World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v5.i4.544

World J Orthop 2014 September 18; 5(4): 544-549
ISSN 2218-5836 (online)

MINIREVIEWS

Rheumatoid arthritis susceptibility genes: An overview

Izabela Korczowska

Izabela Korczowska, Department of Rheumatology and Clinical Immunology, University of Medical Sciences in Poznan, 61-701 Poznan, Poland
Author contributions: Korczowska I solely contributed to this paper.
Correspondence to: Dr. Izabela Korczowska, Department of Rheumatology and Clinical Immunology, University of Medical Sciences in Poznan, Fredry 10, 61-701 Poznan, Poland. ikorcz@post.pl
Telephone: +48-61-8547210 Fax: +48-61-8547212
Received: January 22, 2014 Revised: May 29, 2014
Accepted: June 14, 2014
Published online: September 18, 2014

Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease sustained by genetic factors. Various aspects of the genetic contribution to the pathogenetics and outcome of RA are still unknown. Several genes have been indicated so far in the pathogenesis of RA. Apart from human leukocyte antigen, large genome wide association studies have identified many loci involved in RA pathogenesis. These genes include protein tyrosine phosphatase, nonreceptor type 22, Peptidyl Arginine Deiminase type Ⅳ, signal transducer and activator of transcription 4, cytotoxic T-lymphocyte-associated protein 4, tumor necrosis factor-receptor associated factor 1/complement component 5, tumor necrosis factor and others. It is important to determine whether a combination of RA risk alleles are able to identify patients who will develop certain clinical outcomes, such myocardium infarction, severe infection or lymphoma, as well as to identify patients who will respond to biological medication therapy.

Key words: Rheumatoid arthritis; Gene; Polymorphism; Human leukocyte antigen; Genome wide association study

Core tip: This is a comprehensive review concerning genetic factors in rheumatoid arthritis.

Korczowska I. Rheumatoid arthritis susceptibility genes: An overview. *World J Orthop* 2014; 5(4): 544-549 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i4/544.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i4.544

INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease, afflicting around 0.5%-2% of the human population, especially females, but the precise etiology is still unknown. RA is characterized by chronic, systemic inflammation that may affect many tissues, principally synovial tissue, leading to joint destruction, functional disability and sometimes death[1]. Environmental and genetic factors are responsible for susceptibility and the phenotype. Environmental factors include geography, climate, endemic microbes and lifestyle, such as smoking and diet[2,3]. Native Americans show a relatively higher incidence than African or Asian populations. Familial clustering is important, with the prevalence of RA ranging from 2% to 12% in first degree relatives of patients, 5%-10% in same sex dizygotic twins and almost 12%-30% in monozygotic twins[3,4].

The human leukocyte antigen (HLA) region in the human genome is the most heterogeneous and many diseases are known to be associated with this region. The first risk alleles for RA were identified within 36Mb, the major histocompatibility complex (MHC) region[3]. Several studies beginning in the 1980s explained the strong association of the HLA-DRB1 alleles with RA. The associated alleles encode five amino acids at position 70-74 of the HLA-DRβ1 chain, which is known as a shared epitope (SE). It was established that the HLA-DRB1*01, HLA-DRB1*04 and HLADRB1*10 alleles containing the SE were associated with susceptibility to RA and amino acid sequences QKRAA, QQRAA and KKRAA were known SEs conferring susceptibility, while DERAA sequences were for protective effects[5,6]. Caucasian RA patients have

Table 1 The most relevant alleles associated with susceptibility in rheumatoid arthritis according to genome wide association studies

Gene candidate	Locus	SNP	OR
HLA-DRB1			
PTPN22	1	Rs2476601	1.23-1.75
PADI4	1	Rs 2240340a	1.4
STAT4 T/C	2	Rs1188934	1.22 (0.98-1.53)
FCGR2A	1	Rs12746613	1.1
CTLA4	2	Rs3087243	0.75-1.136
CCL21	9	Rs2812378	1.1
TRAF1	9	Rs3761847	1.1 (0.97-1.32)
IRF5	7	Rs10488631	1.16 (0.72-1.87)
CCR6	6	Rs3093023	0.79 (0.64-0.98)
CD40	20	Rs4810485	0.91-1.02
IL2RA	10	Rs2104286	0.92

RA: Rheumatoid arthritis; HLA: Human leukocyte antigen; IL: Interleukin; PTPN22: Protein tyrosine phosphatase, nonreceptor type 22; TRAF1: Tumor necrosis factor receptor associated factor 1.

been tested for ACPA antibodies, RF and HLA-DR genotype, and the results showed a correlation between the presence of RF and ACPA antibodies within the HLA-DRB1 SE[3,7]. Moreover, current smoking habits and SE, especially homozygous SE, have a strong interaction[3,8]. SE is a risk factor for the development of an extra-articular manifestation and so for more severe, destructive RA. However, the non-SE alleles DRB1*1301, *1302 and *1304 seem to be linked to the DERAA motif[9-11]. The study in Hungarian RA patients recommended that HLA-DRB *1301 allele may protect against ACPA positive or ACPA negative RA[9,12-15]. Also, enhanced production of ACPA has been connected with HLA-DRB1*15 positively in RA[9,16-18]. In a Korean population, heterozygous for HLADRB1 0404 or 0901 have up to a 60-fold increased risk of developing susceptibility to RA[19].

A new taxonomy system for the risk of developing RA has been proposed[9,11]. This new classification depends on whether the RAA (motif which represents susceptibility risk of RA) sequence occupies position 71-74 of HLA-DRB1 but is modulated by amino acids at positions 70; glutamine (Q) and arginine (R) represent a higher risk than aspartic acid (D). Lysine (K) confers the highest risk, arginine (R) intermediate risk and the lowest risk is for alanine (A) and glutamic acid (E) in position 71. According to this new classification, SE alleles are divided into S1, S2, S3P and S3D groups and allele X which denotes all non-RAA motifs. The presence of S2 and S3P alleles are a positive association with RA and also correlated with ACPA production, while S1, S3D and X were found to be low risk alleles[9,11,20].

Genome wide association studies (GWAS), large scale cohorts and Wellcome Trust Case Control Consortium databases have allowed the simultaneous evaluation of thousands of genes[9,21-23] and drawn attention to association with RA susceptibility, determining the phenotype of the disease, and response to therapy. Additional variants in the MHC contribute to the heritability of RA independently of the HLA-DRB1, leading to more consequent results of genetic associations. Alleles associated with the susceptibility with RA according to the GWAS study are shown in Table 1. Loci outside the MHC have been associated in a RA population in approximately 4% to the phenotypic variance of RA risk. One of them is peptidyl arginine deiminase, type Ⅳ (PADI4) encoding peptidylarginine deiminase type Ⅳ.

PADI4

One of the isoenzymes carrying the post-translational conversion of arginine residues to citrulline is known as the type 4 peptidylarginine deiminase type Ⅳ. PADI4 enzyme may be connected to the production of ACPA. PADI4 is present in bone marrow and peripheral blood leukocytes and is one of the four isoforms of PADI enzyme in humans encoded by the *PADI4* gene[3,24]. *PADI4* gene maps on 1p36 locus have been associated with European and Japanese RA populations. A meta-analysis done by Lee *et al*[25] showed that in Asian patients, all 5 researched polymorphisms (PADI4_89, PADI4_90, PADI4_93, PADI4_94 and PADI4_104) were significantly associated with RA, while in Europeans only PADI4_94 was associated with RA risk, much less than in Asian patients[26,27]. The function of this gene in the European RA population is still questionable as the results of large studies from Spain, France and the UK found no association with RA[3,28,29].

Within the genes investigated for susceptibility to RA, protein tyrosine phosphatase type 22 (PTN22) is one of the most strongly associated.

Protein tyrosine phosphatase, nonreceptor type 22

Protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) encodes the intracellular tyrosine phosphatase LYP, known as a powerful inhibitor of T-cell activation. The gene encoding PTPN22 shows the second strongest (just after HLA-DRB1) association with RA. The gene was first associated with type 1 diabetes, systemic sclerosis, Graves disease and lupus erythematosus. Then it was associated with RA in a Caucasian population; rs2476601, C1885T polymorphism leading to an amino acid modification from Arg to Trp at amino acid position 620. This polymorphism resides in a rather large haplotype block encompassing the entire PTPN22 gene[3,30-32]. This SNP has been associated with RF, ACPA positive and SE. ACPA status powerfully supports the early diagnosis of RA. It is worth mentioning that in contrast to SE, C1885T polymorphism may not be associated with smoking[9,33-35]. The important fact is that this polymorphism is not associated with RA in Asian populations, maybe only with Asiatic Indians with RA positive[36].

Signal transducer and activator of transcription 4

The signal transducer and activator of transcription 4 (STAT4) is a transcription factor that intercedes the intracellular signal activation by cytokines such IL-12, IL-23 and IL-27 and type I interferons. STAT4 can be induced

upon activation and maturation of monocytes as well as immature dendritic cells. STAT is also overexpressed in RA synovium. Lee *et al*[37] and Amos *et al*[38] detected linkage at chromosome 2q33 in RA and then revealed that the polymorphism located at 2q33 STAT4 gene is the marker responsible for the linkage signal in 2q33. It has been found that STAT4 rs7574865 polymorphism is associated with European, Asian and Latin American RA patients[37,39-43]. Comparison between ACPA positive and negative patients showed no significant differences[37]. It seems that the intronic variant rs11893432 C/G of *STAT4* gene could also predispose to RA[26,44].

Cytotoxic T lymphocyte-associated antigen 4

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is expressed on T cells, is a member of the immunoglobulin superfamily and performs a critical role in the inhibition of T-cell activation and peripheral tolerance. Three polymorphisms have been described in the *CTLA-4* gene: first, microsatellite at position 642 of the 3' untranslated region of exon 4; second, the polymorphism 49G/A in exon 1 causes a threonine to the alanine substitution of amino acid 17; and the third, -318 of the promoter sequence C/T transition[45]. The CT60 allele has been associated with autoimmune diseases. In the end, CTLA-4 export to the membrane reduces and decreases the inhibitory function of CTLA-4. CTLA4 increased the development of ACPA positive RA in contrast to RA patients with ACPA negative. The meta-analysis showed a positive connection of 49A/G polymorphism susceptibility with RA in Asians, but only 1 in Asians and Europeans[3,46-48]. However, the exact role of this gene in RA is quite modest and still must be clarified.

TRAF1-C5

Two biological candidate genes, TNF receptor associated factor 1 (TRAF1) and complement component 5 (C5), were described by GWAS. TRAF1 is a member of the TNF receptor associated factor family, which are a class of proteins that link TNF receptor family members associated with signaling pathways that play a function in apoptosis, cell proliferation and differentiation, activation and inhibition cytokines and bone remodeling. The most strongly associated SNPs are rs3761847 and rs10818488 in the genome. It seems that the maximal genetic signal is located between the TRAF1 and C5 gene[39,49].

TNF

TNF alpha is a pleiotropic inflammatory cytokine. TNF-308A/G (rs1800629) polymorphism is associated with RA in the Latin American population[26,50] but not in any other ethnic group. Also, the TNF promoter polymorphism -609G/T and -238A/G are not associated with RA[45]. TNF-308A/G polymorphism was associated with radiological damage in a RA patient. Khanna *et al*[51] showed that patients with -308 TNF alpha AA+AG genotypes had considerably higher rates of progression in erosion scores and Sharp scores equal to the GG genotype patients. In contrast, Lacki *et al*[52] suggest that TNF-308 polymorphism cannot serve as an indicator of the disease course in RA patients.

INTERLEUKIN

Interleukins are a large part of cytokines which promote the development and differentiation of lymphocytes T, B and hematopoietic cells. In RA patients, SNPs of cytokines have been investigated regarding an association with erosive damage. One of them is IL-1. Polymorphism -511A/G (rs16944) in promoter IL-1b was positively associated with RA. +3954T allele was associated with more severe structural damage (mainly with Larsen's score in wrist joints)[3,53,54]. IL-6 is a multifunctional cytokine implied in the inflammatory and immune response. Some studies reported that -174G/C (rs1800795) allele was associated with radiological damage in RA patients who were ACPA and RF positive[55]. The presence of two functional polymorphisms in the promoter region of IL-6, the -174G/C and -572G/C, suggests a strong susceptibility for European RA patients compared to Asians. These two polymorphisms (rs1800795 and rs1800795) may also influence the risk of osteoporosis. Another multifunctional cytokine is IL-10, produced by monocytes and lymphocytes, a protein that inhibits the synthesis of a number of cytokines and has a range of anti-inflammatory and immunoregulatory properties. Three polymorphisms placed in the promoter IL-10 were studied, including -1082G/A (rs 1800896), -892C/T (rs1800871) and -592C/A (rs1800872). The results are controversial as one showed that -1082G/A polymorphism is not associated with RA of either European or Asian populations and the other showed a positive association with RA, indicating that the carriers of the G allele could have a decreased liability of RA[26,56]. Some studies reported that the homozygosity of -592C/A was associated with higher Larsen scores in RA patients with ACPA and RF negative[55]. Polymorphisms of the *IL-2* and *IL-21* genes (region 4q27) have been implicated in several autoimmune diseases, including RA. One of them is intronic change A/G rs13151961[57]. Next studied were polymorphisms in RA susceptibility which may modulate gene expression of IL-2 or IL-21 located in the noncoding region, upstream of IL-21 and downstream of IL-2 is the G/T rs6822844. In a study on European Caucasian and South American populations, significant association with RA was shown[26,58,59].

With the use of GWAS, genetic studies can examine many common genetic variants across the entire human genome. There are a lot of other gene and chromosome loci revalidated as RA susceptible regions, such as CD226, CD40, CDK6, MBP, BLK, REL and more[60].

In conclusion, rheumatoid arthritis has a strong genetic influence mediated by alleles. Human genetics should be able to determine the value of RA risk alleles by providing clinical predictions. One of the most direct clinical applications is to use human genetics to lead the development of treatment for RA. It will be crucial to determine whether a combination of RA risk alleles are

able to identify patients who develop certain clinical outcomes, such as myocardium infarction, severe infection or lymphoma, as well as to identify the patients who will respond to biological medication therapy.

REFERENCES

1 **Vandenbroucke JP**, Hazevoet HM, Cats A. Survival and cause of death in rheumatoid arthritis: a 25-year prospective followup. *J Rheumatol* 1984; **11**: 158-161 [PMID: 6726714]
2 **Youinou P**, Pers JO, Gershwin ME, Shoenfeld Y. Geo-epidemiology and autoimmunity. *J Autoimmun* 2010; **34**: J163-J167 [PMID: 20056534 DOI: 10.1016/j.jaut.2009.12.005]
3 **Perricone C**, Ceccarelli F, Valesini G. An overview on the genetic of rheumatoid arthritis: a never-ending story. *Autoimmun Rev* 2011; **10**: 599-608 [PMID: 21545847 DOI: 10.1016/j.autrev.2011.04.021]
4 **MacGregor AJ**, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, Silman AJ. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000; **43**: 30-37 [PMID: 10643697]
5 **Gregersen PK**, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987; **30**: 1205-1213 [PMID: 2446635]
6 **Diogo D**, Okada Y, Plenge RM. Genome-wide association studies to advance our understanding of critical cell types and pathways in rheumatoid arthritis: recent findings and challenges. *Curr Opin Rheumatol* 2014; **26**: 85-92 [PMID: 24276088 DOI: 10.1097/BOR.0000000000000012]
7 **Irigoyen P**, Lee AT, Wener MH, Li W, Kern M, Batliwalla F, Lum RF, Massarotti E, Weisman M, Bombardier C, Remmers EF, Kastner DL, Seldin MF, Criswell LA, Gregersen PK. Regulation of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: contrasting effects of HLA-DR3 and the shared epitope alleles. *Arthritis Rheum* 2005; **52**: 3813-3818 [PMID: 16320316]
8 **Källberg H**, Ding B, Padyukov L, Bengtsson C, Rönnelid J, Klareskog L, Alfredsson L. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann Rheum Dis* 2011; **70**: 508-511 [PMID: 21149499 DOI: 10.1136/ard.2009.120899]
9 **Kurkó J**, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis - a comprehensive review. *Clin Rev Allergy Immunol* 2013; **45**: 170-179 [PMID: 23288628 DOI: 10.1007/s12016-012-8346-7]
10 **van der Helm-van Mil AH**, Wesoly JZ, Huizinga TW. Understanding the genetic contribution to rheumatoid arthritis. *Curr Opin Rheumatol* 2005; **17**: 299-304 [PMID: 15838240]
11 **du Montcel ST**, Michou L, Petit-Teixeira E, Osorio J, Lemaire I, Lasbleiz S, Pierlot C, Quillet P, Bardin T, Prum B, Cornelis F, Clerget-Darpoux F. New classification of HLA-DRB1 alleles supports the shared epitope hypothesis of rheumatoid arthritis susceptibility. *Arthritis Rheum* 2005; **52**: 1063-1068 [PMID: 15818663]
12 **Besenyei T**, Gyetvai A, Szabó Z, Fekete A, Kapitány A, Szodoray P, Laki J, Soós L, Sipka S, Szegedi G, Lakos G, Szekanecz Z. Associations of HLA-shared epitope, anti-citrullinated peptide antibodies and lifestyle-related factors in Hungarian patients with rheumatoid arthritis: data from the first Central-Eastern European cohort. *Joint Bone Spine* 2011; **78**: 652-653 [PMID: 21733730 DOI: 10.1016/j.jbspin.2011.05.018]
13 **Szodoray P**, Szabó Z, Kapitány A, Gyetvai A, Lakos G, Szántó S, Szücs G, Szekanecz Z. Anti-citrullinated protein/peptide autoantibodies in association with genetic and environmental factors as indicators of disease outcome in rheumatoid arthritis. *Autoimmun Rev* 2010; **9**: 140-143 [PMID: 19427413 DOI: 10.1016/j.autrev.2009.04.006]
14 **van der Woude D**, Houwing-Duistermaat JJ, Toes RE, Huizinga TW, Thomson W, Worthington J, van der Helm-van Mil AH, de Vries RR. Quantitative heritability of anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis. *Arthritis Rheum* 2009; **60**: 916-923 [PMID: 19333951 DOI: 10.1002/art.24385]
15 **van der Woude D**, Lie BA, Lundström E, Balsa A, Feitsma AL, Houwing-Duistermaat JJ, Verduijn W, Nordang GB, Alfredsson L, Klareskog L, Pascual-Salcedo D, Gonzalez-Gay MA, Lopez-Nevot MA, Valero F, Roep BO, Huizinga TW, Kvien TK, Martín J, Padyukov L, de Vries RR, Toes RE. Protection against anti-citrullinated protein antibody-positive rheumatoid arthritis is predominantly associated with HLA-DRB1*1301: a meta-analysis of HLA-DRB1 associations with anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis in four European populations. *Arthritis Rheum* 2010; **62**: 1236-1245 [PMID: 20131291 DOI: 10.1002/art.27366]
16 **van der Helm-van Mil AH**, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR. The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. *Arthritis Rheum* 2006; **54**: 1117-1121 [PMID: 16572446]
17 **Laki J**, Lundström E, Snir O, Rönnelid J, Ganji I, Catrina AI, Bengtsson C, Saevarsdottir S, Wick MC, Alfredsson L, Klareskog L, Padyukov L. Very high levels of anti-citrullinated protein antibodies are associated with HLA-DRB1*15 non-shared epitope allele in patients with rheumatoid arthritis. *Arthritis Rheum* 2012; **64**: 2078-2084 [PMID: 22307773 DOI: 10.1002/art.34421]
18 **Zsilák S**, Gál J, Hodinka L, Rajczy K, Balog A, Sipka S, Baráth S, Kapitány A, Zilahi E, Szekanecz Z. HLA-DR genotypes in familial rheumatoid arthritis: increased frequency of protective and neutral alleles in a multicase family. *J Rheumatol* 2005; **32**: 2299-2302 [PMID: 16331753]
19 **Oliver JE**, Worthington J, Silman AJ. Genetic epidemiology of rheumatoid arthritis. *Curr Opin Rheumatol* 2006; **18**: 141-146 [PMID: 16462519]
20 **Gyetvai A**, Szekanecz Z, Soós L, Szabó Z, Fekete A, Kapitány A, Teodorescu M, Sipka S, Szegedi G, Lakos G. New classification of the shared epitope in rheumatoid arthritis: impact on the production of various anti-citrullinated protein antibodies. *Rheumatology* (Oxford) 2010; **49**: 25-33 [PMID: 19920092 DOI: 10.1093/rheumatology/kep338]
21 **Plant D**, Bowes J, Potter C, Hyrich KL, Morgan AW, Wilson AG, Isaacs JD, Barton A. Genome-wide association study of genetic predictors of anti-tumor necrosis factor treatment efficacy in rheumatoid arthritis identifies associations with polymorphisms at seven loci. *Arthritis Rheum* 2011; **63**: 645-653 [PMID: 21061259 DOI: 10.1002/art.30130]
22 **Feng T**, Zhu X. Genome-wide searching of rare genetic variants in WTCCC data. *Hum Genet* 2010; **128**: 269-280 [PMID: 20549515 DOI: 10.1007/s00439-010-0849-9]
23 **Craddock N**, Hurles ME, Cardin N, Pearson RD, Plagnol V, Robson S, Vukcevic D, Barnes C, Conrad DF, Giannoulatou E, Holmes C, Marchini JL, Stirrups K, Tobin MD, Wain LV, Yau C, Aerts J, Ahmad T, Andrews TD, Arbury H, Attwood A, Auton A, Ball SG, Balmforth AJ, Barrett JC, Barroso I, Barton A, Bennett AJ, Bhaskar S, Blaszczyk K, Bowes J, Brand OJ, Braund PS, Bredin F, Breen G, Brown MJ, Bruce IN, Bull J, Burren OS, Burton J, Byrnes J, Caesar S, Clee CM, Coffey AJ, Connell JM, Cooper JD, Dominiczak AF, Downes K, Drummond HE, Dudakia D, Dunham A, Ebbs B, Eccles D, Edkins S, Edwards C, Elliot A, Emery P, Evans DM, Evans G, Eyre S, Farmer A, Ferrier IN, Feuk L, Fitzgerald T, Flynn E, Forbes A, Forty L, Franklyn JA, Freathy RM, Gibbs P, Gilbert P, Gokumen O, Gordon-Smith K, Gray E, Green E, Groves CJ, Grozeva D, Gwilliam R, Hall A, Hammond N, Hardy M, Harrison P, Hassanali N, Hebaishi H, Hines S, Hinks A, Hitman GA, Hocking L, Howard E, Howard P, Howson JM, Hughes D, Hunt S, Isaacs JD, Jain M, Jewell DP, Johnson T, Jolley JD,

Jones IR, Jones LA, Kirov G, Langford CF, Lango-Allen H, Lathrop GM, Lee J, Lee KL, Lees C, Lewis K, Lindgren CM, Maisuria-Armer M, Maller J, Mansfield J, Martin P, Massey DC, McArdle WL, McGuffin P, McLay KE, Mentzer A, Mimmack ML, Morgan AE, Morris AP, Mowat C, Myers S, Newman W, Nimmo ER, O'Donovan MC, Onipinla A, Onyiah I, Ovington NR, Owen MJ, Palin K, Parnell K, Pernet D, Perry JR, Phillips A, Pinto D, Prescott NJ, Prokopenko I, Quail MA, Rafelt S, Rayner NW, Redon R, Reid DM, Renwick SM, Robertson N, Russell E, St Clair D, Sambrook JG, Sanderson JD, Schuilenburg H, Scott CE, Scott R, Seal S, Shaw-Hawkins S, Shields BM, Simmonds MJ, Smyth DJ, Somaskantharajah E, Spanova K, Steer S, Stephens J, Stevens HE, Stone MA, Su Z, Symmons DP, Thompson JR, Thomson W, Travers ME, Turnbull C, Valsesia A, Walker M, Walker NM, Wallace C, Warren-Perry M, Watkins NA, Webster J, Weedon MN, Wilson AG, Woodburn M, Wordsworth BP, Young AH, Zeggini E, Carter NP, Frayling TM, Lee C, McVean G, Munroe PB, Palotie A, Sawcer SJ, Scherer SW, Strachan DP, Tyler-Smith C, Brown MA, Burton PR, Caulfield MJ, Compston A, Farrall M, Gough SC, Hall AS, Hattersley AT, Hill AV, Mathew CG, Pembrey M, Satsangi J, Stratton MR, Worthington J, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand W, Parkes M, Rahman N, Todd JA, Samani NJ, Donnelly P. Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000 shared controls. *Nature* 2010; **464**: 713-720 [PMID: 20360734 DOI: 10.1038/nature08979]

24 **Vossenaar ER**, Zendman AJ, van Venrooij WJ, Pruijn GJ. PAD, a growing family of citrullinating enzymes: genes, features and involvement in disease. *Bioessays* 2003; **25**: 1106-1118 [PMID: 14579251]

25 **Lee YH**, Rho YH, Choi SJ, Ji JD, Song GG. PADI4 polymorphisms and rheumatoid arthritis susceptibility: a meta-analysis. *Rheumatol Int* 2007; **27**: 827-833 [PMID: 17265154]

26 **Chatzikyriakidou A**, Voulgari PV, Lambropoulos A, Drosos AA. Genetics in rheumatoid arthritis beyond HLA genes: what meta-analyses have shown? *Semin Arthritis Rheum* 2013; **43**: 29-38 [PMID: 23768941 DOI: 10.1016/j.semarthrit.2012.12.003]

27 **Lee YH**, Bae SC, Choi SJ, Ji JD, Song GG. Genome-wide pathway analysis of genome-wide association studies on systemic lupus erythematosus and rheumatoid arthritis. *Mol Biol Rep* 2012; **39**: 10627-10635 [PMID: 23053960 DOI: 10.1007/s11033-012-1952-x]

28 **Burr ML**, Naseem H, Hinks A, Eyre S, Gibbons LJ, Bowes J, Wilson AG, Maxwell J, Morgan AW, Emery P, Steer S, Hocking L, Reid DM, Wordsworth P, Harrison P, Thomson W, Worthington J, Barton A. PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population. *Ann Rheum Dis* 2010; **69**: 666-670 [PMID: 19470526 DOI: 10.1136/ard.2009.111294]

29 **Iwamoto T**, Ikari K, Nakamura T, Kuwahara M, Toyama Y, Tomatsu T, Momohara S, Kamatani N. Association between PADI4 and rheumatoid arthritis: a meta-analysis. *Rheumatology* (Oxford) 2006; **45**: 804-807 [PMID: 16449362]

30 **Hinks A**, Worthington J, Thomson W. The association of PTPN22 with rheumatoid arthritis and juvenile idiopathic arthritis. *Rheumatology* (Oxford) 2006; **45**: 365-368 [PMID: 16418195]

31 **Lee AT**, Li W, Liew A, Bombardier C, Weisman M, Massarotti EM, Kent J, Wolfe F, Begovich AB, Gregersen PK. The PTPN22 R620W polymorphism associates with RF positive rheumatoid arthritis in a dose-dependent manner but not with HLA-SE status. *Genes Immun* 2005; **6**: 129-133 [PMID: 15674368]

32 **Steer S**, Lad B, Grumley JA, Kingsley GH, Fisher SA. Association of R602W in a protein tyrosine phosphatase gene with a high risk of rheumatoid arthritis in a British population: evidence for an early onset/disease severity effect. *Arthritis Rheum* 2005; **52**: 358-360 [PMID: 15641088]

33 **Morgan AW**, Thomson W, Martin SG, Carter AM, Erlich HA, Barton A, Hocking L, Reid DM, Harrison P, Wordsworth P, Steer S, Worthington J, Emery P, Wilson AG, Barrett JH. Reevaluation of the interaction between HLA-DRB1 shared epitope alleles, PTPN22, and smoking in determining susceptibility to autoantibody-positive and autoantibody-negative rheumatoid arthritis in a large UK Caucasian population. *Arthritis Rheum* 2009; **60**: 2565-2576 [PMID: 19714585 DOI: 10.1002/art.24752]

34 **Farago B**, Talian GC, Komlosi K, Nagy G, Berki T, Gyetvai A, Szekanecz Z, Nyarady Z, Kiss CG, Nemeth P, Czirjak L, Melegh B. Protein tyrosine phosphatase gene C1858T allele confers risk for rheumatoid arthritis in Hungarian subjects. *Rheumatol Int* 2009; **29**: 793-796 [PMID: 19034456 DOI: 10.1007/s00296-008-0771-9]

35 **Goëb V**, Dieudé P, Daveau R, Thomas-L'otellier M, Jouen F, Hau F, Boumier P, Tron F, Gilbert D, Fardellone P, Cornélis F, Le Loët X, Vittecoq O. Contribution of PTPN22 1858T, TNFRII 196R and HLA-shared epitope alleles with rheumatoid factor and anti-citrullinated protein antibodies to very early rheumatoid arthritis diagnosis. *Rheumatology* (Oxford) 2008; **47**: 1208-1212 [PMID: 18535030 DOI: 10.1093/rheumatology/ken19]

36 **Mastana S**, Gilmour A, Ghelani A, Smith H, Samanta A. Association of PTPN22 with rheumatoid arthritis among South Asians in the UK. *J Rheumatol* 2007; **34**: 1984-1986 [PMID: 17696275]

37 **Lee YH**, Woo JH, Choi SJ, Ji JD, Song GG. Association between the rs7574865 polymorphism of STAT4 and rheumatoid arthritis: a meta-analysis. *Rheumatol Int* 2010; **30**: 661-666 [PMID: 19588142 DOI: 10.1007/s00296-009-1051-z]

38 **Amos CI**, Chen WV, Lee A, Li W, Kern M, Lundsten R, Batliwalla F, Wener M, Remmers E, Kastner DA, Criswell LA, Seldin MF, Gregersen PK. High-density SNP analysis of 642 Caucasian families with rheumatoid arthritis identifies two new linkage regions on 11p12 and 2q33. *Genes Immun* 2006; **7**: 277-286 [PMID: 16691188]

39 **Palomino-Morales RJ**, Rojas-Villarraga A, González CI, Ramírez G, Anaya JM, Martín J. STAT4 but not TRAF1/C5 variants influence the risk of developing rheumatoid arthritis and systemic lupus erythematosus in Colombians. *Genes Immun* 2008; **9**: 379-382 [PMID: 18432273 DOI: 10.1038/gene.2008.30]

40 **Martínez A**, Varadé J, Márquez A, Cénit MC, Espino L, Perdigones N, Santiago JL, Fernández-Arquero M, de la Calle H, Arroyo R, Mendoza JL, Fernández-Gutiérrez B, de la Concha EG, Urcelay E. Association of the STAT4 gene with increased susceptibility for some immune-mediated diseases. *Arthritis Rheum* 2008; **58**: 2598-2602 [PMID: 18759272 DOI: 10.1002/art.23792]

41 **Orozco G**, Alizadeh BZ, Delgado-Vega AM, González-Gay MA, Balsa A, Pascual-Salcedo D, Fernández-Gutierrez B, González-Escribano MF, Petersson IF, van Riel PL, Barrera P, Coenen MJ, Radstake TR, van Leeuwen MA, Wijmenga C, Koeleman BP, Alarcón-Riquelme M, Martín J. Association of STAT4 with rheumatoid arthritis: a replication study in three European populations. *Arthritis Rheum* 2008; **58**: 1974-1980 [PMID: 18576336 DOI: 10.1002/art.23549]

42 **Remmers EF**, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker PI, Le JM, Lee HS, Batliwalla F, Li W, Masters SL, Booty MG, Carulli JP, Padyukov L, Alfredsson L, Klareskog L, Chen WV, Amos CI, Criswell LA, Seldin MF, Kastner DL, Gregersen PK. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med* 2007; **357**: 977-986 [PMID: 17804842]

43 **Zervou MI**, Sidiropoulos P, Petraki E, Vazgiourakis V, Krasoudaki E, Raptopoulou A, Kritikos H, Choustoulaki E, Boumpas DT, Goulielmos GN. Association of a TRAF1 and a STAT4 gene polymorphism with increased risk for rheumatoid arthritis in a genetically homogeneous population. *Hum*

Immunol 2008; **69**: 567-571 [PMID: 18625278 DOI: 10.1016/j.humimm.2008.06.006]

44 **Raychaudhuri S**, Remmers EF, Lee AT, Hackett R, Guiducci C, Burtt NP, Gianniny L, Korman BD, Padyukov L, Kurreeman FA, Chang M, Catanese JJ, Ding B, Wong S, van der Helm-van Mil AH, Neale BM, Coblyn J, Cui J, Tak PP, Wolbink GJ, Crusius JB, van der Horst-Bruinsma IE, Criswell LA, Amos CI, Seldin MF, Kastner DL, Ardlie KG, Alfredsson L, Costenbader KH, Altshuler D, Huizinga TW, Shadick NA, Weinblatt ME, de Vries N, Worthington J, Seielstad M, Toes RE, Karlson EW, Begovich AB, Klareskog L, Gregersen PK, Daly MJ, Plenge RM. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat Genet* 2008; **40**: 1216-1223 [PMID: 18794853 DOI: 10.1038/ng.233]

45 **Miterski B**, Drynda S, Böschow G, Klein W, Oppermann J, Kekow J, Epplen JT. Complex genetic predisposition in adult and juvenile rheumatoid arthritis. *BMC Genet* 2004; **5**: 2 [PMID: 15018649]

46 **Li X**, Zhang C, Zhang J, Zhang Y, Wu Z, Yang L, Xiang Z, Qi Z, Zhang X, Xiao X. Polymorphisms in the CTLA-4 gene and rheumatoid arthritis susceptibility: a meta-analysis. *J Clin Immunol* 2012; **32**: 530-539 [PMID: 22354566 DOI: 10.1007/s10875-012-9650-y]

47 **Han S**, Li Y, Mao Y, Xie Y. Meta-analysis of the association of CTLA-4 exon-1 +49A/G polymorphism with rheumatoid arthritis. *Hum Genet* 2005; **118**: 123-132 [PMID: 16133179]

48 **Daha NA**, Toes RE. Rheumatoid arthritis: Are ACPA-positive and ACPA-negative RA the same disease? *Nat Rev Rheumatol* 2011; **7**: 202-203 [PMID: 21455249 DOI: 10.1038/nrrheum.2011.28]

49 **Plenge RM**, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, Liew A, Khalili H, Chandrasekaran A, Davies LR, Li W, Tan AK, Bonnard C, Ong RT, Thalamuthu A, Pettersson S, Liu C, Tian C, Chen WV, Carulli JP, Beckman EM, Altshuler D, Alfredsson L, Criswell LA, Amos CI, Seldin MF, Kastner DL, Klareskog L, Gregersen PK. TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study. *N Engl J Med* 2007; **357**: 1199-1209 [PMID: 17804836]

50 **Lee YH**, Ji JD, Song GG. Tumor necrosis factor-alpha promoter -308 A/G polymorphism and rheumatoid arthritis susceptibility: a metaanalysis. *J Rheumatol* 2007; **34**: 43-49 [PMID: 17143972]

51 **Khanna D**, Wu H, Park G, Gersuk V, Gold RH, Nepom GT, Wong WK, Sharp JT, Reed EF, Paulus HE, Tsao BP. Association of tumor necrosis factor alpha polymorphism, but not the shared epitope, with increased radiographic progression in a seropositive rheumatoid arthritis inception cohort. *Arthritis Rheum* 2006; **54**: 1105-1116 [PMID: 16572445]

52 **Lacki JK**, Moser R, Korczowska I, Mackiewicz S, Muller W. TNF-alpha gene polymorphism does not affect the clinical and radiological outcome of rheumatoid arthritis. *Rheumatol Int* 2000; **19**: 137-140 [PMID: 10836523]

53 **Buchs N**, di Giovine FS, Silvestri T, Vannier E, Duff GW, Miossec P. IL-1B and IL-1Ra gene polymorphisms and disease severity in rheumatoid arthritis: interaction with their plasma levels. *Genes Immun* 2001; **2**: 222-228 [PMID: 11477478]

54 **Pawlik A**, Kurzawski M, Florczak M, Gawronska Szklarz B, Herczyńska M. IL1beta+3953 exon 5 and IL-2 -330 promoter polymorphisms in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; **23**: 159-164 [PMID: 15895884]

55 **Marinou I**, Healy J, Mewar D, Moore DJ, Dickson MC, Binks MH, Montgomery DS, Walters K, Wilson AG. Association of interleukin-6 and interleukin-10 genotypes with radiographic damage in rheumatoid arthritis is dependent on autoantibody status. *Arthritis Rheum* 2007; **56**: 2549-2556 [PMID: 17665434]

56 **Zhang J**, Zhang Y, Jin J, Li M, Xie K, Wen C, Cheng R, Chen C, Lu J. The -1082A/G polymorphism in the Interleukin-10 gene and the risk of rheumatoid arthritis: a meta-analysis. *Cytokine* 2011; **56**: 351-355 [PMID: 21764596 DOI: 10.1016/j.cyto.2011.05.022]

57 **Stahl EA**, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FA, Zhernakova A, Hinks A, Guiducci C, Chen R, Alfredsson L, Amos CI, Ardlie KG, Barton A, Bowes J, Brouwer E, Burtt NP, Catanese JJ, Coblyn J, Coenen MJ, Costenbader KH, Criswell LA, Crusius JB, Cui J, de Bakker PI, De Jager PL, Ding B, Emery P, Flynn E, Harrison P, Hocking LJ, Huizinga TW, Kastner DL, Ke X, Lee AT, Liu X, Martin P, Morgan AW, Padyukov L, Posthumus MD, Radstake TR, Reid DM, Seielstad M, Seldin MF, Shadick NA, Steer S, Tak PP, Thomson W, van der Helm-van Mil AH, van der Horst-Bruinsma IE, van der Schoot CE, van Riel PL, Weinblatt ME, Wilson AG, Wolbink GJ, Wordsworth BP, Wijmenga C, Karlson EW, Toes RE, de Vries N, Begovich AB, Worthington J, Siminovitch KA, Gregersen PK, Klareskog L, Plenge RM. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet* 2010; **42**: 508-514 [PMID: 20453842 DOI: 10.1038/ng.582]

58 **Coenen MJ**, Trynka G, Heskamp S, Franke B, van Diemen CC, Smolonska J, van Leeuwen M, Brouwer E, Boezen MH, Postma DS, Platteel M, Zanen P, Lammers JW, Groen HJ, Mali WP, Mulder CJ, Tack GJ, Verbeek WH, Wolters VM, Houwen RH, Mearin ML, van Heel DA, Radstake TR, van Riel PL, Wijmenga C, Barrera P, Zhernakova A. Common and different genetic background for rheumatoid arthritis and coeliac disease. *Hum Mol Genet* 2009; **18**: 4195-4203 [PMID: 19648290 DOI: 10.1093/hmg/ddp365]

59 **Maiti AK**, Kim-Howard X, Viswanathan P, Guillén L, Rojas-Villarraga A, Deshmukh H, Direskeneli H, Saruhan-Direskeneli G, Cañas C, Tobön GJ, Sawalha AH, Cherñavsky AC, Anaya JM, Nath SK. Confirmation of an association between rs6822844 at the Il2-Il21 region and multiple autoimmune diseases: evidence of a general susceptibility locus. *Arthritis Rheum* 2010; **62**: 323-329 [PMID: 20112382 DOI: 10.1002/art.27222]

60 **Okada Y**, Wu D, Trynka G, Raj T, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Yoshida S, Graham RR, Manoharan A, Ortmann W, Bhangale T, Denny JC, Carroll RJ, Eyler AE, Greenberg JD, Kremer JM, Pappas DA, Jiang L, Yin J, Ye L, Su DF, Yang J, Xie G, Keystone E, Westra HJ, Esko T, Metspalu A, Zhou X, Gupta N, Mirel D, Stahl EA, Diogo D, Cui J, Liao K, Guo MH, Myouzen K, Kawaguchi T, Coenen MJ, van Riel PL, van de Laar MA, Guchelaar HJ, Huizinga TW, Dieudé P, Mariette X, Bridges SL, Zhernakova A, Toes RE, Tak PP, Miceli-Richard C, Bang SY, Lee HS, Martin J, Gonzalez-Gay MA, Rodriguez-Rodriguez L, Rantapää-Dahlqvist S, Arlestig L, Choi HK, Kamatani Y, Galan P, Lathrop M, Eyre S, Bowes J, Barton A, de Vries N, Moreland LW, Criswell LA, Karlson EW, Taniguchi A, Yamada R, Kubo M, Liu JS, Bae SC, Worthington J, Padyukov L, Klareskog L, Gregersen PK, Raychaudhuri S, Stranger BE, De Jager PL, Franke L, Visscher PM, Brown MA, Yamanaka H, Mimori T, Takahashi A, Xu H, Behrens TW, Siminovitch KA, Momohara S, Matsuda F, Yamamoto K, Plenge RM. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014; **506**: 376-381 [PMID: 24390342 DOI: 10.1038/nature12873]

P- Reviewer: Garip Y, Saviolas G **S- Editor**: Wen LL
L- Editor: Roemmele A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com