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SHORT REPORT

Distribution of *APOE* polymorphism in the ''Paisa'' population from northwest Colombia (Antioquia)

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Abstract

Background: The apolipoprotein E (*APOE*) gene plays a pivotal role in cholesterol metabolism. Since the discovery of the *APOE*2* and *APOE*4* as the major susceptibility alleles for several diseases including dyslipidemia, atherosclerosis, coronary heart disease, late-onset and early Alzheimer's disease, the *APOE* genotype might be considered as a potential predictive factor for both epidemiological research and diagnosis.
Aim: The aim of this study is to report on the polymorphism of the *APOE* gene in the ''Paisa'' population from northwest Colombia (Antioquia) to obtain a population baseline of the existing variation in this locus.
Method: One thousand and one healthy voluntaries were genotyped for the *APOE* polymorphism using polymerase chain reaction–restriction fragment length polymorphism technique.
Results: The *APOE*3/*3* genotype presented the highest frequency (66.33%) and the *APOE*4/*4* had the lowest frequency (1.89%). Genotype frequencies comply with Hardy–Weinberg expectations. Allele frequencies obtained for *APOE*2*, *APOE*3* and *APOE*4* were 0.075 ± 0.005 (95% CI = 0.063–0.086), 0.814 ± 0.009 (0.797–0.831) and 0.111 ± 0.007 (0.098–0.125), respectively.
Conclusion: Although globally the high-to-low *APOE* frequency follows the *E*3 > E*4 > E*2* trend, the present *APOE* frequency data is in disagreement with some reports from South-American countries.

Keywords

APOE, apolipoprotein, genetic distance, paisa, polymorphism

History

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Introduction

Apolipoprotein E gene (*APOE*, OMIM #107741) and its protein product (APOE, 34 kDa, 299 amino acids) play a pivotal role in cholesterol metabolism associated with a number of plasma proteins, such as very-low density lipoprotein and high density lipoprotein chylomicrons. Located in chromosome 19q13.2, *APOE* is polymorphic for cysteine (TGC)/arginine (CGC) interchange at codons 112 and 158 that determine three codominant alleles, designated *APOE*2* (codons TGC^{112}/TGC^{158}), *APOE*3* (codons TGC^{112}/CGC^{158}) and *APOE*4* (codons CGC^{112}/CGC^{158}). Since the discovery of the *APOE*4* as the major susceptibility allele for several diseases including dyslipidemia, atherosclerosis, coronary heart disease, early-onset and late-onset Alzheimer's disease (EO/LO AD) (Liu et al., 2013), the *APOE* genotype might be considered as a potential predictive factor for both epidemiological research and diagnosis. At present, there are no available *APOE* population-based registries in Antioquia.

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The Antioquia region, located in northwest Colombia, has 5 682 276 inhabitants. Family Historical Record studies suggest that this population was established in the 16–17th century by the admixture of a reduced number of Amerindians, European and African individuals and subsequently expanded in relative isolation until the late 19th century (Bedoya et al., 2006; Carvajal-Carmona et al., 2003). Because of this particular demographic characteristic, this population is nowadays known as the ''Paisa'' community and it is considered a genetic population isolate (Arcos-Burgos & Muenke, 2002; Service et al., 2006). In this study, we aimed to establish the *APOE* genotype and allele frequency in 1001 physically and neurologically healthy voluntaries. Based on the present results, we compare the *APOE* allele frequencies with previously published data from around the world, with emphasis in South-America.

Subjects and methods

Blood samples were collected from healthy and randomly selected volunteers belonging to the Antioquia population, Northwest Colombia, after giving written consent. The samples ($n = 1001$; 594 women, 407 men) were collected in collaboration with the Blood Service of the Hospital ''Pablo Tobon Uribe, HPTU''. This investigation was approved by the

Human Ethics Committee of the University of Antioquia, UdeA and HPTU. Genotyping of the *APOE* polymorphism was performed using polymerase chain reaction amplification of a 224 bp fragment followed by digestion with the *HhaI* enzyme. Digestions were analysed by restriction fragment length polymorphism (RFLP), as published elsewhere (Hixson & Vernier, 1990). The allelic and genotypic frequencies of *APOE* were estimated by counting alleles; the statistical significance of differences of frequencies between groups was compared by χ^2 test. For comparative purposes, we identified references where prevalence data on *APOE* allele frequency were published (PubMed database). *APOE* isoforms were coded by the rs429358 and rs7412 genotypes. Arlequin software (v3.1) was used to calculate Hardy–Weinberg equilibrium, Wright F_{st} index and computing genetic distance (i.e. Slatkin linearized F_{st} ($= F_{st}/1-F_{st}$)) was used as a measure of Pairwise distance; Excoffier et al., 2005). Population density data from Antioquia was retrieved from ''*National Administrative Department of Statistics*'' (Spanish: DANE *Departamento Administrativo Nacional de Estadistica*, 2005 census).

Results and discussion

Table 1 shows the genotype and allele frequencies of *APOE* from Antioquia individuals. Data analysis showed that *APOE*3* had the greatest allele frequency, followed by *APOE*4* and *APOE*2*. These data are in agreement with allele frequencies reported worldwide (e.g. *APOE*2* = 0.066 80, 95% CI = 0.065–0.069; *APOE*3* = 0.8057, 95% CI = 0.803–0.809; and *APOE*4* = 0.1275, 95% CI = 0.125–0.130; $n = 40\,408$ healthy individuals from 62 countries or regions (Corbo & Scacchi, 1999; Jemaa et al., 2006; Raygani et al., 2004; Svobodová et al., 2007). Furthermore, there is no statistical difference in allele frequency between the ''Paisa'' population and the allele frequency calculated from the Spanish population (Valveny et al., 1997), from which the ''Paisa'' has been suggested to originate (Carvajal-Carmona et al., 2003). Interestingly, while genetic distance analysis shows no significant genetic divergence (Table 2), differences in the distribution of APOE alleles were found in the analysed populations (Table 3). These data suggest that *APOE* genotype might be used to differentiate the ''Paisa'' population from other people of not Western Eurasian origin. This assumption might explain why we found differences in allele frequency when compared within regions from the same country (e.g. Colombia, Table 3). Indeed, the *APOE* frequencies from ''Paisa'' (present work) were similar to frequencies from Bogota city (mestizo), but differed from another 16 regions from Colombia, wherein the Amerindian population was analysed (Jaramillo-Correa et al., 2001; Table 3). Although globally the high-to-low *APOE* frequency follows the *E*3 > E*4 > E*2* trend, the present *APOE* frequency data reinforce the idea that *APOE* allele frequency might be distinctive of each region and country. Indeed, *APOE* heterogeneity is not exclusive of European and Asian populations, but also present in South American Indians (Crews et al., 1993; De Andrade et al., 2000; Demarchi et al., 2005; Gaya-Vidal et al., 2012; Jaramillo-Correa et al., 2001), wherein the absence of the *APOE*2* allele is notable. Therefore, population ancestry, immigration and admixture might explain the heterogeneous *APOE* distribution among the different analysed populations (Table 3). Alternatively, *APOE* heterogeneity might reflect gene and environmental dynamic interactions which alter carbohydrate and lipid metabolism according to the natural history of each region and country inhabitants (Corbo & Scacchi, 1999). We report for the first time the *APOE* allele frequency in Antioquia. Noticeably, this is the largest chromosome sample ($n = 2002$ chromosomes) analysed in Colombia and the third largest one in South America (Table 3). Given that this community belongs to a genetically, culturally and geographically isolated population (Arcos-Burgos & Muenke, 2002; Service et al., 2006), the present *APOE* allele frequencies might represent baseline data for future studies which may involve populations of Western Eurasian or not Western Eurasian origin

Table 1. Genotype and allele frequencies of the *APOE* gene in the 'Paisa' population from northwest Colombia.

	'Paisa' population				
	n	%	Frequency	95% CI	χ^2 (*p*)
Genotype					
*E*2/E*2*	5	0.49		0.06–0.94	
*E*2/E*3*	128	12.78		10.72–14.86	
*E*2/E*4*	12	1.19		0.53–1.87	
*E*3/E*3*	664	66.33		63.4–69.26	
*E*3/E*4*	173	17.28		14.94–19.62	
*E*4/E*4*	19	1.89		1.05–2.75	
Total	1001				0.13851
Allele					
*E*2*	150		0.075 ± 0.005	0.063–0.086	
*E*3*	1629		0.814 ± 0.009	0.797–0.831	
*E*4*	223		0.111 ± 0.007	0.098–0.125	

APOE, apoliprototein E; CI, 95% confidence interval; χ^2 (*p*), chi square (probability value); *n*, sample size.

Table 2. Autosomal genetic distances (pairwise distance) based on single nucleotide polymorphism (SNPs) rs429358 and rs7412 in *APOE* gene from healthy people in a South American population.

	Paisa	Bogota	Venezuela	Ecuador	Brasil	Peru	Bolivia	Chile	Amerindian
Paisa	0.000								
Bogota	0.000	0.000							
Venezuela	0.001	0.000	0.000						
Ecuador	0.000	0.000	0.000	0.000					
Brasil	0.000	0.000	0.003	0.000	0.000				
Peru	0.039	0.062	0.026	0.012	0.045	0.000			
Bolivia	0.029	0.038	0.018	0.000	0.036	0.000	0.000		
Chile	0.001	0.000	0.013	0.015	0.000	0.170	0.111	0.000	
Amerindian	0.011	0.005	0.007	0.000	0.007	0.054	0.038	0.010	0.000

Table 3. Distribution of *APOE* allelic frequencies from healthy people in a South American population.

Population study	*n*	*E*2*	*E*3*	*E*4*	Origin	References
Colombia	1608					
Paisa (Antioquia Department)	1001	0.075	0.814	0.111	MIX	This work
Bogota (Cundinamarca Department)	61	0.080	0.852	0.068	MIX	Jacquier et al. (2001)
Bogota	44	0.025	0.893	0.082	MIX	Arboleda et al. (2001)
Bogota	100	0.075	0.810	0.115	MIX	Jaramillo-Correa et al. (2001)
Kogui	30	0.000	0.900	0.100	AMER	Jaramillo-Correa et al. (2001)
Ijka	30	0.000	0.866	0.194	AMER	Jaramillo-Correa et al. (2001)
Guahibo	26	0.000	0.813	0.188	AMER	Jaramillo-Correa et al. (2001)
Coreguaje	28	0.000	0.589	0.411	AMER	Jaramillo-Correa et al. (2001)
Nukak	20	0.000	0.625	0.375	AMER	Jaramillo-Correa et al. (2001)
Butaregua	21	0.000	0.900	0.100	AMER	Jaramillo-Correa et al. (2001)
Yuco	30	0.000	1.000	0.000	AMER	Jaramillo-Correa et al. (2001)
Embera	25	0.000	0.860	0.140	AMER	Jaramillo-Correa et al. (2001)
Waunana	30	0.000	0.914	0.086	AMER	Jaramillo-Correa et al. (2001)
Venezuela	1841					
Maracaibo (Zulia State)	1665	0.050	0.840	0.110	N.D.	Molero et al. (2001)
Maracaibo	176	0.100	0.780	0.120	N.D.	Arráiz et al. (2010)
Ecuador	39	0.013	0.885	0.103	N.D.	Paz-y-Miño et al. (2010)
Brasil	2010					
São José do Rio Preto, RS	58	0.040	0.840	0.120	N.D	Souza et al. (2003)
Porto Alegre, RS	414	0.060	0.770	0.170	N.D.	De França et al. (2004)
Bambui city, Belo Horizonte, MG	1408	0.065	0.800	0.134	AFR	Fuzikawa et al. (2007)
Belo Horizonte, MG	130	0.060	0.840	0.100	N.D.	Brito et al. (2011)
Peru	189	0.011	0.939	0.050	N.D.	Marca et al. (2011)
Bolivia	77	0.007	0.942	0.052	AMER	Gayà-Vidal et al. (2012)
Chile	436					
	187	0.070	0.740	0.190	N.D.	Quiroga et al. (1999)
	110	0.243	0.674	0.083	N.D.	Rollan et al. (1994)
	139	0.047	0.802	0.151	N.D.	Leiva et al. (2005)

*APOE**, APOE allele; AFR, African; AMER, Amerindian; EUR, European; MIX, Mixed: AMER-EUR-AFR; ND, not determined; *n*, sample size.

from other regions of Colombia. We therefore anticipate that significant differences in *APOE* estimates would be expected in future studies from those reported in Table 1.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Arboleda GH, Yunis JJ, Pardo R, Gómez CM, Hedmont D, Arango G, Arboleda H. 2001. Apolipoprotein E genotyping in a sample of Colombian patients with Alzheimer's disease. Neurosci Lett 305: 135–138.

Arcos-Burgos M, Muenke M. 2002. Genetics of population isolates. Clin Genet 61:233–247.

Arráiz N, Bermúdez V, Prieto C, Sánchez MP, Escalona C, Sanz E, Rondón N, et al. 2010. Association between apoliprotein E gene polymorphism and hypercholesterolemic phenotype in Maracaibo, Zulia state, Venezuela. Am J Ther 17:330–336.

Bedoya G, Montoya P, García J, Soto I, Bourgeois S, Carvajal L, Labuda D, et al. 2006. Admixture dynamics in Hispanics: a shift in the nuclear genetic ancestry of a South American population isolate. Proc Natl Acad Sci USA 103:7234–7239.

Brito DD, Fernandes AP, Gomes KB, Coelho FF, Cruz NG, Sabino AP, Cardoso JE, et al. 2011. Apolipoprotein A5-1131T>C polymorphism, but not APOE genotypes, increases susceptibility for dyslipidemia in children and adolescents. Mol Biol Rep 38:4381–4388.

Carvajal-Carmona LG, Ophoff R, Service S, Hartiala J, Molina J, Leon P, Ospina J, et al. 2003. Genetic demography of Antioquia (Colombia) and the Central Valley of Costa Rica. Hum Genet 112:534–541.

Corbo RM, Scacchi R. 1999. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? Ann Hum Genet 63: 301–310.

Crews DE, Kamboh MI, Mancilha-Carvalho JJ, Kottke B. 1993. Population genetics of apolipoprotein A-4, E, and H polymorphisms in Yanomami Indians of northwestern Brazil: associations with lipids, lipoproteins, and carbohydrate metabolism. Hum Biol 65:211–224.

De Andrade FM, Coimbra Jr CE, Santos RV, Goicoechea A, Carnese FR, Salzano FM, Hutz MH. 2000. High heterogeneity of apolipoprotein E gene frequencies in South American Indians. Ann Hum Biol 27: 29–34.

De França E, Alves JG, Hutz MH. 2004. Apolipoprotein E polymorphism and its association with serum lipid levels in Brazilian children. Hum Biol 76:267–275.

Demarchi DA, Salzano FM, Altuna ME, Fiegenbaum M, Hill K, Hurtado AM, Tsunetto LT, et al. 2005. APOE polymorphism distribution among Native Americans and related populations. Ann Hum Biol 32: 351–365.

Excoffier, Laval LG, Schneider S. 2005. Arlequin ver. 3.0: an integrated software package for population genetics data analysis. Evol Bioinform Online 1:47–50.

Fuzikawa AK, Peixoto SV, Taufer M, Moriguchi EH, Lima-Costa MF. 2007. Apolipoprotein E polymorphism distribution in an elderly Brazilian population: the Bambuí Health and Aging Study. Braz J Med Biol Res 40:1429–1434.

Gayà-Vidal M, Athanasiadis G, Carreras-Torres R, Via M, Esteban E, Villena M, Vasquez R, et al. 2012. Apolipoprotein E/C1/C4/C2 gene cluster diversity in two native Andean populations: Aymaras and Quechuas. Ann Hum Genet 76:283–295.

Hixson JE, Vernier DT. 1990. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 31:545–548.

Jacquier M, Arango D, Villareal E, Torres O, Serrano ML, Cruts M, Montañes P, et al. 2001. APOE epsilon4 and Alzheimer's disease: positive association in a Colombian clinical series and review of the Latin-American studies. Arq Neuropsiquiatr 59:11–17.

Jaramillo-Correa JP, Keyeux G, Ruiz-Garcia M, Rodas C, Bernal J. 2001. Population genetic analysis of the genes APOE, APOB(3'VNTR) and ACE in some black and Amerindian communities from Colombia. Hum Hered 52:14–33.

Jemaa R, Elasmi M, Naouali C, Feki M, Kallel A, Souissi M, Sanhaji H, et al. 2006. Apolipoprotein E polymorphism in the Tunisian population: frequency and effect on lipid parameters. Clin Biochem 39: 816–820.

Leiva E, Mujica V, Orrego R, Prieto M, Arredondo M. 2005. Apolipoprotein E polymorphism in type 2 diabetic patients of Talca, Chile. Diabetes Res Clin Pract 68:244–499.

Liu CC, Kanekiyo T, Xu H, Bu G. 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 9:106–118.

Marca V, Acosta O, Cornejo-Olivas M, Ortega O, Huerta D, Mazzetti P. 2011. Genetic polymorphism of apolipoprotein E in a Peruvian population. Rev Peru Med Exp Salud Publica 28:589–594.

Molero AE, Pino-Ramírez G, Maestre GE. 2001. Modulation by age and gender of risk for Alzheimer's disease and vascular dementia associated with the apolipoprotein E-epsilon4 allele in Latin Americans: findings from the Maracaibo Aging Study. Neurosci Lett 307:5–8.

Paz-y-Miño C, Carrera C, López-Cortés A, Muñoz MJ, Cumbal N, Castro B, Cabrera A, Sánchez ME. 2010. Genetic polymorphisms in apolipoprotein E and glutathione peroxidase 1 genes in the Ecuadorian population affected with Alzheimer's disease. Am J Med Sci 340: 373–377.

Quiroga P, Calvo C, Albala C, Urquidi J, Santos JL, Pérez H, Klaassen G. 1999. Apolipoprotein E polymorphism in elderly Chilean people with Alzheimer's disease. Neuroepidemiology 18:48–52.

Raygani AV, Zahrai M, Soltanzadeh A, Doosti M, Javadi E, Pourmotabbed T. 2004. Analysis of association between butyrylcholinesterase K variant and apolipoprotein E genotypes in Alzheimer's disease. Neurosci Lett 371:142–146.

Rollan A, Loyola G, Covarrubias C, Giancaspero R, Acevedo K, Nervi F. 1994. Apolipoprotein E polymorphism in patients with acute pancreatitis. Pancreas 9:349–353.

Service S, DeYoung J, Karayiorgou M, Roos JL, Pretorious H, Bedoya G, Ospina J, et al. 2006. Magnitude and distribution of linkage disequilibrium in population isolates and implications for genome-wide association studies. Nat Genet 38:556–560.

Souza DR, de Godoy MR, Hotta J, Tajara EH, Brandão AC, Pinheiro Júnior S, Tognola WA, dos Santos JE. 2003. Association of apolipoprotein E polymorphism in late-onset Alzheimer's disease and vascular dementia in Brazilians. Braz J Med Biol Res 36: 919–923.

Svobodová H, Kucera F, Stulc T, Vrablík M, Amartuvshin B, Altannavch TS, Ceska R. 2007. Apolipoprotein E gene polymorphism in the Mongolian population. Folia Biol (Praha) 53:138–142.

Valveny N, Esteban E, Kandil M, Moral P. 1997. APO E polymorphism in Spanish and Moroccan populations. Clin Genet 51:354–356.