Review Articles

Roles of Genes in the Susceptibility to and Severity of Rheumatoid Arthritis - A Review

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Abstract:

Rheumatoid arthritis (RA) is a chronic heterogeneous autoimmune disorder of unknown etiology. Genetic factors play an important role in susceptibility to RA as the heritability of RA is between 50% and 60%, with the human leukocyte antigen (HLA) locus accounting for at least 30% of overall genetic risk. It is conceivable that there is more than one susceptible gene(s) operative in RA, and an interaction of the relevant genes may predispose the offspring to develop the disease under certain conditions .Outside the major histocompatibility complex (MHC) region, some additional risk loci have been identified and validated including PTPN22, STAT4, PADI4, CTLA4 and others Genetic factors are also important in RA pharmacotherapy due to the gene-dependent activity of enzymes involved in the pharmacokinetics and/or pharmacodynamics of RA medications. Indeed, there is great variability in drug efficacy as well as adverse events associated with any anti-rheumatic therapy and genetics is thought to contribute significantly to this inter-individual variability in response. The ability to screen the entire genome for association to complex diseases has great potential for identifying gene effects.

***Keyword**: Rheumatoid Arthritis (RA), Human Leukocyte Antigen (HLA), Gene*

Introduction:

Rheumatoid arthritis is the most common cause of inflammatory polyarthritis in adults.[1] Many studies suggest that RA involves a combination of genetic factors, including genetic markers as well as familial transmission and environmental factors. The most compelling evidence for a genetic component is in monozygotic twins, in whom the concordance rate is 12% to 15% when one twin is affected compared with 1% for the general population. The risk for a fraternal twin of a patient with RA also is high (about 2% to 5%), but this is not more than the rate for other first-degree relatives.[2,3,4,5] Although the immunogenetics is, at best, incompletely understood, one of the best-studied and perhaps most influential genetic risk factors is the class II MHC haplotype of an individual.

Role of HLA-DR in rheumatoid arthritis

A genetic link between HLA-DR and RA was initially described in the 1970s with the observation that HLA-DR4 occurred in 70% of RA patients compared with about 30% of controls, giving a relative risk of having RA of approximately 4 to 5 to individuals with HLA-DR4.[6] Many population studies confirmed the original association with DR4, but as

a wider range of populations were studied, a number of interesting findings emerged. First, RA is not associated with all subtypes of HLA-DR4.[7] Second, in some populations, other DRB1 alleles, including DRB1*0101, DRB1*1001, DRB1*1402, are also associated with RA.[8,9,10] The structure of class II MHC molecules in antigen presenting cells is associated with increased susceptibility and severity of RA.[8] Van Zeben et al, 1991 has shown DR4-positive patients had more swollen joints, higher scores on Ritchi articular index, Health Assessment Questionnaire, higher radiological scores, and use of second-line drugs compared with DR4-negative patients.[9] Higher frequency of DR4 and DR1 is found in patients with mild RA but DR4 and DR4 is associated with DQw7 in patients with severe RA.[10] In a prospective study in Middlesex hospital, London among RA patients showed a positive correlation between HLA-Dw4 and the eventual severity of peripheral radiological changes.[11]

What is special about the shared epitope?

Molecular analysis have shown that all RA- associated DRB1 alleles have in common a highly conserved sequence of amino acids (70 through 74) (QKRAA, QRRAA, or RRRAA) in the third hypervariable region of the molecule,

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and this led to the formulation of the RA "shared epitope" hypothesis, is thought to be responsible for the susceptibility of RA.[12]

The epitope is glutamine-leucine-arginine-alanine-alanine (QKRAA), a sequence found in DR4 and DR14 (in which RA is more prevalent), in addition to some DR1â-chains. The QKRAA epitope predicts the severity of established RA, with a greater prevalence of extra-articular disease and erosions in patients with two susceptibility alleles compared with one.[13] But it is not prominent in some ethnic and racial groups like Greeks, Pakistanis, Chileans, and African-Americans. Current nomenclature attempts to clarify these ambiguities by including information on the specific DRâ sequences. The DR4â-chains with the greatest association with RA are referred to as DRB¨0401, DRB¨0404, DRB¨0101, and DRB¨1402. When the structure of this sequence is considered, 96% of patients with RA exhibit the appropriate HLA-DR locus in some populations.[12]

There is a significant association between the shared epitope and RA. RA patients who carry two shared epitopes have significantly greater prevalence of anti-CCP than those with one or none.[4,5]

RA Susceptibility Genes-
Outside the major histocompatibility complex (MHC) region, some additional risk loci have been identified and validated, and include the following:

- PTPN22 gene -The tyrosine phosphatase PTPN22 allele 1858T has been associated with rheumatoid arthritis (RA) and other autoimmune diseases. RA is the most frequent of those multifactorial diseases. The RA association was usually restricted to serum rheumatoid factor positive disease (RF+).The linkage proof for the PTPN22-1858T allele and RF+ RA is proved.[14,15]
- STAT4 gene — STAT4 encodes a transcription factor that transmits signals induced by several key cytokines, including interleukin (IL)-12 and type 1 interferons, as well as IL-23. STAT4-dependent signaling by IL-12 receptors plays a critical role in the development of Th1-type responses. A variant allele of STAT4 confers an increased risk of RA. Homozygosity of the risk allele is associated with a more than doubled risk of SLE and a 60 percent increased risk of RA.[16]
- TRAF1-C5 gene locus — The TRAF1 gene encodes TNF receptor-associated factor 1, and the C5 gene encodes complement component 5. A genome-wide analysis of North American and Swedish patients revealed that a common genetic variant at the TRAF1-C5 locus on chromosome 9, identified by the rs3761847 SNP, appeared to increase the risk of anti-CCP antibody-positive RA.[17]

- Chromosome 6q23 - an intergeneic region between the OLIG3 and TNFAIP3 genes on chromosome 6q23 has been associated with RA susceptibility in both US and UK populations.[18,19]
- PADI-4 gene - Peptidylarginase deaminase (PADI) genes responsible for post-translational modification of arginine to citrulline, Four isoforms have been identified, known as PADI 1 through PADI 4. In the light of striking associations of RA with anticitrulinated peptide antibodies, several groups have investigated potential associations with these genes.[20]
- CTLA-4 gene — Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is important for downregulation of T-cell activation, and CTLA-4 gene polymorphisms have been implicated as risk factors for rheumatoid arthritis (RA) .[21]
- PRKCQ gene - RA is associated with a variant that map to chromosome 10p15[21].
- KIF5A gene - A SNP mapping to intron 15 of the KIF5A gene has also been associated with RA susceptibility.[21]
- IL2RB gene - A SNP in the promoter region of the gene for the beta unit of the IL-2 receptor (IL2RB) has shown strong evidence for association with RA.[22]
- CD40 gene - a meta-analysis of available data from genome-wide association studies of RA showed strong evidence for association of the CD40 gene with RA susceptibility.[21]

Protective alleles
Although the predisposing effects of the SE-encoding HLA–DRB1 alleles are generally accepted, controversy exists regarding the possible protective effects of certain HLA–DRB1 alleles. These alleles contain, instead of the SE, another common anchor region consisting of the amino acids DERAA. HLA–DRB1 alleles that express this DERAA sequence (DRB1*0103, *0402, *1102, *1103, *1301, *1302, and *1304) may protect against RA.[23]

• Combinations of genetic markers —
As many of the markers noted above have weak associations with RA, it was logical to determine whether various combinations of these markers had greater predictive value for determining who is at risk for the development of RA. In a study involving 4238 RA patients and 1811 controls, while the presence of the SE, PTPN22, STAT4 and TRAF1/C5 alone had odds ratios (OR) for RA of 3.75, 1.45, 1.31 and 1.03, respectively, the following combinations had far higher odds ratios: [24]

- SE + PTPN22 + STAT4 + TRAF/C5 (OR 9.94)
- SE + PTPN22 (OR 9)

Clinical Use of Genetic Markers

- For diagnosis or screening of RA —

  Although certain HLA alleles are strongly associated with severe RA, these alleles are common in the normal population, the absolute risk of developing RA among Caucasians carrying the DR alleles 0401, 0404, or 0101 is approximately 1 in 46.[25] The highest calculated absolute risk is present in individuals expressing both 0401 and 0404, but is still only about one in seven. Even knowing the genotype at the second confirmed RA susceptibility locus, the PTPN22 gene, the predictive value remains too low to be useful for either diagnosis or population screening.

- For estimating prognosis —

  Genotyping for SE alleles may help predict which patients are at highest risk of severe, erosive disease, and thus candidates for early, aggressive intervention. This information may be less important clinically if patients with early RA are aggressively treated with potent DMARD regimens, consistent with current approaches to disease management.

  The presence of HLA SE alleles is strongly correlated with the presence of anti-CCP antibodies.[26,27]

- Genes determining response to treatment-

  Limited data suggest that knowledge of a patient's HLA status may be useful in predicting the response to specific therapies.

Tan et al, 2009 showed that anti-tumour necrosis factor (anti-TNF) therapy has proved to be highly successful in treating rheumatoid arthritis (RA), although 30-40% of patients have little or no response, which may be genetically determined. In other complex diseases, susceptibility genes have been shown to influence treatment response. AFF3 and CD226, two confirmed RA susceptibility genes, found to have an additional role in influencing the response to anti-TNF treatment.[28]

Conclusion:

We hope that by knowing which genes are modestly involved in a complex disease like rheumatoid arthritis is not very useful from a practical point of view, but it is very important for giving insight into the disease's pathogenesis. It is predicted that once all susceptibility genes are identified individuals could be screened for the presence of these genetic variants. Those with several of the identified alleles can be identified as being at high risk for developing the disease, and prophylactic measures could be taken or specific treatment options can be selected. We believe that one day; these genetic findings will help identify which patients will receive relief from anti-TNF therapy and which patients should focus on another therapy, perhaps B-cell depletion.

Conflict of Interest: None

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