0.265]	
C18						
Mean (SD)	0.166 (0.0788)	0.195 (0.104)	**0,005**	0.108 (0.0659)	0.105 (0.0574)	0,893
Median [Min, Max]	0.151 [0.0497, 0.365]	0.176 [0.0117, 0.707]		0.0887 [0.0198, 0.338]	0.0963 [0.00541, 0.314]	
C20						
Mean (SD)	0.137 (0.0743)	0.156 (0.106)	0,278	0.102 (0.0768)	0.0920 (0.0676)	0,189
Median [Min, Max]	0.127 [0.00307, 0.347]	0.146 [0.00243, 0.469]		0.0826 [0.00531, 0.387]	0.0825 [0.00347, 0.335]	
C22						
Mean (SD)	0.123 (0.0589)	0.157 (0.0884)	**0,001**	0.0999 (0.0700)	0.105 (0.0690)	0,135
Median [Min, Max]	0.111 [0.0427, 0.281]	0.144 [0.0247, 0.429]		0.0770 [0.0228, 0.370]	0.0878 [0.0122, 0.376]	
C23						
Mean (SD)	0.144 (0.0782)	0.195 (0.109)	**0,000**	0.108 (0.0726)	0.114 (0.0636)	0,126
Median [Min, Max]	0.121 [0.0395, 0.337]	0.184 [0.0448, 0.554]		0.0916 [0.0223, 0.382]	0.102 [0.0163, 0.296]	
C24						
Mean (SD)	0.118 (0.0776)	0.162 (0.0971)	**0,000**	0.108 (0.0874)	0.113 (0.0826)	0,171
Median [Min, Max]	0.0960 [0.0164, 0.468]	0.142 [0.0217, 0.430]		0.0797 [0.0123, 0.458]	0.0906 [0.0169, 0.382]	
C25						
Mean (SD)	0.159 (0.0873)	0.190 (0.101)	**0,003**	0.107 (0.0654)	0.116 (0.0698)	0,092
Median [Min, Max]	0.146 [0.0352, 0.470]	0.186 [0.0399, 0.507]		0.0941 [0.0202, 0.345]	0.0997 [0.0198, 0.350]	
	ALPHA-1			ALPHA-2		
	V0 (N=93)	V2 (N=93)	p-value	V0 (N=93)	V2 (N=93)	p-value
C14						
Mean (SD)	0.117 (0.0795)	0.105 (0.0667)	0,079	0.110 (0.0822)	0.0973 (0.0676)	0,054
Median [Min, Max]	0.0920 [0.00768, 0.498]	0.0881 [0.00992, 0.320]		0.0801 [0.00991, 0.448]	0.0819 [0.0139, 0.397]	
C15						
Mean (SD)	0.105 (0.0737)	0.0983 (0.0594)	0,637	0.0743 (0.0520)	0.0696 (0.0418)	0,437
Median [Min, Max]	0.0840 [0.0143, 0.443]	0.0828 [0.0105, 0.300]		0.0620 [0.0130, 0.349]	0.0600 [0.0174, 0.238]	
C18						
Mean (SD)	0.172 (0.0973)	0.157 (0.105)	**0,020**	0.114 (0.0736)	0.0997 (0.0606)	**0,025**
Median [Min, Max]	0.151 [0.0183, 0.464]	0.124 [0.0119, 0.536]		0.0933 [0.0152, 0.461]	0.0893 [0.0151, 0.428]	
C20						
Mean (SD)	0.159 (0.0986)	0.138 (0.0943)	**0,002**	0.0985 (0.0615)	0.0930 (0.0647)	0,069
Median [Min, Max]	0.151 [0.00711, 0.549]	0.112 [0.00635, 0.478]		0.0907 [0.0103, 0.345]	0.0797 [0.0116, 0.330]	
C22						
Mean (SD)	0.208 (0.127)	0.192 (0.121)	**0,025**	0.144 (0.0818)	0.133 (0.0837)	**0,019**
Median [Min, Max]	0.181 [0.0246, 0.618]	0.165 [0.0179, 0.546]		0.125 [0.0212, 0.406]	0.116 [0.0225, 0.397]	
C23						
Mean (SD)	0.225 (0.128)	0.196 (0.121)	**0,001**	0.126 (0.0852)	0.109 (0.0755)	**0,010**
Median [Min, Max]	0.210 [0.0394, 0.657]	0.167 [0.0173, 0.554]		0.0988 [0.0276, 0.438]	0.0840 [0.0193, 0.387]	
C24						
Mean (SD)	0.282 (0.162)	0.250 (0.160)	**0,002**	0.153 (0.110)	0.133 (0.0994)	**0,013**
Median [Min, Max]	0.264 [0.0330, 0.715]	0.206 [0.0247, 0.759]		0.124 [0.0305, 0.558]	0.106 [0.0193, 0.488]	
C25						
Mean (SD)	0.233 (0.132)	0.210 (0.128)	**0,011**	0.161 (0.102)	0.146 (0.102)	**0,016**
Median [Min, Max]	0.211 [0.0430, 0.527]	0.170 [0.0187, 0.561]		0.138 [0.0321, 0.546]	0.118 [0.0209, 0.488]	

	BETA-1			BETA-2		
	V0	V2	p-value	V0	V2	p-value
	(N=93)	(N=93)		(N=93)	(N=93)	
C14						
Mean (SD)	0.176 (0.0518)	0.181 (0.0526)	0,314	0.0724 (0.0270)	0.0690 (0.0246)	0,055
Median [Min, Max]	0.169 [0.0738, 0.325]	0.171 [0.0922, 0.335]		0.0639 [0.0215, 0.173]	0.0654 [0.0300, 0.169]	
C15						
Mean (SD)	0.136 (0.0485)	0.141 (0.0472)	0,120	0.0577 (0.0213)	0.0568 (0.0199)	0,863
Median [Min, Max]	0.120 [0.0659, 0.308]	0.132 [0.0562, 0.294]		0.0549 [0.0112, 0.126]	0.0541 [0.0189, 0.106]	
C18						
Mean (SD)	0.153 (0.0494)	0.156 (0.0514)	0,685	0.0583 (0.0237)	0.0551 (0.0215)	0,083
Median [Min, Max]	0.142 [0.0445, 0.296]	0.156 [0.0530, 0.298]		0.0529 [0.00566, 0.124]	0.0525 [0.0130, 0.145]	
C20						
Mean (SD)	0.156 (0.0451)	0.153 (0.0443)	0,525	0.0552 (0.0192)	0.0539 (0.0202)	0,498
Median [Min, Max]	0.149 [0.0501, 0.342]	0.154 [0.0551, 0.308]		0.0549 [0.0110, 0.109]	0.0509 [0.0158, 0.116]	
C22						
Mean (SD)	0.171 (0.0610)	0.167 (0.0588)	0,317	0.0583 (0.0249)	0.0525 (0.0250)	**0,000**
Median [Min, Max]	0.162 [0.0398, 0.361]	0.164 [0.0522, 0.373]		0.0541 [0.00584, 0.151]	0.0489 [0.0108, 0.179]	
C23						
Mean (SD)	0.132 (0.0529)	0.128 (0.0505)	0,205	0.0445 (0.0195)	0.0405 (0.0156)	**0,021**
Median [Min, Max]	0.127 [0.0443, 0.354]	0.121 [0.0443, 0.411]		0.0436 [0.0112, 0.124]	0.0380 [0.00619, 0.0805]	
C24						
Mean (SD)	0.126 (0.0609)	0.126 (0.0504)	0,765	0.0396 (0.0195)	0.0382 (0.0195)	0,277
Median [Min, Max]	0.120 [0.0356, 0.349]	0.122 [0.0307, 0.255]		0.0352 [0.00929, 0.104]	0.0347 [0.0111, 0.107]	
C25						
Mean (SD)	0.149 (0.0645)	0.143 (0.0547)	0,108	0.0433 (0.0202)	0.0393 (0.0189)	**0,004**
Median [Min, Max]	0.141 [0.0434, 0.472]	0.132 [0.0392, 0.366]		0.0399 [0.0101, 0.126]	0.0353 [0.00804, 0.129]	

	BETA-3			GAMMA		
	V0	V2	p-value	V0	V2	p-value
	(N=93)	(N=93)		(N=93)	(N=93)	
C14						
Mean (SD)	0.169 (0.0652)	0.169 (0.0640)	0,759	0.160 (0.131)	0.164 (0.135)	0,875
Median [Min, Max]	0.170 [0.0349, 0.341]	0.161 [0.0506, 0.379]		0.121 [0.0157, 0.567]	0.117 [0.0282, 0.562]	
C15						
Mean (SD)	0.156 (0.0663)	0.158 (0.0665)	0,966	0.147 (0.117)	0.151 (0.122)	0,646
Median [Min, Max]	0.148 [0.0161, 0.356]	0.144 [0.0310, 0.348]		0.115 [0.00864, 0.539]	0.112 [0.0190, 0.561]	
C18						
Mean (SD)	0.123 (0.0628)	0.121 (0.0561)	0,665	0.105 (0.0982)	0.111 (0.106)	0,635
Median [Min, Max]	0.111 [0.00792, 0.335]	0.112 [0.0348, 0.265]		0.0730 [0.00436, 0.498]	0.0737 [0.0137, 0.558]	
C20						
Mean (SD)	0.126 (0.0548)	0.130 (0.0578)	0,483	0.167 (0.143)	0.184 (0.157)	0,247
Median [Min, Max]	0.122 [0.0241, 0.275]	0.126 [0.0266, 0.303]		0.114 [0.0157, 0.583]	0.128 [0.0180, 0.586]	
C22						
Mean (SD)	0.102 (0.0543)	0.0989 (0.0540)	0,702	0.0936 (0.0891)	0.0957 (0.104)	0,893
Median [Min, Max]	0.0974 [0.00734, 0.294]	0.0822 [0.0246, 0.253]		0.0608 [0.00375, 0.433]	0.0573 [0.00835, 0.486]	
C23						
Mean (SD)	0.0954 (0.0555)	0.0939 (0.0516)	0,600	0.126 (0.112)	0.125 (0.106)	0,827
Median [Min, Max]	0.0784 [0.0197, 0.247]	0.0811 [0.00952, 0.237]		0.0809 [0.0102, 0.431]	0.0836 [0.00791, 0.464]	
C24						
Mean (SD)	0.0754 (0.0534)	0.0764 (0.0516)	0,884	0.0983 (0.111)	0.101 (0.113)	0,515
Median [Min, Max]	0.0560 [0.0117, 0.227]	0.0609 [0.0135, 0.239]		0.0536 [0.00429, 0.448]	0.0559 [0.00760, 0.493]	
C25						
Mean (SD)	0.0754 (0.0439)	0.0759 (0.0463)	0,722	0.0717 (0.0802)	0.0796 (0.0941)	0,768
Median [Min, Max]	0.0665 [0.0151, 0.223]	0.0601 [0.0108, 0.231]		0.0405 [0.00547, 0.449]	0.0461 [0.00714, 0.425]	

5.5. Manuscrito en proceso de sometimiento para publicación No. 5: "Pathophysiological basis of synaptic dysfunction in Alzheimer's disease: A systematic review"

RESUMEN

Introducción: La enfermedad de Alzheimer es una patología neurodegenerativa que compromete la cognición y la funcionalidad. Los eventos neuropatológicos que resaltan de la enfermedad son el acúmulo de amiloide beta en forma de placas neuríticas y de proteína tau hiperfosforilada en ovillos neurofibrilares. Sin embargo, la disfunción sináptica ha sido el foco de investigación reciente por ser un evento fisiopatológico temprano que se correlaciona con deterioro cognitivo temprano y muerte neuronal. En este estudio se expone una revisión sistemática de la literatura sobre la evidencia hasta el momento de experimentos que correlacionan disfunción sináptica y enfermedad de Alzheimer.

Métodos: Se realizó una revisión sistemática de la literatura en la que se consideraron 875 artículos de PubMed, Embase, Cochrane y Bireme. Se excluyeron 27 duplicados y 817 referencias debido a un diseño de estudio erróneo, un tipo de publicación erróneo, un artículo de fondo, un resultado erróneo o una población errónea.

Resultados: Se incluyeron 31 referencias de las cuales 23 analizaron mecanismos relacionados con amiloidosis, 6 con taupatía y 2 relacionados con respuesta inflamatoria en EA. En cuanto al diseño del estudio, 18 (58%) eran estudios in vitro, 4 (13%) eran estudios in vivo y 9 (29%) estudios in vivo/in vitro.

Conclusiones: La DS en la EA es el resultado de alteraciones a diferentes niveles moleculares y celulares. Este fenómeno se produce al principio del curso de la enfermedad y está relacionado principalmente con formas solubles de Aβ y proteína tau.

Pathophysiological basis of synaptic dysfunction in Alzheimer's disease: A systematic review

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Keywords: synaptic dysfunction, Alzheimer's disease, amyloidosis, tauopathy.

ABSTRACT

Background: Alzheimer's disease (AD) is a neurodegenerative condition that impairs cognition and functionality. The neuropathological hallmarks of AD are neuritic plaques of amyloid beta (AB) and neurofibrillary tangles of hyperphosphorylated tau protein (NFTs). Nevertheless, synaptic dysfunction (SD) has gained attention as an early pathophysiological event that triggers neuronal apoptosis and early cognitive dysfunction. In this study we aim to consolidate the current information regarding synaptic dysfunction in AD.
Methods: A systematic review of literature was carried out in which 875 articles were considered from PubMed, Embase, Cochrane and Bireme. 27 duplicates were excluded as well as 817 references due to wrong study design, wrong publication type, background article, wrong outcome, or wrong population.
Results: 31 references were included out of which 23 analyzed mechanisms related to amyloidosis, 6 to tauopathy and 2 inflammatory responses in AD. Regarding the study design, 18 (58%) were in vitro studies, 4 (13%) were in vivo studies and 9 (29%) in vivo/in vitro studies.
Conclusion: SD in AD is the result of impairment at different molecular and cellular levels. This phenomenon occurs early in the disease course and is mainly related with soluble forms of Aβ and tau protein.

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition that impairs cognition and functionality. Given that there are no treatments to prevent or reverse AD, efforts have been focused on better understanding the causes of the disease (1). Traditionally, the neuropathological characteristics of AD are the presence of beta amyloid (Aβ) aggregation, Tau-induced neurofibrillary tangles, and neuronal loss. A key observation is that these pathological changes during AD begin many years prior to the onset of dementia (2).

Keeping in mind that AD is conceptualized as a clinical continuum, the initial pathological event in AD is amyloidosis and can be found many years before clinical manifestation. Nevertheless, Aβ accumulation is not enough to produce symptoms, thus additional factors contribute to neurodegeneration during the disease course (2). Synaptic dysfunction (SD) has gained attention as the major pathophysiological event and the trigger of both neuronal death and early cognitive dysfunction. Synapses and dendritic spines are dynamic structures, thus molecular changes may cause changes in synaptic connections and plasticity mechanisms (2).
SD in AD is thought to be caused by intermediate peptides, such as soluble AB oligomers (Aβo) and tau oligomers, and it is mainly characterized by impairment in synaptic plasticity mechanisms namely long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus (4). Nevertheless, the pathophysiological pathways by which SD occurs in AD are not completely understood. In this study we consolidate the current information regarding synaptic dysfunction in AD.

Methods

1. Search strategy and selection criteria

An exhaustive search was carried out in the databases "Medline", "Embase", "Bireme Lilacs", Cochrane and Gray Literature. The main objective was to perform a systematic review of the literature on the mechanisms that trigger synaptic dysfunction from the pathophysiological process of Alzheimer's disease.

The inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Methodological design involving the relationship of some pathophysiological processes (amyloidosis, tauopathy, inflammation, oxidative stress) of AD with synaptic dysfunction.
- In vitro or in vivo models.

Exclusion criteria:

- Narrative review type studies, systematic review, clinical trials.
- Studies involving pharmacological intervention
- Post-mortem studies

The search strategy was as follows in each database:

MEDLINE

((Alzheimer Disease[Mesh] OR Alzheimer Disease[tiab]) AND (synaptic dysfunction[tiab])) AND ((((((((((Amyloidosis[Mesh] OR Amyloidosis[tiab]) OR ("beta amyloid production"[tiab])) OR ("beta amyloid aggregation"[tiab])) OR (neurodegeneration[tiab])) OR ("neuronal death"[tiab])) OR (Inflammation[Mesh] OR Inflammation[tiab])) OR (neuroinflammation[tiab])) OR (Tauopathies[Mesh] OR Tauopathies[tiab])) OR ("Tau production"[tiab])) OR ("Tau aggregation"[tiab]))

EMBASE

(('alzheimer disease'/exp OR 'alzheimer disease') AND ('synaptic dysfunction'/exp OR 'synaptic dysfunction') AND (('amyloidosis'/exp OR amyloidosis) OR 'beta amyloid production' OR 'beta amyloid aggregation' OR ('neurodegeneration'/exp OR neurodegeneration) OR 'neuronal death' OR ('inflammation'/exp OR 'inflammation') OR ('neuroinflammation'/exp OR neuroinflammation) OR ('tauopathy'/exp OR 'tauopathy') OR 'tau production' OR 'tau aggregation')) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

BIREME-LILACS

(English and Spanish):

("Alzheimer Disease") AND ("synaptic dysfunction") AND (amyloidosis OR "beta amyloid production" OR "beta amyloid aggregation" OR neurodegeneration OR "neuronal death" OR inflammation OR neuroinflammation OR tauopathies OR "Tau production" OR "Tau aggregation") AND (db:("IBECS" OR "LILACS"))

("Enfermedad de Alzheimer") AND ("Disfunción sináptica") AND (amiloidosis OR "Producción de beta amiloide" OR "Agregación de beta amiloide" OR neurodegeneración OR "muerte neuronal" OR inflamación OR neuroinflamación OR taupatía OR "Producción de tau" OR "Agregación de tau")

COCHRANE

("Alzheimer Disease" and "synaptic dysfunction" and (Amyloidosis or "beta amyloid production" or "beta amyloid aggregation" or neurodegeneration or "neuronal death" or Inflammation or neuroinflammation or Tauopathies or "Tau production" or "Tau aggregation")).

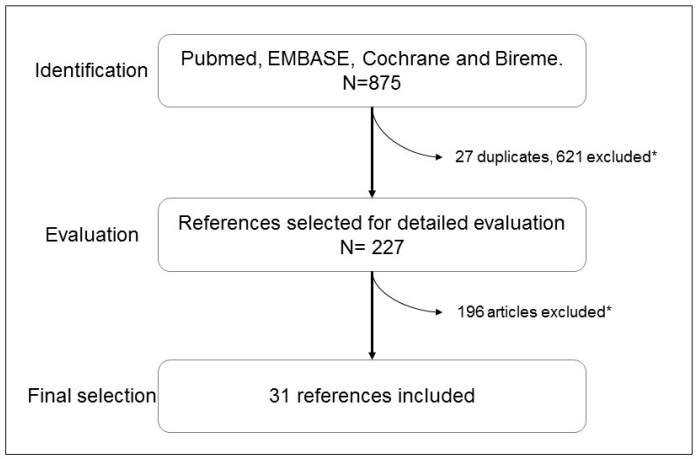
OPENGREY

(Alzheimer disease AND synaptic dysfunction).

No restrictions were placed by language or year of publication. Two independent reviewers (D-A and AGN) carried out the selection of articles; when there were discrepancies, a third reviewer was used.

A total of 875 articles were included. In the first screening, a careful reading of titles and abstracts was performed; 27 duplicate manuscripts were excluded. The criteria used to exclude were: wrong study design (those relating SD and other factors like physical activity, CNS infections), wrong publication type, background article, wrong outcome or wrong population. A total of 621 papers were excluded in this first phase. In the second part, the article was read to define its inclusion in the study. The same criteria were taken into account. Finally, 31 articles were selected. (Figure 1.)

Figure 1. Flow chart of eligibility criteria



*Articles excluded for wrong study design, wrong publication type, background article, wrong outcome or wrong population

2. Data extraction

After the selection process of experiments, 31 papers were included. A detailed reading of the text was performed, and relevant information was collected in a comparative table. (Table 1).

Results

1. Study characteristics

Out of the 31 studies, 23 analyzed mechanisms related to amyloidosis, 6 to tauopathy and 2 inflammatory responses in AD. Regarding the study design, 18 (58%) were in vitro studies, 4 (13%) were in vivo studies and 9 (29%) in vivo/in vitro studies.
Most of the experiments were developed in the United States (14 papers), England (3 papers), Italy (3 papers), France (2 papers), India (2 papers), Belgium (1 paper), China (1 paper), Germany (1 paper), Korea (1 paper), Mexico (1 paper), Portugal (1 paper).

Discussion

1. Amyloidosis and synaptic dysfunction

a. Specific molecules involved in synaptic transmission

AD is thought to be primarily a synaptopathy due to synapse loss and altered connectivity in early stages of the disease. The implication of SD in AD has been subject of investigation, mainly in animal models. Regarding neural structure, the major synaptic change reported is reduction of axons terminals without impairment in dendritic spines. Nevertheless, instability in both axons and dendrites can be found in transgenic mice models, and this is not related to proximity to Aβ plaques (5).

Several molecules have been involved between Aβ and SD. Synaptophysin has been proposed as a major molecule involved in the pathophysiology of synaptic impairment in AD. This molecule is an integral membrane protein localized in synaptic vesicles (SV) and is part of the pore complex, thus involved in neurotransmitter release. One study demonstrated that Aβ interacts with synaptophysin and interferes with the

formation of the complex VAMP2/Synaptophysin, affecting the formation of the SNARE complex during the formation of the fusion pore complex (6).

Similarly, endophilin 1 is a molecule widely spread in the human brain and is a key regulator of SV endocytosis. A study performed with cultured hippocampal cells from rats demonstrated that endophilin 1 expression was higher in neurons exposed to Aβ oligomers (Aβo) prior neuronal death, in comparison with controls. In the same vein, silencing the expression of endophilin 1 in cells treated with Aβo, miniature excitatory postsynaptic currents (mEPSC) increased, suggesting a negative effect of endophilin 1 in neuronal plasticity (4). These findings are supported by a previous study in which increased levels of endophilin 1 in neurons exposed to Aβ was linked to an increase in the activation of the stress kinase c-Jun-N-terminal and subsequent neuronal death (7).

Scaffold proteins in dendritic spines have also been related with SD in AD. To analyze Shank and Homer protein involvement, an experiment with cultured hippocampal cells from rats that underwent exposure to synthetic Aβ1-40, showed that Aβo triggered reduction of Shank and Homer proteins in postsynaptic density by either impairment of protein synthesis or increased degradation. The latter was mediated by glutamate receptor activation (8).

As mentioned before, various molecules have been studied in Aβ-induced SD. In an experiment with cultured hippocampal cells from rats exposed to Aβo, impairment of dynamin 1 was found. They reported decrease in full length and increase in its proteolytic fragment. This results in lost ability to release neurotransmitters successively due to ineffective vesicle recycling, accumulation of synaptic vesicles at the cellular membrane and reduced synaptic vesicle pool (9).

Also, synapsin is a protein that links actin to SV and is critically involved in vesicular trafficking. This protein can be phosphorylated by protein kinase A (PKA) and Ca2+/calmodulin-dependent protein kinase IV (CaMKIV), resulting in disassociation of the actin-SV binding. We found a report that demonstrated in an animal model that soluble Aβ1-42 (sAβ1-42) promotes phosphorylation of synapsin and thus inhibits actin-SV coupling (10). This finding suggests that sAβ1–42 increases the Ca2+-dependent phosphorylation of Ser9 of synapsin through CaMKIV, disrupting SV reallocation and preventing neurons forming new synapses during plasticity.

b. Presynaptic regulation

There is increased evidence of deficits in presynaptic mechanisms and presynaptic forms of plasticity in AD. Disruption of the excitatory/inhibitory synaptic balance and network hyperactivity are greatly influenced by presynaptic dysregulation. Another aspect regarding presynaptic mechanisms is SV regulation and distribution.

We found two studies that aimed to explore how intersynaptic vesicular trafficking might be involved in synaptic dysfunction in AD. One of them, a live-cell imaging technique, was used to monitor SV in hippocampal cultured neurons from embryonic day 18 Sprague-Dawley rat embryos. They performed a chemically induced long term potentiation (LTP) with forskolin, and exposed some of the cultures to sAβ1-42. They found that sAβ1-42 blocked the stimulatory effect of forskolin in synaptogenesis and inhibited chemically induced LTP new synapse formation. Furthermore, the process

of intersynaptic vesicular trafficking, that is critically involved in presynapse formation, was significantly reduced in cells exposed to sAβ-142 (10).

In the same vein, the second report found that sAβ1-42 strongly inhibited activity-dependent synaptogenesis and intersynaptic vesicular trafficking. The latter is critically involved in new synapses formation and synaptic plasticity, and it is explained by the fact that direct recruitment of vesicles promotes synaptic strength, modulates SV pools in presynaptic terminals, without disrupting the integrity of neighboring synapses (10).

c. Mechanisms of neuronal plasticity

Hippocampus is a well-studied part of the vertebrae brain, and it has been recognized for its important role in memory storage. Long term potentiation (LTP) and long-term depression (LTD) serve as electrophysiological correlates of basic cellular mechanisms involved in learning and memory in mammals. Specifically, LTP has been related to conditioned fear memory, conversion of short-term memory into long-term memory, acquisition of information about novel space, among others (11,12).

The CA1 region is a hippocampal section of special interest for its neuronal distribution. A descriptive analysis aimed to evaluate LTP and LTD variations between apical and basal dendrites of the CA1 region, when exposed to Aβo. They found that LTP is impaired in both apical and basal dendrites, specifically homosynaptic LTP. Additionally, LTD was induced in the presence of Aβo in both apical and basal dendritic compartments. This Aβ-facilitated-LTD was completely blocked when a metabotropic glutamate receptor antagonist was added, thus glutamatergic signaling helps regulate synaptic depression (13).

Similarly, one study reported that LTP threshold was increased in pre-fibrillary stages of amyloidosis and this was accompanied by reductions in short-term potentiation, synaptic response to burst stimulation and NMDA receptor-mediated component of excitatory synaptic transmission (14). These findings suggest that synaptic dysfunction happens early in the disease course, before neuritic plaques are detected. Supporting these findings, a different report determined that Aβo produced a reduction of the amounts of potentiation in early and late-phase of LTP. When applying synthetic Aβ in fibrillary form, the reduction was only evident in late-phase LTP without affecting the early phase (15).

In the same vein, a report aimed to analyze how relative levels of pre-fibrillary Aβ in the hippocampus relate to synaptic and genomic changes. A mouse model of increasing Aβ (Transgenic for familial Alzheimer's disease genes APP/PSEN1) was used and electrophysiological measures were performed three times. In the third week of culture, Aβ was detectable just above the limit of detection and Aβ38:Aβ40:Aβ42 ratio was 3:6:2. By two months, the Aβ peptides were detected and the ratio among peptides subtypes was similar but the levels were approximately 50% higher. By 4-month-old, plaques were already detectable, levels of Aβ42 increased approximately 25-fold and Aβ40 by 7-fold, thus Aβ42 levels were similar to Aβ40. These findings suggest that the rate of deposition accelerates when Aβ40:Aβ42 ratio is 1:1, but synaptic changes are not dependent on this. Thus, regarding synaptic function, changes in spontaneous excitatory postsynaptic currents were similar as those seen in the 2nd month, a stage in which no plaques were reported and overall Aβ levels and

ratio Aβ40:Aβ42 was 3-fold lower. This demonstrated that synaptic impairment is an early event in the pathophysiology of AD (16).

Nevertheless, exposure to amyloid requires additional elements in order to become deleterious. It was demonstrated that short exposures to picomolar (pM) concentrations of Aβ facilitate synaptic potentiation both in hippocampal cultures and slices and enhance memory in mice. In contrast, longer exposures lasting for several hours lead to reduction of synaptic plasticity, memory formation and altered expression of molecules involved in synaptic transmission like synaptophysin and synapsin (17).

d. Glutamate neurotransmission

It is well known that neurotoxicity and neuronal cell death in AD might be mediated by augmented release of glutamate. In fact, glutamatergic neurotransmission has been closely involved with synaptic dysfunction. It has been proposed that Aβ1-42 induces N-methyl-D-aspartate receptor (NMDAr) endocytosis and impairs its transport to the cellular membrane (18). The underlying mechanism is thought to be activation of α-7 nicotinic receptor and protein phosphatase 2B (PP2B), resulting in dephosphorylation of tyrosine phosphatase STEP which in turn generates endocytosis of NMDAr (18).

Another study wanted to describe the natural course of synaptic dysfunction with cultured hippocampal cells from transgenic mice with Swedish-Indiana APP mutation. The evaluation was performed in the CA1 region and in the dentate gyrus (DG). They observed that in early stages of the disease there was absence of amyloid plaques in both CA1 and DG regions, but interestingly, the CA1 showed a decrease in the ratio NMDAr/AMPAr and reduction of LTP. Electrophysiological experiments exhibited a higher amount of peptides in the CA1 region in comparison to DG in early stages. Throughout the disease, the CA1 region showed reduction of the ratio NMDAr/AMPAr, in the DG this was only evident in late stages. Impairment of LTP and accumulation of Aβ was similar in both regions in the final phase (19).

In order to assess the contribution of AMPAr in LTP impairment, rectification indexes in CA1 and DG regions were performed. No differences in AMPAr currents were found between transgenic (TG) and wild type (WT) groups of neurons. This suggests that AMPAr do not seem to play a major role in LTP impairment. Finally, paired-pulse facilitation was not altered, supporting the view that impairment in LTP in this model is mediated through NMDAr dysfunction postsynaptically in both CA1 and DG regions (19).

e. Cytoskeletal structure, amyloidosis, and synaptic dysfunction

Dendritic spines, among neurites, are the primary site for receiving information and cellular substrates for synaptic plasticity. They can undergo synaptic-activity-dependent modifications such as enlargement or shrinkage during LTP or LTD respectively. F-actin is a protein involved in spine formation and synaptic-activity-dependent structural changes in dendritic spines. One report found that alteration of F-actin equilibrium occurs during initial stages of AD pathogenesis and affects cytoskeletal architecture in postsynaptic neurites. This was due to Aβ1-42-induced-depolymerization of F-actin, affecting total dendritic spines, spine total extent, spine surface area, diameter of the spine head and spine cross-sectional area. The pathophysiological mechanism involved in F-actin conversion to G-actin is thought to

be dephosphorylation of p-cofilin, which leads to decrease in the p-cofilin/cofilin ratio and in consequence F-actin loss (20).

These findings are supported by a report in which alpha-tubulin, another component of cytoskeletal architecture, got altered when exposing hippocampal neurons to Aβ. Additionally, beta-III tubulin was significantly correlated with reduced neurite length and neuronal DNA fragmentation. In the presence of memantine, Aβ-induced decline in beta-III tubulin was not significant, but it did not prevent the toxic effect completely. The latter gives insight into the involvement of NMDA signaling in microtubule disassembling associated with neurite retraction and DNA fragmentation (21).

2. Tau pathology and synaptic dysfunction

Tau is a microtubule binding protein that, in physiological conditions, serves to stabilize microtubules, mediates microtubule assembly, axonal transport and neurite outgrowth. Under pathological conditions, tau gets phosphorylated 3-4 times more than normal conditions, leading to its detachment from microtubules and further accumulation in the somatodendritic compartment (22).
In order to analyze the contribution of tau protein to synaptic dysfunction in AD, one of the studies described the role of synaptogyrin-3 in this process. They reported that tau binds to synaptogyrin-3, a transmembrane SV protein, affecting SV mobility and lowering neurotransmission. Given that synaptogyrin-3 is only present in SVs, these results give insight to the relationship between tau and SD in AD (23). The latter is supported by a previous study, which reported that low levels of tau protein were capable of induce cognitive decline, reduce synapses and proteins related to synaptic formation, neuronal death and inflammatory response mediated by astrocytic activation (24).

As reported in Aβo-induced synaptic dysfunction, it seems that pre-filaments forms of tau may be more cytotoxic than neurofibrillary tangles (NFTs). Indeed, it has been described that cellular death precedes formation of NFTs (25). An in vivo/in vitro experiment performed in mice gave evidence supporting this hypothesis. They found a higher neuronal damage in neurons treated with oligomeric tau versus NFTs. To assess synaptic function, biochemical and histochemical analysis was performed to evaluate synaptophysin, synapsin-1 and septin-11 levels. It was reported that synaptophysin and septin-11 levels decreased in tau oligomers-treated neurons of the CA1 region of the hippocampus (26).

Furthermore, calcium homeostasis has been related to tau pathology in AD. In fact, a study found that oligomeric tau accumulated in astrocytes and in consequence astrocytes exhibited a significant reduction in the amplitude of ATP-induced Ca2+ currents. Also, gliotransmitter release from astrocytes was impaired in neurons treated with oligomeric tau, especially glutamate and serine, through ATP signaling impairment (27). In the same vein, it was demonstrated that tau limited the depolarization-evoked glutamate release, likely acting on regulation of intracellular calcium dynamics. One hypothesis that helps explain this association is that tau might interact with cellular membrane, affecting its viscosity and in consequence partitioning the voltage-gated calcium-channels (28).

3. Inflammatory response, SD and AD

Even though amyloidosis and tauopathy are both related to local inflammatory response, there is not much evidence relating inflammation, SD and AD. The first study found that in mice with the APP/PSEN1 mutation there was a loss of protein translation caused by an increase in reactive oxygen species (ROS). The latter caused impairment in the signaling pathway of AKT1-mTOR (Mammalian target of rapamycin), critically involved in activity-dependent protein translation and in consequence in synaptic plasticity (29).

Previous reports have also described the involvement of prostaglandin E2 (PGE2) in AD. It is thought that PGE2 can stimulate AB production (30). One of the analyzed studies found that PGE2 impairs LTP through activation of the PGE2 receptor 3 (EP3), in the mossy fibers of the hippocampus CA3 region. The previous finding was reported in cultured hippocampal cells from male mice with the APP(Sweden)/PSEN1 mutation (31).

Conclusion

SD in AD is the result of impairment at different molecular and cellular levels. This phenomenon occurs early in the disease course and is mainly related with soluble forms of AB and tau protein.

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Table 1. Description of analyzed articles

Title	First author	Year of publication	Country	Study design	Population	Pathophysiological pathway	Target	Methods	Results
Endophilin 1 knockdown prevents synaptic dysfunction induced by oligomeric amyloid β	Yin, Y.	2019	China	In vitro	Hippocampal cell culture of rats and preparation of Aβ derived from human samples	Amyloidosis	Endophilin 1	Hippocampal cell cultures and transfection, Western blotting, fluorescence immunostaining, determination of neuronal survival rate, electrophysiology.	Oligomeric amyloid beta caused synaptic dysfunction and endophilin 1 was highly expressed prior to neuronal death of cultured hippocampal neurons.

Dopaminergic neurotransmission dysfunction induced by amyloid-b transforms cortical long-term potentiation into long-term depression and produces memory impairment	Moreno-Castiilla, P	2016	Mexico	In vivo	Triple transgenic and wild type male mice.	Amyloidosis	Dopamin	Behavioral tasks, free-moving microdialysis, in vivo electrophysiological recordings, pharmacologic manipulations, and histologic and immunohistochemical analyses in the 3Tg-AD model,	Amyloid beta decreased cortical dopamine levels and converted in vivo long-term potentiation (LTP) into long-term depression (LTD).
Aβ mediates F-actin disassembly in dendritic spines leading to cognitive deficits in Alzheimer's disease	Kommaddi, R	2018	India	In vivo / In vitro	Transgenic (TG) APP/PS1 mice for in vivo measurements. Cultured neurons from TG APP/PS1 mice, wild type (WT) mice and C57BL/6 mice neurons exposed to low concentrations of Aβ 42.	Amyloidosis	F-actina	In vivo behavioral and in vitro biochemical experiments were performed in TG and WT mice. Synaptosomal levels of F-actin,G-actin, and total actin were measured in postmortem frontal cortex neurons from NCI, MCI and AD subjects.	TG male mice (APPswe/PS1) at 1 month age showed depolymerization of synaptosomal F-actin accompanied by increased globular-actin (G-actin). At 2 months of age, deficits in recall after fear conditioning was found in TG mice.
A critical role for the PAR-1/MARK-tau axis in mediating the toxic effects of Ab on synapses and dendritic spines	Yu, W.	2012	United States	In vitro	Rat E18 hippocampal neuron primary cultures	Amyloidosis	PAR-1/MAPK	Neuron cultures and exposure to 5 mcg of Aβ42. Immunofluorescence analysis and electrophysiological records were obtained to count the number of dendritic spines, GluR1, synapsin 1 and PSD-95. Recombinant RNA was built to induce overexpression of PAR1 and MARK4.	PAR-1/MAPK family kinases play a critical role in Aβ toxicity on synapses and dendritic spines. Overexpression of MARK4 led to tau hyperphosphorylation and synaptic dysfunction, phenotypes also observed after Aβ exposure.
Amyloid-Beta Peptide 1-42 Causes Microtubule Deregulation through Nmethyl-D-aspartate Receptors in Mature Hippocampal Cultures	Mota, S.	2012	Portugal	In vitro	Wistar fetal rats at embryonic 18-19 day.	Amyloidosis	Beta III-tubulin and polymerized tubulin	Primary hippocampal cell culture, exposure to 500 nM of Aβ and NMDA treatment. Antagonists of rNMDA were added (MK-801, memantine, ifenprodil). Immunocytochemistry analysis and fluorescence microscopy was performed.	Aβ1-42 caused a decrease in total and polymerized levels of beta-III tubulin and polymerized alpha-tubulin, suggesting microtubule disassembly. This finding was significantly correlated with reduced neurite length. Also, Aβ induced DNA fragmentation in both neuronal and non-neuronal cells.

Soluble Aβ Oligomers Impair Dipolar Heterodendritic Plasticity by Activation of mGluR in the Hippocampal CA1 Region	Zhao, J.	2018	United States	In vitro	Mice C57BL/6 and 129 (male and female, 6~8 weeks old)	Amyloidosis	mGluR	Cultured hippocampal cells from mice were exposed to human oligomeric Aβ. A protocol to record postsynaptic potentials in the CA1 region was performed. LTP was induced with 2 consecutive trains of stimuli at 100 Hz separated by 20s, or 10 pulses at 10 Hz separated by 10s in basal and apical dendrites.	oAβ induced LTD in both apical and basal dendrites as well as reduction in neurotransmission. Basal dendrites are more resistant to Aβ-mediated synaptotoxicity.
Longitudinal testing of hippocampal plasticity reveals the onset and maintenance of endogenous human Aβ-induced synaptic dysfunction in individual freely behaving pre-plaque transgenic rats: rapid reversal by anti-Aβ agents	Qi, Y.	2014	Ireland	In vivo, in vitro	Male TG rats expressing APP751 with Swedish and Indiana mutations under the control of the murine Thy1.2 pro-moter (McGill-R-Thy1-APP) and their age-matched WT.	Amyloidosis	N/A	For in vivo measures, a surgery was performed to place electrodes in the CA1 region. Then the brain was removed and hippocampal samples were taken, electrodes were placed in the cultured neurons. Immunohistochemistry and staining was carried out.	Longitudinal in vivo studies revealed an age-dependent inhibition of long-term potentiation without a change in baseline synaptic transmission. In vitro analyses showed reduction in NMDA receptor-mediated synaptic currents.
Disassembly of Shank and Homer Synaptic Clusters Is Driven by Soluble β-Amyloid1-40 through Divergent NMDAR-Dependent Signalling Pathways	Roselli, F.	2009	Germany	In vitro	Primary cell cultures from cortical tissues from 4-day-old Winstar rats.	Amyloidosis	Homer1b and Shank1	Frontal cortex neurons were cultured and analyses were carried out after 10-13 days after culture. Electron microscopic visualization of cells was performed, as well as Western blot and staining techniques. Synthetic Aβ1-40 was used.	Aβ disrupts Homer and Shank scaffold proteins, decreases postsynaptic density and reduces synaptic availability of mGluR1.
Amyloid-β Acts as a Regulator of Neurotransmitter Release Disrupting the Interaction between Synaptophysin and VAMP2	Russell, CL.	2012	England	In vitro	Sprague Dawley E18 rat embryos.	Amyloidosis	Synaptophysin / VAMP2	Primary cultures of CA3-CA1 hippocampal cells were prepared. Immunocytochemistry and FM1-43FX labeling was performed, proteins were extracted and underwent immunoprecipitation. Electrophysiological recordings were taken. Synthetic Aβ peptides were used.	Aβ disrupts the complex formed between synaptophysin and VAMP2, increasing the number of primed vesicles and exocytosis. Aβ impaired synaptic transmission.

Imbalance in the response of pre and post-synaptic components to amyloidopathy	Stephen, TL.	2019	England	In vivo, in vitro	Adult female of the J20 line (Aβ-overexpressing mice with Swedish and Indiana mutations) and their WT littermates controls.	Amyloidosis	N/A	For in vivo recordings, cranial windows were surgically placed in the somatosensory cortex. Imaging process was performed with a two-photon microscope.	Synaptic turnover is higher in the presence of Aβ and this is accompanied by a reduction in pre but not postsynaptic densities. These findings are independent of plaque proximity.
Fibrillar β-Amyloid Impairs the Late Phase of Long Term Potentiation	Puzzo, D.	2006	United States	In vivo	C57/BL6 male mice.	Amyloidosis	N/A	Electrons were placed in the stratum radiatum of the CA1 region. Fibrillary and oligomeric Aβ was administered.	Aβ impaires the late protein-synthesis dependent phase of LTP.
TRPA1 channels promote astrocytic Ca2+ hyperactivity and synaptic dysfunction mediated by oligomeric forms of amyloid-β peptide	Bosson, A.	2017	France	In vitro	TG mice with the APP/PS1-21 mutation, Swiss mice and WT controls.	Amyloidosis	N/A	Hippocampal cells were cultured. Astrocytes were dyed with Fluo-4 and calcium imaging was performed. Whole-cell recordings were taken and spontaneous excitatory postsynaptic currents were collected. oAβ was applied.	oAβ caused calcium hyperactivity in the astrocytic population. This phenomenon is independent of neuronal activity and is repaired by transient receptor potential A1 (TRPA1) channels blockade. TRPA1 hyperactivity triggers glutamate spontaneuos activity in neurons.
β-amyloid impairs axonal BDNF retrograde trafficking	Poon, WW.	2011	United States	In vitro	Embryos from E18 rat and E16 mice. Mice Tg2576 with the double APP mutation K670N M671L.	Amyloidosis	Brain-derived neurotrophic factor (BDNF)	Hippocampal neurons were cultured in a microfluidic chamber, BDNF-GFP molecules and oAβ were added. Immunocytochemistry analyses and quantification of TrkB, Rab7 y BDNF-GFP were performed.	Aβ affects BDNF-mediated TrkB retrograde trafficking.
Regulation of NMDA receptor trafficking by amyloid-b	Snyder, EM.	2005	United States	In vitro/In vivo	Mice with APP Swedish mutation.	Amyloidosis	N-methyl-D-aspartate receptor (NMDAr)	Hippocampal neurons from the CA1 region were extracted and cultured. NMDA currents were induced with glycine infusion. Patch-clamp recordings and biotinylation procedures were carried out.	Aβ reduced expression of NMDAr by increased endocytosis. This was mediated by activation of the a-7 nicotinic receptor, protein phosphatase 2B (PP2B) and the tyrosine phosphatase STEP. Reducing Aβ by treating neurons with gamma-secretase inhibitor restored surface expression of NMDAr.

Region- and age-dependent reductions of hippocampal long-term potentiation and NMDA to AMPA ratio in a genetic model of Alzheimer's disease	Tozzi, A.	2015	Italy	In vitro	TG mice expressing the Swedish and/or Indiana APP mutation and age-matched WT.	Amyloidosis	rNMDA/rAMPA	Hippocampus was extracted and electrodes were placed in the CA1 region and in the dentate gyrus (DG). Excitatory postsynaptic potentials were induced with different amplitude stimuli.	Presence of oAβ was seen in 2-month old mice in the CA1 region but not in the DG. In 6-month-old mice, the presence of oAβ and plaques was evident and LTP was reduced in CA1 and DG regions. Loss of LTP was linked to reduced NMDA/AMPA ratio. LTP was rescued in the presence of neostigmine in the CA1 region at early stages, memantine restored LTP selectively in DG at later stages.
β-Amyloid-induced Dynamin 1 Degradation Is Mediated by N-Methyl-D-Aspartate Receptors in Hippocampal Neurons	Kelly, BL.	2006	United States	In vitro	Embryonic day 18 rat embryos.	Amyloidosis	Dynamin 1	Primary cultures of hippocampal neurons were performed. Then pre-fibrillary Aβ was added to the culture medium. Cultures were transferred to Inmobilon for immunodetection. Immunocytochemistry and calcium imaging techniques were carried out.	oAβ induced sustained calcium influx, calpain activation, and dynamin 1 degradation.
Time-dependent reversal of synaptic plasticity induced by physiological concentrations of oligomeric Aβ42: an early index of Alzheimer's disease	Koppensteiner, P.	2016	United States	In vivo/ In vitro	C5BLJ/6J mice at postnatal day 0-1.	Amyloidosis	N/A	Primary hippocampal cell cultures were prepared, an infusion of Aβ was added and electrophysiological measures were recorded. In vivo procedures consisted of Aβ infusion and fear conditioning tasks.	Short exposures to Aβ enhanced synaptic plasticity and longer exposures impaired it. The latter was concomitant with an increase in the basal frequency of spontaneous neurotransmitter release, a higher basal number of functional presynaptic release sites, and a redistribution of synaptic proteins including the vesicle-associated proteins synapsin I, synaptophysin, and the postsynaptic glutamate receptor I. These findings were in line with in vivo reports.
First effects of rising amyloid-b in transgenic mouse brain: synaptic transmission and gene expression	Cummings, DM.	2014	England	In vivo	TG mice with APP/PSEN1 mutation and WT controls.	Amyloidosis	N/A	Acute brain slices were prepared and immersed in synthetic LCR, patch-clamp recordings were made and histological evaluation of hippocampal cells was performed. Data was obtained from 3	In the third postnatal week, Aβ peptides were not detectable. At 2 months levels increased 50% and the first changes in synaptic currents were detected. At 4 months, Aβ42:Aβ40 ratio increased and plaques appeared.

								weeks-old, 2 months and 4 months-old mice.	
Caspase Activation and Caspase-Mediated Cleavage of APP Is Associated with Amyloid b-Protein-Induced Synapse Loss in Alzheimer's Disease	Park, G.	2020	United States	In vitro	TG mice with the D664A mutation in APP.	Amyloidosis	Caspase	Hippocampal cell culture, dendritic spines analysis, treatment with gamma-secretase and caspase inhibitors, immunohistological assessment to evaluate caspase activity.	The caspase inhibition model, reduction of Aβ-induced synaptic injury was reported, as well as attenuation of reduction in dendritic spines.
Amyloid-β Induces a Caspase-Mediated Cleavage of P2X4 to Promote Purinotoxicity	Varma, R.	2009	United States	In vitro	Embryonic day 18 Sprague-Dawley rat embryos.	Amyloidosis	Purinergic receptor P2X4	Cell cultures, immunoblot analysis, immunofluorescence microscopy. Neurons were exposed to a lentivirus to induce expression of P2X4, quantification of cell survival was performed, as well as measurements of intracellular calcium, caspase activity and electrophysiological recordings.	Aβ1-42 promoted accumulation of the calcium permeable purinergic P2X4 in neurons. Additionally, it induced a caspase-3 mediated cleavage of the receptor that slowed channel closure times.
Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction	Oddo, S.	2003	United States	In vivo	Triple transgenic mice (Swedish APP mutation, human tau p301L y PS1 m146v) and WT controls.	Amyloidosis	NA	Human APP cDNA harboring the Swedish double mutation was subcloned into exon 3 of the Thy1.2 expression cassette. ELISAs, immunoblot, immunohistochemistry and electrophysiological measures.	Synaptic dysfunction, including LTP impairment, manifests in an age-dependent manner, but before plaques and tangle formation.
Impaired AMPA signaling and cytoskeletal alterations induce early synaptic dysfunction in a mouse model of Alzheimer's disease	Baglietto-Vargas, D.	2018	United States	In vitro	Triple transgenic mice (APP, tau y PS1) and WT controls, of 3 months and 7-8 months old.	Amyloidosis	AMPAr	Cell cultures, immunotherapy, electrophysiological measures, Immunohistochemistry analysis and electron microscopy visualization.	AMPA signaling is impaired early in the disease course in an AD. It is associated with changes in dendritic spine structure and is correlated with the presence of soluble Aβ and tau.

Activation of CaMKIV by soluble amyloid-β 1-42 impedes trafficking of axonal vesicles and impairs activity-dependent synaptogenesis	Park, D.	2017	Korea	In vitro	Embryonic day 18 Sprague-Dawley rat embryos.	Amyloidosis	Ca2+/calmodulin-dependent protein kinase IV (CaMKIV)	Plasmid construction for synapsin 1a and CaMKIV, antibodies selection (phospho-Ser9 –synapsin, synapsin I, phosphoThr196–CaMKIV, CaMKIV, mCherry, b-tubulin , 6E10 , Aβ1–42-1 or Aβ1–42-2, synaptophysin, actin, and glutathione S-transferase), synthetic Aβ1-42 preparation, hippocampal cells cultures, transfection, treatment with gamma-secretase inhibitor, LTP chemically induced, immunocytochemistry measures and microtubule staining, calcium measurements.	Exposure to low concentrations of Aβ1-42 impaired Ca2+ clearance from presynaptic terminals and increased the basal Ca2+ concentration. This caused an increase in the phosphorylation of CaMKIV and its substrate synapsin, which markedly inhibited SV trafficking along axons between synapses. The latter was prevented by an inhibitor of CaMK kinase, by antibodies against Aβ1-42, or by expression of a phosphodeficient synapsin mutant.
Synaptogyrin-3 Mediates Presynaptic Dysfunction Induced by Tau	McInnes J	2018	Belgium	In vitro, In vivo	PS19 mice expressing human TauP301S(1N 4R isoform) under control of the mouse prion promoter, neuromuscular junction experiments in larvae of Drosophila melanogaster, hippocampal human neurons.	Tauopathy	Synaptogyrin-3	Isolation of synaptic vesicles (SV) from human brain tissue and Drosophila brain, purification of human recombinant Tau protein, in vitro essays to evaluate binding of SV-Tau, mass spectrometry to identify SV-related proteins. Then immunofluorescence and electrophysiological recordings were performed in the neuromuscular junction of Drosophila and in hippocampal neurons of mice.	Tau binds to presynaptic vesicles through synaptogyrin-3. In fly and mouse models of Tauopathy, reduction of Synaptogyrin-3 prevents the association of presynaptic Tau with vesicles, alleviates Tau-induced defects in vesicle mobility, and restores neurotransmitter release.
Abnormal tau induces cognitive impairment through two different mechanisms: synaptic dysfunction and neuronal loss	Di J	2016	United States	In vitro, In vivo	Murine model with expression of phospho-tau, cellular culture from neuroblastoma cells of mouse.	Tauopathy	NA	Mouse neuroblastoma cells were cultured and transfected to induce phosphorylation of Tau. Then immunochemistry and immunofluorescence was performed to evaluate neuronal death and synaptic dysfunction. Electron microscopy was used	Low phosphorylated tau levels resulted in significant cognitive deficits, decrease in the number of synapses, and reduction of synaptic proteins. Induction tau triggered neuronal death, astrocytosis, and loss of the processes in CA1.

								to assess synapses length and postsynaptic density. Mice of 15–24 months were subjected to memory and learning tasks.	
Reduced gliotransmitter release from astrocytes mediates tau-induced synaptic dysfunction in cultured hippocampal neurons	Piacentini R	2017	Italy	In vitro	WT E18 C57/bl6 mice	Tauopathy	Gliotransmitters	Primary cultures of hippocampal neurons and astrocytes, recombinant tau protein and human AD tau preparation and oligomerization, assessment of tau uploading, confocal calcium imaging, high performance liquid chromatography (HPLC) measurements, whole cell patch-clamp recordings, immunocytochemistry and western blot.	Extracellular tau oligomers are abundantly and rapidly accumulated in astrocytes where they disrupt intracellular Ca2+ signaling and release of gliotransmitters, especially ATP. Consequently, synaptic vesicle release, the expression of pre- and post-synaptic proteins, and miniature excitatory postsynaptic currents frequency and amplitude were reduced in neighboring neurons. Tau uploading from astrocytes required APP.
Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice	Lasagna-Reeves CA	2011	United States	In vitro, In vivo	C57BL/6 mice	Tauopathy	Synaptophysin, septin-11, mitochondrial complex.	Tau subcortical stereotaxic injection was performed in mice and then object recognition tasks were performed. Hippocampal neurons samples were isolated and western blot was carried out to identify proteins related to synaptic and mitochondrial function. To assess neuronal damage and neurodegeneration immunohistochemical and microscopic analysis was completed.	Tau oligomers impaired memory consolidation, whereas tau fibrils and monomers did not. Additionally, tau oligomers induced synaptic dysfunction by reducing the levels of synaptic vesicle-associated proteins synaptophysin and septin-11. Tau oligomers produced mitochondrial dysfunction and activated caspase-9,
Extracellular truncated tau causes early presynaptic dysfunction associated with Alzheimer's disease and other tauopathies	Florenzano F	2017	Italy	In vitro	Wistar rats	Tauopathy	NA	Preparation of tau peptides, purification of synaptosomes from rats, intracellular calcium imaging, immunofluorescence, western blot and densitometry analysis.	Low levels of tau protein accumulate at presynaptic terminals and affect glutamate transmission. Neuritic dystrophy, microtubules breakdown, deregulation in presynaptic proteins and loss of mitochondria was only seen

									with prolonged exposures to tau protein.
Phosphorylation in two discrete tau domains regulates a stepwise process leading to postsynaptic dysfunction	Teracski s PJ	2021	United States	In vitro	Sprague Dawley rats	Tauopathy	NA	Primary hippocampal neuron culture, transfection with human tau. Electrophysiological measurements of excitatory postsynaptic currents, microscopic imaging to evaluate dendritic spines and immunocytochemistry analysis.	Tau phosphorylation in the C-terminal domains results in mislocalization to dendritic spines. When phosphorylated in the N-terminal domain, reduction of functional AMPA receptors was reported.
Reactive Oxygen Species-Mediated Loss of Synaptic Akt1 Signaling Leads to Deficient Activity-Dependent Protein Translation Early in Alzheimer's Disease	Ahmad, F.	2017	India	In vivo, in vitro	Mice with the APP/PSEN1mutation divided in three groups by age: 1-1.5, 3-4, 9-12 months old and WT controls.	Inflammation	Akt1	Primary antibodies against pAkt1 y Akt1 were prepared. Synaptoneurosomes were prepared tissue from mice and postmortem human brains, then immunoblotting and immunoprecipitation of Akt1 was performed. Then primary neuronal cultures were established and assays to evaluate ROS and Akt1 expression were performed.	It was demonstrated that ROS-mediated oxidative modification of Akt1 contributes to synaptic dysfunction in AD, seen as loss of activity-dependent protein translation, a process essential for synaptic plasticity.
PGE2-EP3 signaling pathway impairs hippocampal presynaptic long-term plasticity in a mouse model of Alzheimer's disease	Maingret, V.	2017	France	In vitro	Male mice with the APP(Swe)/PS1 mutation and paired controls.	Inflammation	PGE2-EP3	Acute hippocampal slices were transferred into a recording chamber to record electrophysiological variables. Then RNA isolation, reverse transcription, and quantitative PCR was performed, as well as immunohistochemistry analyses.	PGE2 had no effect on either basal transmission or short-term plasticity. But it strongly impaired presynaptic Mf-CA3 long-term potentiation (LTP) by acting on PGE2 receptor 3 (EP3) receptors.

6. OTRAS PUBLICACIONES Y TRABAJOS COLABORATIVOS.

6.1. Publicaciones relacionadas con el desarrollo de la tesis.

Publicación y contexto: Durante el desarrollo del proyecto de Doctorado se realizó un trabajo colaborativo con un estudiante de maestría y una estudiante de Doctorado en Bioingeniería, con el objetivo de explorar el entrenamiento de máquina por inteligencia artificial para clasificar los sujetos portadores de los sujetos no portadores de la variante PSEN1-E280A. Se trabajó con la misma población de estudio con la visita inicial de este protocolo de investigación. Se obtuvo una precisión de discriminación de 83% entre estas dos poblaciones.

"Automatic Classification of subjects of the PSEN1-E280A Family at risk of developing Alzheimer's Disease using Machine Learning and Resting State electroencephalography."

Antecedentes: El estudio de portadores de variantes genéticas brinda la oportunidad de identificar cambios neurofisiológicos en etapas preclínicas. La electroencefalografía (EEG) es una técnica mínimamente invasiva y de bajo costo que, junto con el aprendizaje automático, brinda la posibilidad de construir sistemas que clasifican a los sujetos que pueden desarrollar la enfermedad de Alzheimer (EA).

Objetivo: El objetivo de este artículo es evaluar la capacidad de las técnicas de aprendizaje de máquina para clasificar los No Portadores sanos (NonCr) de los Portadores Asintomáticos (ACr) de la variante PSEN1-E280A para la enfermedad de Alzheimer autosómica dominante (ADAD), utilizando características espectrales de Canales de EEG y componentes independientes (IC) relacionados con el cerebro obtenidos mediante análisis de componentes independientes (ICA).

Métodos: se registró EEG en 27 ACr y 33 NonCr. Se aplicó un análisis de significancia estadística a la información espectral de los canales y el grupo ICA (gICA), y también se aplicó un análisis de tomografía estandarizada de baja resolución (sLORETA) sobre los IC. Se evaluaron estrategias para la selección y clasificación de características como Chi-cuadrado, información mutua y máquinas de vectores de soporte (SVM) sobre el conjunto de datos.

Resultados: Se obtuvo una precisión de prueba de hasta el 83% al implementar un SVM con características espectrales derivadas de gICA. Los principales hallazgos están relacionados con los ritmos theta y beta, generados en las regiones parietal y occipital, como el precúneo y el lóbulo parietal superior.

Conclusión: Se pueden entrenar modelos prometedores para la clasificación de la EA preclínica por la variante PSEN-1-E280A utilizando características espectrales, y se destaca la importancia de la banda beta y la región de la precuña en estadios asintomáticos, lo que abre la posibilidad de su uso como herramienta de tamizaje.

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6.2. Publicaciones relacionadas con búsqueda de Biomarcadores en EA

Contexto: Se realizaron colaboraciones internacionales para estudio de pacientes con enfermedad de Alzheimer autosómico dominante u otras enfermedades neurodegenerativas. Todos ellos encaminados en la búsqueda de biomarcadores tempranos de EA. A continuación, registro los títulos de estas publicaciones:

- Guzmán-Vélez, Edmarie; … **Aguillon David.** et al. (2021). **Associations between plasma neurofilament light, in vivo brain pathology, and cognition in non-demented individuals with autosomal dominant Alzheimer's disease**. Alzheimer's & Dementia. 17. 10.1002/alz.12248.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Sanchez, Justin; … **Aguillon David**. et al. (2021). **Longitudinal amyloid and tau accumulation in autosomal dominant Alzheimer 's disease: findings from the Colombia-Boston (COLBOS) biomarker study.** Alzheimer 's Research & Therapy. 13. 10.1186/s13195-020-00765-5.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Sepúlveda-Falla D, Sanchez JS, … **Aguillon D**, et al. **Distinct tau neuropathology and cellular profiles of an APOE3 Christchurch homozygote protected against autosomal dominant Alzheimer 's dementia.** Acta Neuropathol. 2022 Sep;144(3):589-601. doi: 10.1007/s00401-022-02467-8. Epub 2022 Jul 15. PMID: 35838824; PMCID: PMC9381462.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- J. Nicholas Cochran*, Juliana Acosta-Uribe*, … **David Aguillón** et al. **Genetic Associations with Age at Dementia Onset in the PSEN1 E280A Colombian Kindred.** Paper accepted in Alzheimer's & Dementia Ref. No.: ADJ-D-22-01040R1 Febrero 2023.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Villar-Vesga J, Henao-Restrepo J, … **Aguillon D**, et al. **Differential Profile of Systemic Extracellular Vesicles From Sporadic and Familial Alzheimer's Disease Leads to Neuroglial and Endothelial Cell Degeneration**. Front Aging Neurosci. 2020 Nov 11;12:587989. doi: 10.3389/fnagi.2020.587989. PMID: 33281599; PMCID: PMC7705379.
  Rol en la investigación: Trabajo de campo

- Ramirez Aguilar L, Acosta-Uribe J, … **Aguillon D**, et al. **Genetic origin of a large family with a novel PSEN1 mutation (Ile416Thr).** Alzheimers Dement. 2019 May;15(5):709-719. doi: 10.1016/j.jalz.2018.12.010. Epub 2019 Feb 10. PMID: 30745123; PMCID: PMC6511480.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Vallejo-Diez S, Fleischer A, … **Aguillon D**, et al. **Generation of one iPSC line (IMEDEAi006-A) from an early-onset familial Alzheimer's Disease (fAD) patient carrying the E280A mutation in the PSEN1 gene.** Stem Cell Res. 2019 May;37:101440. doi: 10.1016/j.scr.2019.101440. Epub 2019 Apr 15. PMID: 31026686.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Arboleda-Velasquez JF, Lopera F, … **Aguillon D**, et al. **Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report.** Nat Med. 2019 Nov;25(11):1680-1683. doi: 10.1038/s41591-019-0611-3. Epub 2019 Nov 4. PMID: 31686034; PMCID: PMC6898984.
  Rol en la investigación: Trabajo de campo y redacción de artículo científico.

- Llibre-Guerra JJ, Behrens MI, … **Aguillón D**, et al. **Frontotemporal Dementias in Latin America: History, Epidemiology, Genetics, and Clinical Research.** Front Neurol. 2021 Sep 6;12:710332. doi: 10.3389/fneur.2021.710332. PMID: 34552552; PMCID: PMC8450529.
  Rol en la investigación: Recolección y análisis de datos en Colombia, redacción de artículo científico.

6.3. Otras publicaciones no relacionadas con Biomarcadores

Contexto: Se realizaron colaboraciones nacionales para estudio de pacientes con enfermedades neurodegenerativas. A continuación, registro los títulos de estas publicaciones:

- **Aguillon D**, Vasquez D, et al. **Ataxia with Ocular Apraxia Type 1 (AOA1) (APTX, W279* Mutation): Neurological, Neuropsychological, and Molecular Outlining of a Heterogenous Phenotype in Four Colombian Siblings.** Mol Neurobiol. 2022 Jun;59(6):3859. doi: 10.1007/s12035-022-02874-8. Erratum for: Mol Neurobiol. 2022 Jun;59(6):3845-3858. PMID: 35585447.

- Ramos C, Villalba C, … **Aguillón D**, et al. **Substance Use-Related Cognitive Decline in Families with Autosomal Dominant Alzheimer's Disease: A Cohort Study.** J Alzheimers Dis. 2022;85(4):1423-1439. doi: 10.3233/JAD-215169. PMID: 34924385.

- Jaramillo-Jimenez A, Bocanegra Y, … **Aguillón DF**, et al. **Subjective Cognitive and Communicative Complaints and Health-Related Quality of Life in Parkinson's Disease with and without Mild Cognitive Impairment.** Rev Colomb Psiquiatr (Engl Ed). 2021 Sep 3:S0034-7450(21)00134-7. English, Spanish. doi: 10.1016/j.rcp.2021.07.005. Epub ahead of print. PMID: 34489098.

- Vasquez D, … **Aguillon D**, et al. **Quality of life in early-onset Alzheimer's disease due to a PSEN1-E280A mutation**. Neurol Sci. 2021 Nov;42(11):4637-4645. doi: 10.1007/s10072-021-05136-y. Epub 2021 Mar 5. PMID: 33675003.

- M. Gómez-Vega, … D. Aguillon, et al. (2021): **Nutritional assessment in patients with early-onset Autosomal Dominant Alzheimer's Disease due to PSEN1- E280A genetic variant: a cross-sectional study.** The Journal of Aging and Lifestyle (JARLife). http://dx.doi.org/10.14283/jarlife.2021.6

- Garcia-Cifuentes E, … **Aguillon D**, et al. **The Role of Gait Speed in Dementia: A Secondary Analysis from the SABE Colombia Study**. Dement Geriatr Cogn Disord. 2020;49(6):565-572. doi: 10.1159/000510494. Epub 2020 Nov 18. PMID: 33207340.

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7. CONCLUSIONES GENERALES, IMPLICACIONES CLÍNICAS Y TEÓRICAS.

La presente tesis doctoral tuvo como objetivo general analizar los cambios en la actividad eléctrica cerebral como medida neurofisiológica de disfunción sináptica en un seguimiento longitudinal, usando como modelo una población con la variante genética PSEN1-E280A para la enfermedad de Alzheimer autosómica dominante.

Para llevar a cabo este objetivo, fueron desarrollados cinco estudios orientados a:

- Describir las poblaciones con riesgo genético de causalidad para Demencia en Latinoamérica y Colombia como modelos ideales de estudio de disfunción sináptica
- Describir las variantes genéticas patogénicas en Latinoamérica de enfermedad de Alzheimer y Demencia Frontotemporal y su ancestría.
- Evaluar una asociación entre los niveles plasmáticos basales de p-tau217 con marcadores posteriores de patología cerebral in vivo medidos por PET y el rendimiento cognitivo.
- Evaluar el comportamiento en un seguimiento longitudinal de medidas de potencia espectral y reactividad Alpha/Theta en población con la variante genética PSEN1-E280A para ADAD.
- Realizar una revisión sistemática de la literatura sobre disfunción sináptica y electroencefalograma en población con enfermedad de Alzheimer como base para el modelo de disfunción sináptica.

En cada uno de los artículos que se incluyeron en la tesis doctoral se describe una discusión detallada de los resultados encontrados. A continuación, se presentan las conclusiones generales de los estudios, así como las implicaciones clínicas y teóricas.

El primer estudio permitió conocer las variantes genéticas que se han descrito en Latinoamérica tanto para enfermedad de Alzheimer como para Demencia

Frontotemporal (DFT). En el caso específico para enfermedad de Alzheimer y de acuerdo con la literatura, la mayor proporción de casos se encuentran con variantes en PSEN1, se reportaron 9 variantes patogénicas, 1 no patogénica y 1 de significado incierto. De estas 9 variantes para el momento de la publicación, en Colombia sólo se habían reportado 3 variantes genéticas: PSEN1-E280A en el año 1995 en Antioquia(81), PSEN1-117A en el Valle del Cauca en el año 2004 (82) y PSEN1-I416T en 2019 en Antioquia (23). En cuanto al fenotipo clínico, la mayoría de estas familias son de presentación amnésica, sin embargo, en familias en México se han descrito familias con fenotipo caracterizado por paraparesia espástica previo a los síntomas cognitivos. En los últimos reportes de prevalencia e incidencia global de demencia precoz, no existen reportes de variantes genéticas en Colombia, pero sí reportes de demencia precoz en Argentina, Brasil y Venezuela (9,10). Se considera que existe un subregistro de la población con demencia precoz en Latinoamérica y que las variantes genéticas que se han identificado en otros países podrían estar presentes también en Colombia por fenómenos de migración y mestizaje desde hace varios años.

Esta revisión ayudó a demostrar la necesidad de realizar una búsqueda más exhaustiva de genes de causalidad en diferentes enfermedades neurodegenerativas como la enfermedad de Alzheimer y la demencia Frontotemporal en Colombia. En este sentido, el segundo estudio presentado en esta tesis analiza 900 genomas de sujetos con demencia de inicio precoz o demencia con agregación familiar en búsqueda de genes candidatos para EA y DFT. Se identificaron 21 variantes patogénicas, 11 de ellas en el gen de PSEN1 con fenotipo clínico de enfermedad de Alzheimer. Estas variantes identificadas tenían las 3 ascendencias continentales (amerindio, europeo, africano) casi todas atribuidas a efectos fundadores. Se postulan en este artículo diferentes hipótesis sobre la presencia de estas variantes raras en la población colombiana, entre ellas, el aislamiento geográfico de estas poblaciones y el posible efecto antimicrobiano del Aβ que podría haberlos protegido de los diferentes cuellos de botella como enfermedades infecciosas que diezmaron la población hace varios años (83). Con relación al fenotipo clínico de estas variantes en PSEN1, se trata de pacientes con edades de inicio desde los 32 años (PSEN1-P117A) hasta los 57 años (PSEN1-T119I), y en el caso de los pacientes con la variante PSEN1-E280A se ha descrito una edad promedio de 44 años (43-45) para el inicio del DCL y 49 años (49-50) para el inicio de la demencia(26), todos ellos con un perfil amnésico progresivo

excepto en la variante PSEN1-P284L que tiene una presentación atípica con paraparesia espástica previo al inicio de síntomas cognitivos. La importancia de este descubrimiento en Colombia radica en la posibilidad de realizar estudios de investigación con biomarcadores en familias con genes de causalidad para EA, asimismo, evaluar la variabilidad de estos biomarcadores o del curso fisiopatológico de la enfermedad. Las poblaciones con variantes genéticas causales de EA se convierten en un modelo ideal de estudio para biomarcadores que permitan un diagnóstico temprano y oportuno, así como poder probar terapias modificadoras del curso de la enfermedad en el contexto de ensayos clínicos de prevención primaria o secundaria.

Se tomó como modelo de estudio para esta tesis a la población PSEN1-E280A por ser una población extensa con un seguimiento por más de 30 años por parte del Grupo de Neurociencias de Antioquia, lo que ha permitido conocer los diferentes etapas preclínicas y su comportamiento con diferentes biomarcadores (26). Para profundizar un poco en este punto, se realizó un trabajo colaborativo con el objetivo de analizar las tasas de progresión de diferentes biomarcadores en neuroimágenes funcionales comparado con otros biomarcadores cognitivos. Se encontró una acumulación esperada para pacientes con ADAD, acumulación de proteína Aβ 16 años antes del inicio de síntomas, seguido de tau en la corteza entorrinal (CE) 9 años antes del inicio de síntomas, tau neocortical y atrofia del hipocampo 6 años antes y deterioro cognitivo 4 años antes de la edad de inicio del DCL. Las tasas de acumulación de tau entre los portadores fueron más rápidas en la corteza parietal (~ 9% / año). Se destaca la importancia de tau en la corteza entorrinal como biomarcador temprano y un vínculo potencial entre la carga de Aβ y la acumulación neocortical de tau en ADAD (84). Este hallazgo resalta la importancia de la precuña como un sitio temprano y clave de acumulación de Aβ, Tau y neurodegeneración en esta población. Se han realizado otros estudios transversales en esta misma población en relación con la precuña encontrando menor deactivación en los portadores de PSEN1-E280A en tareas de memoria mediante fMRI (85,86), hipometabolismo mediante PET-FDG, disminución del grosor cortical medido mediante MRI (87) y aumento de la conectividad en tareas de procesamiento visual mediante EEG (88).

Este tipo de biomarcadores in vivo han mejorado el estudio, diagnóstico y seguimiento de la EA (89), sin embargo, se ha planteado una necesidad prioritaria de biomarcadores en EA que sean sensibles, costo-efectivos y mínimamente invasivos. Las mediciones plasmáticas de tau fosforilada (p-tau) son menos costosas e invasivas que el PET o la punción lumbar, y se ha evidenciado un aumento en sus concentraciones plasmáticas desde estadíos tempranos de la enfermedad y que permite diferenciar entre la EA y otras enfermedades neurodegenerativas incluyendo taupatías (90,91). En estudios previos en la población con variante genética PSEN1-E280A se ha demostrado que p-tau217 permite discriminar portadores asintomáticos de no portadores 20 años antes de la edad de inicio estimada para esta población (92). El tercer estudio de esta tesis demostró una asociación entre las concentraciones plasmáticas de p-tau217 y los hallazgos subsecuentes de patología in vivo en PET amiloide, PET Tau y bajo desempeño en tareas de memoria 7.61 años después de haber tomado la muestra de plasma. En un análisis regional con PET amiloide y PET Tau se encontró asociación con 3 regiones anatómicas claves: corteza temporal inferior, corteza entorrinal y precuña. Esta última, como mencionamos previamente, se ha reportado como una región tempranamente afectada por patología asociada a EA (84,93) y resalta el interés de esta región en el curso clínico de la enfermedad y su interacción con los diferentes biomarcadores. Otros autores han descrito asociación entre p-tau217 y patología in vivo en PET amiloide y Tau en EA esporádica, sin embargo, son asociaciones concurrentes o con 1 a 2 años de intervalo entre la muestra de plasma y las neuroimágenes funcionales (15,35); estos resultados respaldan a p-tau217 como un potencial biomarcador mínimamente invasivo, con un potencial diagnóstico y pronóstico de EA.

Este hallazgo en p-tau217 fortalece la hipótesis con relación al inicio fisiopatológico de la EA, ya que inicialmente se ha considerado las formas poliméricas de Aβ y Tau como las responsables del daño y muerte neuronal, sin embargo, la presencia de estos biomarcadores periféricos como p-tau217 o neurofilamentos de cadena liviana (NFL) (94) en etapas más tempranas que los hallazgos en LCR o PET, retoman la discusión del rol del efecto de los oligómeros de Aβ y los pre-filamentos de tau en el proceso de disfunción sináptica y citotoxicidad (40). Se realizó una revisión sistemática para analizar el rol de la disfunción sináptica en EA y los productos intermedios de amiloidosis y tau en esta patología. Se describe la disfunción sináptica

como un evento fisiopatológico que altera las conexiones neuronales a múltiples escalas: Molecular, celular, redes cerebrales, corteza cerebral, entre otros (12). Existen diferentes mecanismos que interactúan para desencadenar alteraciones en la homeostasis de la función sináptica, entre ellos los más destacados son la amiloidosis, taupatía e inflamación (32) . En los últimos años se ha propuesto la disfunción sináptica como un evento que ocurre temprano en el proceso fisiopatológico de la EA, y una vez instaurado permanece presente de manera transversal durante las diferentes etapas de la enfermedad. Glutamato, GABA y acetilcolina son neurotransmisores que generan alteración en la fisiopatología de la EA a través de alteraciones en el calcio favoreciendo la disfunción en la actividad eléctrica cerebral, lo que conlleva a disfunción de las redes cerebrales. En modelos murinos se ha demostrado alteración de las redes excitatorias glutamatérgicas y la pérdida sináptica asociada, lo que provoca patrones aberrantes de actividad eléctrica neuronal de sincronización entre las sinapsis glutamatérgicas funcionantes, en vez de aumento de la actividad excitatoria. Este fenómeno de sincronización puede a su vez generar actividad eléctrica epileptiforme caracterizada por la presencia de *spike and sharp waves* (45). Esto ha sido previamente evidenciado en estudios en humanos con electroencefalograma (EEG) (68).

El EEG se ha utilizado en los últimos años como una alternativa rentable, portátil y no invasiva para el estudio de biomarcadores en la enfermedad de Alzheimer (95,96). Consideramos que el EEG podría ser una herramienta que permitiría rastrear la progresión de la enfermedad teniendo en consideración el proceso fisiopatológico subyacente de disfunción sináptica a lo largo de la enfermedad en etapas preclínicas y clínicas. Diferentes estudios en EEG en reposo han descrito diferencias en personas con EA y controles; en estadios clínicos se ha descrito un aumento de las bandas de frecuencias lentas (Delta y Theta) y un enlentecimiento de las bandas de frecuencias rápidas (Alfa, Beta y Gamma) (95). Por el contrario, en estadios preclínicos de la enfermedad, se ha descrito un fenómeno opuesto, disminución de la densidad espectral en bandas de frecuencia lenta y aumento en bandas de frecuencia rápida (97). En un estudio transversal con esta misma población, se encontró una precisión del 83% utilizando aprendizaje de máquina con características espectrales derivadas de gICA (siglas en inglés *Group independent component analysis)*. Los principales hallazgos se encontraron con las bandas de frecuencia espectral theta y beta,

generados en regiones como la precuña y el lóbulo parietal superior (98). El cuarto artículo de esta tesis tenía como objetivo realizar un análisis longitudinal con EEG en reposo en población asintomática portadora y no portadora de la variante genética PSEN1-E280A. Este sería el primer estudio longitudinal utilizando esta herramienta en esta población.

En el análisis de las bandas de frecuencia espectral por medio de qEEG en estado de reposo en 2 registros con 1 año diferencia entre ambas visitas, tomando como referencia los componentes con origen neural definidos por gICA y el uso de ICLabel; se encontró que las bandas de frecuencia Alfa1 y Alfa2 no presentaron cambios significativos en el tiempo, la banda de frecuencia Delta presentó diferencias estadísticamente significativas en 6 de los 8 componentes analizados pero en los gráficos de distribución por deciles presentaba pendiente no lineales. Finalmente, la banda de frecuencia Beta3 en el componente 20 y Beta2 en el componente 22 se encontraron diferencias estadísticamente significativas, pero con baja precisión explicado por la distribución de los datos en los gráficos de distribución por deciles, con una pendiente con poca inclinación, lo que indica una modesta fuerza en la diferencia entre ambos grupos con amplios intervalos de confianza. En otros estudios longitudinales con población con deterioro cognitivo subjetivo y amiloide positivo medidos por PET, encontraron una mayor potencia theta en aquellos sujetos que progresaron (media 0,13 [DE 0,05]) frente a sujetos que no progresaron (media 0,10 [DE 0,03]; $p < 0,01$) (99); otro estudio con adultos menores de 65 años con amiloide positivo, encontró una mayor potencia theta relativa que se relacionaba con la progresión clínica de estos individuos (100). Sin embargo, se encontraron diferencias en los rangos de las bandas de frecuencia espectral utilizados por estos dos estudios comparado con las bandas de frecuencia recomendados por la IFCN (International Federation of Clinical Neurophysiology) en 2020 y utilizados en nuestra investigación (101), en este sentido, cambios reportados en la banda de frecuencia Delta en el grupo de portadores asintomáticos toman relevancia y serían congruentes con los reportados en la literatura.

La banda de frecuencia Beta es un potencial marcador neurofisiológico que en estadios preclínicos de ADAD muestra diferencias estadísticamente significativas entre portadores asintomáticos y no portadores. Además, esta señal está relacionada

con componentes cuyo origen se estima en regiones posteriores (Componente 22 y Componente 25), lo que pone de manifiesto la importancia de los hallazgos previos en la precuña. Se ha propuesto que las regiones posteriores del cerebro son una de las primeras áreas con compromiso funcional y patológico en las fases preclínicas de la EA (102). Esto se puede soportar por otras investigaciones que han reportado cambios en la precuña en esta misma población con diferentes biomarcadores como RMf (85), PET FDG, MRI (87) y EEG (88).

Finalmente, podríamos considerar la identificación de la banda de frecuencia Beta como un potencial marcador neurofisiológico con una media de aparición a los 30.4 años en la población con variante genética PSEN1-E280A, 2 años posterior al hallazgo en PET amiloide y 2 años antes de biomarcador cognitivo encontrado en esta población con la evocación de la lista de memoria de palabras del CERAD (103). La baja precisión de los resultados se puede explicar por el pequeño tamaño de la muestra, la pérdida del seguimiento (atribuible a los problemas de restricciones de asistencia generados por la pandemia), al corto período de seguimiento (un año); en fin, a otros diferentes factores intervinientes, como la edad media de la población, es posible que en edades más avanzadas y quizás en relación con el inicio de la taupatía el proceso de disfunción sináptica sea más agresivo y su identificación en el EEG tenga mayor precisión. Debemos considerar también la variabilidad intrínseca que puede tener esta población por ejemplo por asociación con otros factores genéticos adicionales y la edad de inicio de la enfermedad como los reportados por Cochran y colaboradores (104), las diferencias en sexo reportadas en diferentes biomarcadores (105) o la presencia de variantes protectoras que podrían alterar, retrasar o enlentecer el proceso fisiopatológico de la enfermedad (106). Se requieren futuras investigaciones con una muestra mayor y con seguimientos más prolongados para evaluar los cambios en la progresión de la enfermedad y comparar los resultados con los instrumentos de cribado disponibles para esta patología.

CONCLUSIONES GENERALES

Esta tesis permite concluir lo siguiente:

- Las formas genéticas autosómicas dominantes son un modelo ideal de estudio de EA para la búsqueda de biomarcadores que permitan un diagnóstico temprano o predictivo de la enfermedad.
- Existe un subregistro de poblaciones con variantes genéticas en Colombia y Latinoamérica.
- La disfunción sináptica es un proceso fisiopatológico transversal en la enfermedad de Alzheimer que involucra diferentes niveles moleculares y celulares.
- La disfunción sináptica es un fenómeno fisiopatológico temprano en la EA relacionado con formas solubles de AB y Tau.
- Biomarcadores periféricos como ptau-217 en plasma permiten predecir la patología in vivo de personas con PSEN1-E280A.
- EEG es una herramienta portable, no invasiva y costo-efectiva que permite establecer diferencias estadísticamente significativas desde los 30.4 años entre portadores y no portadores de la variante PSEN1-E280A a través de qEEG en estado de reposo con un 83% de capacidad de clasificación.
- Banda de frecuencia espectral Beta pudiera ser considerado como un marcador neurofisiológico precoz en etapas preclínicas del ADAD porque establece diferencias significativas entre portadores y no portadores, aunque con baja precisión.
- Predecimos que la precisión de este marcador neurofisiológico podría aumentar con la edad a medida que el sujeto se acerca a la edad de los 38 años cuando se inicia el pre-deterioro cognitivo leve sintomático asociado al inicio de taupatía y neurodegeneración.
- Varios estudios son congruentes en hallazgos patológicos con diferentes biomarcadores en la precuña como un sitio clave en las fases iniciales de la EA.

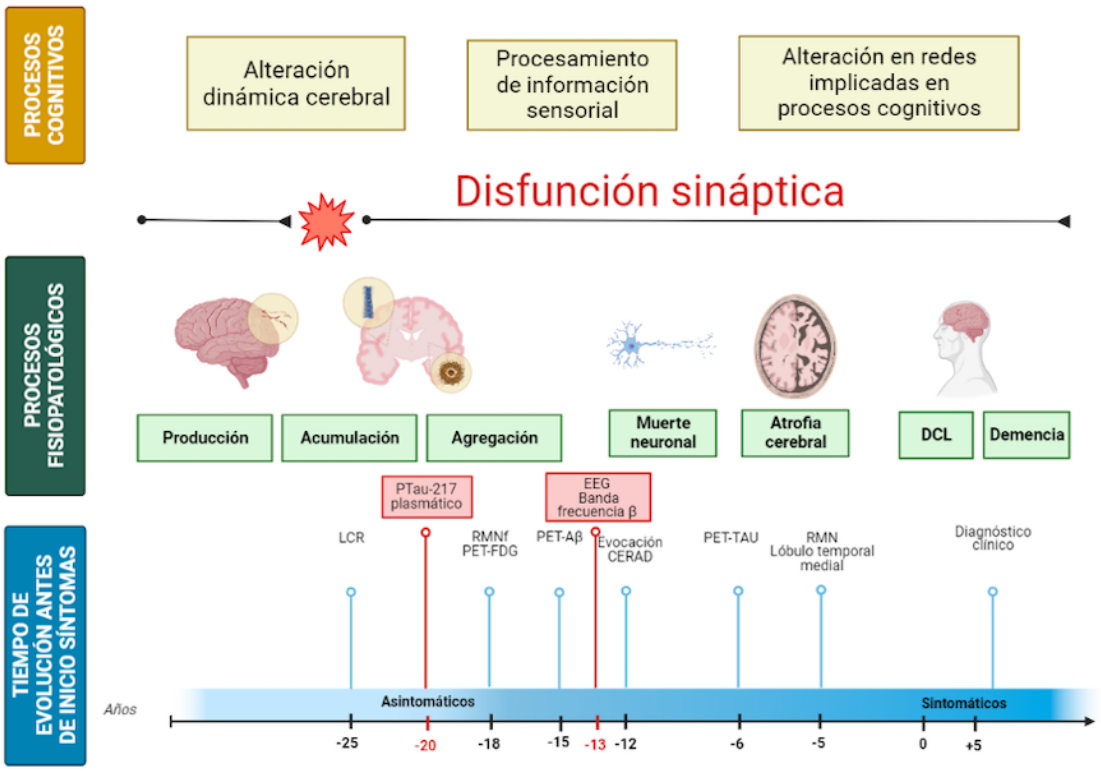

Figura 4: Modelo Fisiopatológico de disfunción sináptica asociado a enfermedad de Alzheimer autosómico dominante.

8. LIMITACIONES Y PERSPECTIVAS DE INVESTIGACIÓN

1. Los resultados de esta investigación deben ser asumidos con cautela porque sólo serían aplicables a esta población con la variante genética PSEN1-E280A para ADAD. Sería recomendable en futuras investigaciones incluir poblaciones con otras variantes patogénicas para EA y posteriormente incluir población con riesgo para EA esporádico.
2. Se tuvo una pérdida del 11.1% en la población evaluada en este proyecto por diferentes motivos: adherencia al protocolo por disconfort con la realización del EEG, viajes o dificultades laborales que limitaban la asistencia a las visitas, comorbilidades en algunos sujetos como cáncer, pandemia por Covid-19 que no permitió atender de forma oportuna a las citas. Este trabajo a pesar de tener un número mayor de sujetos comparado con otros estudios con EEG en esta misma población, el total de la muestra era pequeño lo que limita el poder estadístico de los análisis. Futuros estudios deberían incluir un tamaño muestral mucho más grande especialmente del grupo de interés (portadores asintomáticos).
3. El estudio de p-tau217 se realizó con muestras en plasma que se habían tomado 7.6 años antes de realizar los estudios en PET o estudios cognitivos; no fue posible realizar nuestra investigación con EEG con los mismos participantes, lo que limita la comparación entre estas dos métricas (p-tau217 vs Beta3 en EEG). Estudios futuros podrían comparar estos dos potenciales marcadores de progresión de la EA.
4. El seguimiento con EEG fue realizado a los participantes solo por 1 año, es un tiempo corto en el cual ninguno de los participantes progresó a un estadio clínico de enfermedad, y limita el alcance de los resultados. Estudios futuros deberían considerar realizar seguimiento a poblaciones que tengan registros previos de EEG y puedan tener un seguimiento mucho más amplio y que permita rastrear con mayor certeza los cambios fisiopatológicos derivados de la disfunción sináptica.

5. Estudios futuros podrían incluir población en un espectro de edad más amplio que logre abarcar población asintomática cercana a los hallazgos patológicos en PET Tau (mayores de 36 años) y evaluar este marcador neurofisiológico (Beta3) en este grupo etario. Consideramos que la disfunción sináptica será mucho más severa en esta etapa de la enfermedad preclínica y los cambios en el EEG en esta banda de frecuencia deben ser más marcados.

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