Rheumatoid arthritis susceptibility genes: An overview

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Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease sustained by genetic factors. Various aspects of the genetic contribution to the pathogenesis 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.

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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.

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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 HLA-DRB1*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...
been tested for ACFA antibodies, RF and HLA-DR gen-
otype, and the results showed a correlation between the
presence of RF and ACFA antibodies within the HLA-
DRB1 SE\(^{[37]}\). Moreover, current smoking habits and SE, especially homozygous SE, have a strong interaction\(^{[38]}\). 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 DERRA motif\(^{[9-11]}\). The study in Hungarian RA patients recommended that HLA-
DRB *1301 allele may protect against ACPA positive or ACFA negative RA\(^{[9,12-15]}\). Also, enhanced production of ACFA has been connected with HLA-DRB1*15 positively in RA\(^{[9,16-18]}\). In a Korean population, heterozygous for HLA-DRB1 0404 or 0901 have up to a 60-fold increased risk of developing susceptibility to RA\(^{[10]}\).

A new taxonomy system for the risk of developing RA has been proposed\(^{[11]}\). 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\(^{[24-26]}\) 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 peptidylargi-

**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 ACFA. 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\(^{[21,22]}\). PADI4 gene maps on 1p36 locus have been associated with European and Japanese RA populations. A meta-analysis done by Lee et al\(^{[30]}\) 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\(^{[28,29]}\).

Within the genes investigated for susceptibility to RA, protein tyrosine phosphatase type 22 (PTPN22) 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\(^{[3,24]}\). This SNP has been associated with RF, ACFA positive and SE. ACFA 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\(^{[3,11]}\). The important fact is that this polymorphism is not associated with RA in Asian populations, maybe only with Asiatic Indians with RA positive\(^{[30]}\).

**Signal transducer and activator of transcription 4**

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

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**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       | 1     | Rs2476601 | 1.23-1.75 |
| PADI4          | 1     | Rs2403540 | 1.4 |
| STAT4 T/C      | 2     | Rs1189094 | 1.22 (0.96-1.53) |
| FCGR2A         | 1     | Rs12946613 | 1.1 |
| CTLA4          | 2     | Rs3087243 | 0.75-1.136 |
| CCL2           | 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.
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upon activation and maturation of monocytes as well as immature dendritic cells. STAT is also overexpressed in RA synovium. Lee et al[23] and Amos et al[29] 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[30,37,39-43]. Comparison between ACPA positive and negative patients showed no significant differences[23]. It seems that the intronic variant rs11893432 C/G of STAT4 gene could also predispose to RA[25,44].

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[31,46-48]. 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[49,50].

TNF

TNF alpha is a pleiotropic inflammatory cytokine. TNF-308A/G (rs1800629) polymorphism is associated with RA in the Latin American population[26,58] 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[22] 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)[33,34]. 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[56,59]. Some studies reported that the homozygosity of -592C/A was associated with higher Larsen scores in RA patients with ACPA and RF negative[53]. 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[52,53,54].

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 revaluated as RA susceptible regions, such as CD226, CD40, CDK6, MBP, BLK, REL and more[58].

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 myocardial infarction, severe infection or lymphoma, as well as to identify the patients who will respond to biological medication therapy.

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