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Rheumatoid arthritis susceptibility genes: An overview

Korczowska I.Rheumatoid arthritis susceptibility genes

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**Abstract**

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease sustained by genetic factors. Various aspect of genetic contribution to the pathogenetics and outcome of RA is still unknown. So far several genes have been indicate in pathogenesis in RA. Apart of human leukocyte antigen large genome wide association study have indentifies many loci involved in RA pathogenesis. This genes includes protein tyrosine phosphatase, nonreceptor type 22, PADI4, signal transducer and activator of transcription 4, CTLA4, TRAF1-C5, tumor necrosis factor and other. It will be important to determine whether combination of RA risk allele are able to subset patients who develop certain clinical outcomes such myocardium infarction, severe infection or lymphoma as well as subset the patient to categories who response to biological medication therapy or not.

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

**Core tip:** This is a comprehensive review concerning genetics factor in rheumatoid arthritis.

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**INTRODUCTION**

Rheumatoid arthritis (RA) is the most common autoimmune disease. The disease is afflicting around 0.5%-2% of the human population, especially in females, but the precise etiology is still unknown. RA is characterized by chronic, systemic inflammation that may affect many tissue, principally of the synovial tissue, leading to joint destruction, functional disability and somethimes death[1]. Environmental as well as a genetic factors are responsible for susceptibility and the phenotype. Environmental factors they are geography, climate, endemic microbes, lifestyle such as smoking and dietary[2,3]. Some of Native American show a relatively higher preferences than African or Asian population. We cannot forget about familial clustering. The prevalence of RA ranges 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 it is known that many diseases have been associated with this region. The first risk alleles for RA were identified within 3,6Mb, 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 establish that the HLA-DRB1\*01 and HLA-DRB1\*04 and HLADRB1\*10 alleles containing the SE were associated with susceptibility of RA, and amnio acides sequences QKRAA, QQRAA and KKRAA were known SEs conferring susceptibility while DERAA sequences for protective effects[5,6]. Caucasian RA patients have 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 present smoke habits and SE, especially homozygous SE, have a strong interaction[3,8]. SE is a risk factor for the development of an extraarticular manifestation and so for more severe, destructive RA. But the non-SE alleles DRB1\*1301, \*1302 and \*1304 seems to be linked to the DERAA motif[9-11]. The study in Hungarian RA patients recommended that HLA-DRB \*1301 allele may care for 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 Korean population, heterozygous for HLADRB1 0404 or 0901 have up to a 60-fold increased risk to developed 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 is represented susceptibility risk of RA) sequence occupies position 71-74 of HLA–DRB1 but is modulated by amnio acids at positions 70; glutamine (Q) and arginine (R) represtend higher risk than aspartic acid (D). And the risk in position 71; lysine (K) confers the higest risk, arginine (R) intermediate risk and the lowest risk is for alanine (A) and glutamic acid (E). According to this new classification, SE alleles have been 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 positive association with RA and also correlated with ACPA production, while S1 and S3D and X was found as a low risk alleles[9,11,20].

Genome wide association studies (GWAS) and large scale cohorts - Wellcome Trust Case Control Consortium (WTCCC) databases have allowed the simultaneous evaluation of thousands genes[9,21-23] and raised to attention not only in association with RA susceptibility, determining phenotype of the disease but also response to therapy. Although there are additional variants in the MHC contributed 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 is shown at Table 1. Loci outside the MHC have been associated in RA population in approximately 4% to the phenotypic variance of RA risk. One of them is PADI4 encoding peptidylarginine deiminase type IV.

**PADI4**

One of the isoenzymes carrying the post-translational conversion of arginine residues to citruline is known as the type 4 peptidylarginine deiminase type IV. PADI4 enzyme may be connected to the production of ACPA. PADI4 is very 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 1p36locus has been associated with RA population in European and Japanese. But meta-analysis done by Lee *et al*[25] shown that in Asian patients all with 5 researches polymorphism (PADI4\_89, PADI4\_90, PADI4\_93, PADI4\_94 and PADI4\_104) were significantly associated with RA, while in European only PADI4\_94 was associated with RA risk, much poorly than in Asian patients[26,27]. The function of this gene in the RA European population is still questionable, because results of large studies from Spain, France and the UK did not find any 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 associated.

**PTPN22**

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. Than it has been associated with RA in Caucasian population; rs2476601, C1885T polymorphism leading to an amino acid modificate from Arg to Trp at amnio 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 and ACPA positive and moreover to SE and 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 importance fact is that this polymorphism is not associated with RA in Asian populations, may be only with Asiatic Indians with RA positive[36].

**STAT4**

The signal transducer and activator of transcription 4 (STAT4) is a transcription factor that intercede 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 dendritis cells. STAT is also overexpressed in RA synovium. **Lee** *et al*[37] and Amos *et al*[38] detect linkage at chromosome 2q33 in RA and then revealed that polymorphism located at 2q33 STAT4 gene is the marker responsible for the linkeage signal in 2q33. It has been found that STAT4 rs7574865 polymorphism is associated with RA patients in European and Asians as well as Latin American[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].

**CTLA-4**

Cytotoxic T lymphocyte-associated antigen 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 such as microsatelite at position 642of 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 sequnce C/T transition[45]. The CT60 allele has been associated with autoimmune diseases. In the end CTLA-4 export to the membrane is reducing and decrease in the inhibitory function of CTLA-4. Daha *et al*[48] shown that CTLA4 rised the development of ACPA positive RA contrast to RA patients with ACPA negative. The meta-analyses shown a positive connection of 49A/G polymorphism susceptibility with RA in Asians but only 1 in Asians and Europeans[3, 46,47]. 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. The TRAF1 is a member of the TNF receptor associated factor family which are class of proteins that link TNF receptor family members associated with signaling pathways that play a function in apoptosis, in 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 to the maximal genetic signal are 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 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 RA patient. Khanna *et al*[51]showed that patients with -308 TNF alpha AA+AG genotypes had considerable higher rates of progression in erosion scores and Sharp scores equated to the GG genotypes patients. In contrast Lacki *et al*[52] suggests that in RA patients TNF-308 polymorphism cannot serve as an indicator of the disease course.

**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 investigating, 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 being associated with more severe structural damage, (mainly with Larsen's score in wrist joints)[3,53,54]. IL-6 is a mulifunctional cytokine imply 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 polymorphism in the promoter region of IL-6; the -174G/C and -572G/C suggests a strong susceptibility to European RA patients compared to Asian. These two polymorphism (rs1800795 and rs1800795) may also influence the risk of osteoporosis. Another multifunctional cytokine is IL-10. IL-10 produced by monocytes and lymphocytes is a protein that inhibits the synthesis of a number of cytokines and has a range of anti-inflammatory and immunoregulatory properities. Three polymorphism placed in the promoter IL-10, were studied, including: -1082G/A (rs 1800896), -892C/T (rs1800871) and -592C/A (rs1800872). The results are controversial one of them showed that -1082G/A polymorphism is not associated with the RA of either European nor Asian populations, and another one showed a positive association with RA indicating that the carriers of the G allele could have a decreased liability to 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]. Polymorphism of the IL-2 and IL-21 genes (region 4q27) have been implicated in several autoimmune diseases also with RA. One of them is intronic change A/G the rs13151961[57]. Next studied was polymorphism 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 IL-2 is the G/T rs6822844. It was study on European Caucasian population and South American and the result shown significant association with RA[26,58,59].

The use of GWAS, genetic studies which could exam of many common genetic variants, can now be lead 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 conclude, rheumatoid arthritis has a strong genetic influence mediated by allele. Human genetics should be able to determine the value of RA risk alleles by providing clinical prediction. One of the most unmediated clinical applications is to use human genetics to lead the development of the treat RA. It will be crucial to determine whether a combination of RA risk allele are able to subset patients who develop certain clinical outcomes, such as myocardium infarction, severe infection or lymphoma, as well as to subset the patient to categories who response to biological medication therapy or not.

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