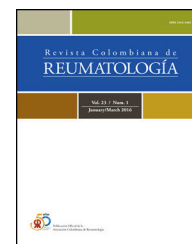




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## Review Article

# Pharmacogenomics of etanercept, infliximab, adalimumab and methotrexate in rheumatoid arthritis. A structured review<sup>☆</sup>



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## ABSTRACT

**Introduction:** Individual genetic variability favors the capacity of response and toxicity to the drugs is different in each person. Rheumatoid arthritis reported rates of response to the drugs etanercept, infliximab, adalimumab and methotrexate is close to 60%. This variability can be explained by genetic polymorphisms characteristic of each patient.

**Objective:** To identify genetic polymorphisms reported in scientific articles that may affect the pharmacokinetics and pharmacodynamics of etanercept, infliximab, adalimumab, and methotrexate, and their response in patients with rheumatoid arthritis.

**Materials and method:** A systematic search was performed in PubMed and Medline, with the key terms: "rheumatoid arthritis" and "pharmacogenomic" and "polymorphisms" and "methotrexate" and "infliximab" and "adalimumab" and "etanercept", obtaining 164 articles, 117 non-duplicates, and 19 articles that met the inclusion criteria.

**Results:** Of the 19 articles, 2 reported polymorphisms affecting the pharmacokinetics of infliximab, adalimumab, etanercept, methotrexate, and 17, pharmacodynamics. In the 19 articles, 23 polymorphisms of clinical relevance were identified in European, Japanese, Jordanian, and Indian populations.

**Conclusions:** A total of 23 polymorphisms with clinical relevance were identified, which could be the basis for the design of a specific test sequencing in rheumatoid arthritis patients being considered for treatment with infliximab, adalimumab, etanercept, or methotrexate. The

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practical usefulness of this strategy requires evidence in specific clinical studies, associated with a targeted and personalized genetic test, and its effect on the effectiveness and safety of drug therapy with these drugs prescription.

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## Farmacogenómica de etanercept, infliximab, adalimumab y metotrexato en artritis reumatoide. Revisión estructurada

### R E S U M E N

#### Palabras clave:

Farmacogenómica  
Artritis reumatoide  
Polimorfismo  
Etanercept  
Infliximab  
Adalimumab  
Metotrexato

**Introducción:** La variabilidad genética individual favorece que la capacidad de respuesta y toxicidad a los fármacos sea diferente en cada persona. En la artritis reumatoide se reportan índices de respuesta a los medicamentos etanercept, infliximab, adalimumab y metotrexato cercanos al 60%. Esta variabilidad puede explicarse por polimorfismos genéticos característicos de cada paciente.

**Objetivo:** Identificar polimorfismos genéticos reportados en artículos científicos que pueden afectar la farmacocinética y la farmacodinámica de etanercept, infliximab, adalimumab y metotrexato, y su respuesta en pacientes con artritis reumatoide.

**Materiales y método:** Se realizó una búsqueda sistemática en PubMed/Medline, con los términos clave: «rheumatoid arthritis» and «pharmacogenomic» and «polymorphisms» and «metotrexato» and «infliximab» and «adalimumab» and «etanercept» obteniendo 164 artículos, 117 no duplicados y 19 artículos que cumplieron los criterios de inclusión.

**Resultados:** De los 19 artículos, 2 reportaron polimorfismos que afectan la farmacocinética de infliximab, adalimumab, etanercept y metotrexato, y 17, la farmacodinámica. En los 19 artículos se identificaron 23 polimorfismos de relevancia clínica en población europea, japonesa, jordana e india.

**Conclusiones:** Se identifican 23 polimorfismos de relevancia clínica, los cuales podrían ser el soporte para el diseño de un test de secuenciación específica en pacientes con artritis reumatoide, en los que se considere la utilización de infliximab, adalimumab, etanercept o metotrexato. La utilidad práctica de este tipo de estrategia requiere ser evidencia en estudios clínicos específicos, relacionados con una prescripción orientada por test genéticos y personalizada, y su efecto sobre la efectividad y seguridad de la farmacoterapia con estos medicamentos.

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## Introduction

Human beings exhibit genetic variation associated with differences in their DNA sequences, which entails that the capacity to respond to the therapeutic and toxic effects of the drugs may be different in each individual.<sup>1,2</sup> The discipline that studies this genetic variability in the response to a drug, at an individual level, is pharmacogenetics; meanwhile, pharmacogenomics also includes the environmental variables thereof.<sup>3-5</sup> These disciplines are useful in clinical practice to predict the individual response of patients to different drugs, especially for the treatment of autoimmune diseases.<sup>6</sup> Rheumatoid arthritis (RA) is a chronic heterogeneous autoimmune disease that causes inflammation in the synovial membrane, the cartilage and the bone; and over time it generates deformity, disability and deterioration in the quality of life.<sup>7,8</sup> Among the drugs used in its treatment are the inhibitors of tumor necrosis factor alpha (TNF- $\alpha$ ) etanercept,

infliximab, adalimumab, which report a response rate of 40%, and methotrexate (MTX) with 50%.<sup>8</sup> This variability can occur due to genetic single-nucleotide polymorphisms that affect the pharmacokinetics and pharmacodynamics of these drugs.

A systematic review of the International Journal of Rheumatology in 2013 reports that approximately 50% of patients with RA in Europe interrupt their TNF- $\alpha$  inhibitor during the first 5 years due to problems of effectiveness or safety of the respective medication.<sup>9</sup> Similarly, the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS), conducted in Boston, reports that 42% of patients with RA informed the withdrawal of their anti-TNF- $\alpha$  treatment.<sup>10</sup> In this context of a large number of patients who discontinue the treatment with anti-TNF- $\alpha$ , the generation of information that improves the ability to predict which patients will respond to specific therapies would be a significant contribution in the proper management of RA.

The mentioned problems of effectiveness and safety could be associated with the genetic variability of each patient, including the environmental variables, which are expressed by genetic polymorphisms. In general, a genetic polymorphism is a variation in a determined DNA sequence present in more than 1% of the individuals of a population.<sup>11</sup> According to the Canary Institute for Cancer Research “they are classified into: variable number of tandem repeats polymorphism (VNTR), restriction fragment length polymorphisms (RFLP) and single nucleotide polymorphisms (SNP)”.<sup>12</sup> In this context, the genetic variability is associated in 90% with SNPs, due to the activity of the genes dependent on enzymes involved in the pharmacokinetics or pharmacodynamics of the drugs used in the treatment of RA, thus affecting their efficacy and safety.<sup>13</sup>

RA is a major public health problem; in the last years, better health outcomes have been achieved with the incorporation of synthetic and biological disease modifying drugs. However, problems of variability in response are reported, which lead to ineffectiveness and adverse reactions in 30%–40% of patients.<sup>14</sup> In this sense, pharmacogenomics, through the study of genetic variants of proteins involved in the pharmacokinetics and pharmacodynamics of the drugs, becomes a way to maximize the efficacy and safety of the pharmacotherapy. In this aspect, pharmacogenomics favors a better understanding of the biological mechanisms and thus, the development of clinical models that predict the antirheumatic drug with greater benefit for each patient.

It is estimated that at 10 years of evolution of the RA, almost 80% of patients have some degree of limitation. The prognosis is uncertain and the lesions, which appear in the first years of disease, may continue despite clinical improvement, since the pathogenesis of these lesions may differ from a simple acute joint inflammation.<sup>15</sup>

Common risk factors regarding the development of RA, such as smoking, female sex, the presence of HLA DRB1 and the educational level, have been found in Colombia.<sup>16</sup>

### **Epidemiological data**

In Canada and the United States the prevalence ranges between 0.8% and 1.1%.<sup>17,18</sup> Similarly, the data of prevalence in Europe range between 0.5% and 1%.<sup>19,20</sup> In Latin America, it has been reported between 0.45% and 0.9%.<sup>21–23</sup> On the other hand, different studies show that the incidence of RA tends to decrease; thus, between 1955 and 1994 the incidence would have been reduced by 50%.<sup>24</sup> In Europe, the reported incidence rates of RA range between 0.009%–0.045%; in North America they vary between 0.024%–0.075% in Caucasian population and between 0.09%–0.89% in American Indian population. Although it is not clear, several factors have been proposed to explain the differences in incidence, among which are genetic, environmental and cultural factors.<sup>25</sup>

### **Etiology and pathogenesis of rheumatoid arthritis**

RA is characterized by the presence of rheumatoid factor and anti-citrullinated peptide antibodies. It is observed in

the initial phase of RA and involves the activation of both T and B cells. Proinflammatory cytokines, such as TNF, IL-1 and IL-17, stimulate the inflammation and degradation of bone and cartilage. However, there is no decrease in the number of Treg cells, which could contribute to the pathophysiology of the disease.<sup>26</sup>

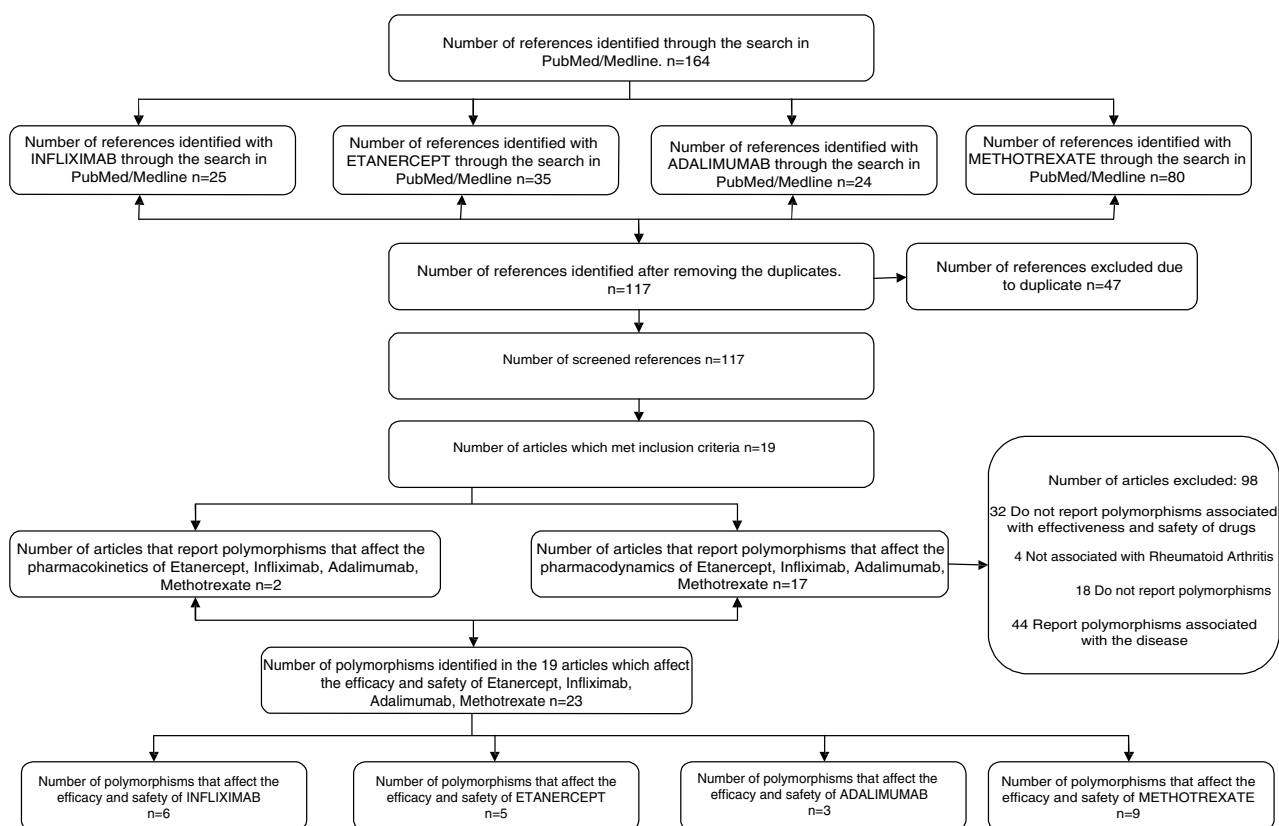
### **Genetic susceptibility**

It is estimated that up to 66% of patients with RA have genetic risk, which has been associated with the presence of certain alleles of the major histocompatibility complex, especially with the HLA-DR4 type. In this sense, it is accepted that the disease is associated with a given genetic load that generates a greater susceptibility to the immune response against an antigen (Ag) and thus, inflammation of the synovial membrane and osteoarticular destruction is generated.<sup>27</sup>

Globally, individuals respond to pharmacotherapy in a different way and no medication is 100% effective in all patients,<sup>28</sup> which may be due to an alteration in the pharmacokinetics and pharmacodynamics of the drugs associated with genetic-environmental conditions.<sup>29</sup> In this context, the study of pharmacogenomic candidate genes has been more successful than the study of the candidate genes of the disease in identifying and explaining the variation of the pharmacological response,<sup>30</sup> which has favored personalized prescription.<sup>31</sup> Within this framework, it is necessary to have systematic information on the pharmacogenomics of RA, identifying polymorphisms of clinical relevance in the response and toxicity of TNF- $\alpha$  inhibitors and methotrexate. This type of information could contribute to the development of genetic tools to support the pharmacotherapeutic decision and improve the response to the treatment of this disease. Therefore, the objective of this work was to identify the polymorphisms to be used in the design of the specific sequencing test in patients with RA before the prescription of infliximab, adalimumab, etanercept and methotrexate.

### **Methods**

Systematic review in PubMed/Medline. To identify the studies, a search in PubMed/Medline was conducted from September 2011 to September 2016, without limits in language and type of study, using the terms: “rheumatoid arthritis” and “pharmacogenomic” and “polymorphisms” and “methotrexate” and “infliximab” and “adalimumab” and “etanercept”. Specifically, it was contemplated the combination of keywords and filters: “rheumatoid arthritis” [MeSH Terms] AND “pharmacogenomic” [MeSH Terms] AND “polymorphisms” [MeSH Terms] AND “methotrexate” [MeSH Terms] AND “infliximab” [MeSH Terms] AND “adalimumab” [MeSH Terms] and “etanercept” [MeSH Terms]. Studies that reported polymorphisms of a single nucleotide and that affected the efficacy and safety of infliximab, adalimumab, etanercept and methotrexate were defined as inclusion criteria.



**Fig. 1 – Flow chart for screening and selection of evidence.**

## Data extraction

The articles that met the inclusion criteria were analyzed for data extraction. It was created a data collection form that included: the author and reference of the article reporting the polymorphism, the medication(s) studied, the type of study, the year of publication, the population, the polymorphism of interest, its manifestation and the report or not of pharmacodynamic or pharmacokinetic variability. Finally, each identified polymorphism was searched in Hap Map, in order to identify the gene to which it belongs, together with its alias, the organism, lineage, location and exon.

## Results

Applying the defined search criteria, 164 articles were found (25 related to infliximab, 24 to adalimumab, 35 to etanercept and 80 to methotrexate), of which 47 were repeated, remaining 117. Of this group of 117 articles, 19 met the inclusion criteria (Fig. 1). Of the 19 articles, two reported polymorphisms that affect the pharmacokinetics of infliximab, adalimumab, etanercept and methotrexate, which are associated with increased plasma concentrations, while 17 articles identified polymorphisms that affect their pharmacodynamics, which is associated with blockade of receptors and is manifested by ineffectiveness of the drugs (Table 1).

The 19 selected articles correspond to European, Japanese, Jordanian and Indian populations and they report the following 23 single nucleotide polymorphisms: rs10919563 PTPRC G, NLRP3 (rs10754558), FCGR2A H131R, 174C (rs1800795), TNFR1A, BACH2 (6q15), rs3761847 SNP in the TRAF1/C5 region, SNP -308 A/A, ATIC 347C>G, ABCB1 rs868755, rs10280623, rs1858923, GGH, SHMT1 and TS, TS5'UTR, C677T (rs1801133), SLC22A11, 3435C MDR1>T, SLC19A1, SLC46A1 and SLC01B1, G80A RFC1 and C3435T MDR1 genotypes (Table 1). Specifically, of these 23 polymorphisms, 6 were associated with infliximab, 5 with etanercept, 3 with adalimumab and 9 with methotrexate (Fig. 1).

The search of the 23 identified polymorphisms in the HapMap database allowed to register, for each of them, the gene that encodes it, the organism in which it is manifested, its lineage, its location or locus and the exon. In this sense, of the 23 identified polymorphisms stood out (Table 2):

- Nineteen (82.6%) correspond to the *Homo sapiens* species.
- In the polypeptide sequence, the regions that are translated into amino acids come mainly from exon 10 (5 polymorphisms), from exon 29 (3 polymorphisms) and from exon 17 (2 polymorphisms).
- The SLC gene (of different genetic families) was found associated with 4 polymorphisms, while the ABCB1 (ATP binding cassette subfamily B member 1) was found associated with 3 of the 23 polymorphisms and the MDR1 gene with 2 polymorphisms.

**Table 1 – Single nucleotide polymorphisms associated with variability in pharmacokinetics and pharmacodynamics of methotrexate and tumor necrosis factor inhibitors: infliximab, etanercept, adalimumab.**

Author/reference	Drug	Type of study	Year	Population	SNP code	Polymorphism of interest	Pharmacokinetic variability	Pharmacodynamic variability	Manifestation
Lee YH, Bae SC <sup>32</sup>	Infliximab, Etanercept, Adalimumab	Metaanalysis	2014	European	1	rs10919563 PTPRC G	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness
Sode J <sup>33</sup>	Infliximab, Etanercept, Adalimumab	Case-control	2015	Danish	2	NLRP3 (rs10754558)	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness
Montes A <sup>34</sup>	Infliximab	Cohorts	2014	Spanish	3	FCGR2A H131R	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness
Dávila-Fajardo CL <sup>35</sup>	Infliximab	Cohorts	2014	Spanish	4	174C (rs1800795) polymorphism	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness
Morales-Lara <sup>36</sup>	Infliximab	Cohorts	2012	European	5	TNFR1A	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (the p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness

<b>Table 1 – (Continued)</b>									
Author/reference	Drug	Type of study	Year	Population	SNP code	Polymorphism of interest	Pharmacokinetic variability	Pharmacodynamic variability	Manifestation
Honne K <sup>37</sup>	Etanercept	Cohorts	2016	Japanese	6	BACH2 (6q15)	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the binding sites (p55 and p75 portions) of the cell surface receptors for TNF- $\alpha$	Ineffectiveness
Canhão H <sup>38</sup>	Infliximab, Etanercept, Adalimumab	Cohorts	2015	South European	7	rs3761847 SNP in the TRAF1/C5 region	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the receptors	Ineffectiveness
Montes A <sup>39</sup> , Morales-Lara <sup>40</sup>	Etanercept	Review	2014	European	8	SNP -308 A/A	Not reported	Prevents the blockade of the interaction between TNF- $\alpha$ and the receptors	Ineffectiveness
Muralidharan N <sup>41</sup> , Salazar J <sup>42</sup>	Methotrexate	Case-control	2016	South Indian	9	ATIC 347C>G	Not reported	Associated with gastrointestinal safety problems	Presence of gastrointestinal adverse drug reactions
Moya P <sup>43</sup> , Lee YH <sup>44</sup>	Methotrexate	Cohorts	2015	European	10, 11, 12	Three ABCB1 SNPs, rs868755, rs10280623 and rs1858923	Not reported	Associated with increased toxicity	Presence of adverse drug reactions
Ghodke-Puranik Y <sup>45</sup>	Methotrexate	Cohorts	2015	Indian	13,14	GGH, SHMT1 and TS	The polymorphisms in genes of the folate -MTX pathway contribute to the MTX response and affect the concentrations of MTX in Indian patients with RA	NA	Presence of adverse drug reactions

<b>Table 1 – (Continued)</b>									
Author/reference	Drug	Type of study	Year	Population	SNP code	Polymorphism of interest	Pharmacokinetic variability	Pharmacodynamic variability	Manifestation
Ghodke-Puranik Y <sup>45</sup>	Methotrexate	Cohorts	2015	Indian	15	TS5'UTR and SHMT1	Increases plasma levels of MTX	NA	Presence of adverse drug reactions
Uribarri M <sup>46</sup> , Chaabane S <sup>47</sup>	Methotrexate	Cohorts	2015	European	16	C677T (rs1801133)	Not reported	Associated with problems of effectiveness and safety	Ineffectiveness and ADR
Lima A <sup>48</sup>	Methotrexate	Cohorts	2015	European	17	SLC22A11	Not reported	Associated with low response	Ineffectiveness
Muralidharan N <sup>49</sup>	Methotrexate	Cohorts	2015	Indian	18	3435C MDR1>T	Not reported	Associated with toxicity	Presence of clinical adverse drug reactions
Lima A <sup>50</sup>	Methotrexate	Cohorts	2014	Portuguese	19, 20	SLC19A1, SLC46A1 and genotypes SLCO1B1	Not reported	Associated with toxicity	Presence of adverse drug reactions
Lima A <sup>50</sup>	Methotrexate	Cohorts	2014	Portuguese	21	SLC19A1 and SLCO1B1 genotypes and haplotypes SLC19A1	Not reported	Associated with toxicity	Presence of gastrointestinal adverse drug reactions
Samara SA <sup>51</sup>	Methotrexate	Cohorts	2014	Jordanian	22,23	G80A RFC1 and C3435T MDR1	Not reported	Associated with toxicity	ADR



**Table 2 – Location and exons of genes identified with single nucleotide polymorphism that affect the effectiveness and safety of infliximab, etanercept, adalimumab and methotrexate.**

Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
1	rs10919563 PTPRC G	Lee YH, Bae SC <sup>32</sup>	PTPRC protein tyrosine phosphatase, receptor type C	LCA; LY5; B220; CD45; L-CA; T200; CD45R; GP180	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae	1q31.3–q32.1	34
2	NLRP3 (rs10754558)	Sode J <sup>33</sup>	NLRP3 NLR family pyrin domain containing 3	AVP; FCU; MWS; FCAS; CIAS1; FCAS1; NALP3; C1orf7; CLR1.1; PYPAF1; ACTAVPRL	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae	1q44	10
3	FCGR2A H131R	Montes A <sup>34</sup>	FCGR2A Fc fragment of IgG receptor lia	CD32; FCG2; FcGR; CD32A; CDw32; FCGR2; IGFR2; FCGR2A1	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae	1q23.3	11
4	Polimorfismo-174C (rs1800795)	Dávila-Fajardo CL <sup>35</sup>	IL6 interleukin 6	CDF; HGF; HSF; BSF2; IL-6; BSF-2; IFNB2; IFN-beta-2	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae	7p15.3	6



Table 2 – (Continued)								
Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
5	TNFR1A	Morales-Lara <sup>36</sup>	TNFRSF1A TNF receptor superfamily member 1A	FPF; p55; p60; TBP1; TNF-R; TNFAR; TNFR1; p55-R; CD120a; TNFR55; TNFR60; TNF-R-I; TNF-R55	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae	12p13.31	10
6	BACH2 (6q15)	Honne K <sup>37</sup>	BACH2 BTB domain and CNC homolog 2	BTBD25	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	6q15	16
7	rs3761847 SNP en la región TRAF1/C5	Canhão H <sup>38</sup>	TNF receptor associated factor 1	EBI6; MGC:10353	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	9q33.2	10
8	SNP -308 A/A	Montes A <sup>39</sup> , Morales-Lara <sup>40</sup>	BIVM-ERCC5 readthrough	ERCC5-202	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	13q33.1	23

Table 2 – (Continued)								
Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
9	ATIC 347C>G	Muralidharan N <sup>41</sup> , Salazar J <sup>42</sup>	ATIC 5-aminoimidazole-4- carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase	PURH; AICAR; AICARFT; IMPCHASE; HEL-S-70p	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	2q35	17
10	Tres ABCB1 SNPs, rs868755	Moya P <sup>43</sup> , Lee YH <sup>44</sup>	ABCB1 ATP binding cassette subfamily B member 1	CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	7q21.12	29
11	Tres ABCB1 SNPs, rs10280623	Moya P <sup>43</sup> , Lee YH <sup>44</sup>	ABCB1 ATP binding cassette subfamily B member 1	CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	7q21.12	29
12	Tres ABCB1 SNP rs1858923	Moya P <sup>43</sup> , Lee YH <sup>44</sup>	ABCB1 ATP binding cassette subfamily B member 1	CLCS; MDR1; P-GP; PGY1; ABC20; CD243; GP170	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	7q21.12	29

Table 2 – (Continued)								
Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
13	GGH	Ghodke-Puranik Y <sup>45</sup>	GGH gamma-glutamyl hydrolase	GH	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	8q12.3	10
14	SHMT1	Ghodke-Puranik Y <sup>45</sup>	SHMT1 serine hydroxymethyltransferase 1	SHMT; CSHMT	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	17p11.2	14
15	TSS'UTR	Ghodke-Puranik Y <sup>45</sup>	ADAMT5	Not reported	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	Chromosome 1	8
16	G677T (rs1801133)	Uribarri M <sup>46</sup> , Chaabane S <sup>47</sup>	MTHFR methylene-tetrahydrofolate reductase	Not reported	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	1p36.22	13

Table 2 – (Continued)								
Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
17	SLC22A11	Lima A <sup>48</sup>	SLC22A11 solute carrier family 22 member 11	OAT4; hOAT4	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	11q13.1	10
18	3435C MDR1>T	Muralidharan N <sup>49</sup>	MDR1 multidrug-resistance transporter	Not reported	Scheffersomyces stipitis CBS 6054	Eukaryota; Fungi; Dikarya; Ascomycota; Saccharomycotina; Saccharomycetes; Saccharomycetales; Debaryomycetaceae; Scheffersomyces	Chromosome: 6	2
19	SLC19A1	Lima A <sup>50</sup>	SLC19A1 solute carrier family 19 member 1	CHMD; FOLT; IFC1; REFC; RFC1	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	21q22.3	17
20	SLC46A1	Lima A <sup>50</sup>	SLC46A1 solute carrier family 46 member 1	G21; HCP1; PCFT	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	17q11.2	6

Table 2 – (Continued)

Number	Polymorphism	Author/Reference	Gene	Gene also known as	Organism	Lineage	Location	Exon
21	SLCO1B1	Lima A <sup>50</sup>	SLCO1B1 solute carrier organic anion transporter family member 1B1	LST1; HBLRR; LST-1; OATP2; OATPC; OATP-C; OATP1B1; SLC21A6	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	12p12.1	15
22	G80A RFC1	Samara SA <sup>51</sup>	RFC1 replication factor C subunit 1	A1; RFC; PO-GA; RECC1; MHCBBF; RFC140	Homo sapiens	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo	4p14	25
23	C3435T MDR1	Samara SA <sup>51</sup>	MDR1 Major Facilitator Transporter; beno- myl/methotrexate resistance; aka BMR; closest <i>S. cerevisiae</i> gene is FLR1 (YBR008C) multidrug transporter	Not reported	<i>Candida albicans</i> SC5314 (strain: SC5314)	Eukaryota; Fungi; Dikarya; Ascomycota; Saccharomycotina; Saccharomycetes; Saccharomycetales; mitosporic Saccharomycetales; <i>Candida</i>	Chromosome 6	1

## Discussion and conclusions

In RA, drugs such as methotrexate and TNF- $\alpha$  inhibitors like infliximab, adalimumab and etanercept are very important to achieve remission in patients; however, the genetic variability of the individuals implies that the capacity of response and toxicity to these medicines is different and that the reported rates are lower than 60%.<sup>8</sup> Pharmacogenomics deals with the possible associations of genetic polymorphisms with responses to drugs, it is a branch of medical science that is still in its initial phase and requires more time to demonstrate positive results, so it depends on a good articulation between the research sector, legislation, pharmaceuticals companies and healthcare institutions that in the future, medicines can be developed for the benefit of improving health conditions and cost of treatments in small target groups; likewise, the value of non-genetic variables in the progression of a disease, such as age, gender, diet and lifestyle, which are also key in the response to a therapy, should not be left aside.

The relevance of this study consists in providing the possibility of applying the research of candidate genes selected for their biological importance, either in the kinetics or because of their relationship in the pharmacological action, in the identification of individuals at risk of experiencing adverse effects or with probability of being resistant to treatment. Therefore, it is expected that the information generated would be susceptible to be used in the design of specific sequencing tests, contributing to identify the best therapeutic option (greater effectiveness and safety) in patients with RA.<sup>18</sup>

In the treatment of RA, the possibility of associating certain polymorphisms with the efficiency of the treatment, reducing the adverse effects of the use of a drug, can be of great value both for the patient and for the medical practice and its economic aspect.<sup>1</sup> The results obtained with this systematic review are a basis for the design of the specific sequencing test in patients with RA before the prescription of infliximab, adalimumab, etanercept and methotrexate; hence the importance of designing and validating with multicenter studies specific genomic tests that contribute to a personalized prescription to improve the effectiveness and safety of treatments with these drugs and achieve lower healthcare costs. The identification of the 23 polymorphisms of clinical relevance obtained with the review is very important for the design of genomic tests; however, it is necessary to include other genes in the multicentre studies, during exome sequencing, before validating and standardizing a test for use in clinical practice.

## Conflicts of interest

The authors declare they do not have any conflict of interest.

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