GENETIC DIFFERENCES BETWEEN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract
Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease. RA likely develops beginning with genetic risk. Investigating of preclinical period of RA will lead to understanding of the relationships between genetic and environmental factors. The recently studies confirm the polygenic contribution of the major histocompatibility complex (MHC) to RA. Various genetic factors involved in the pathogenesis of RA have been discovered. HLA genes contribute only a portion of the genetic susceptibility to RA. There is also evidence for a contribution of non-class II genes to susceptibility. Non-HLA genes are also involved in disease pathogenesis, and identifying them remains a challenge. The association between RA and certain MHC alleles may be important in the pathogenesis of RA. In the future, research into genetic factors correlated with the severity of RA is expected to yield interesting and hopefully clinically relevant results. In this article we review the current data supporting the existence of susceptibility gene for RA.

Key words: rheumatoid arthritis, genetic approaches

Rheumatoid arthritis (RA) is a complex heterogeneous genetic disease. Based on twin studies the contribution of genetic factors to the pathogenesis has been estimated to be about 60% (1,2).

Several novel approaches have been used in the attempt to unravel the complex association of RA with the human leukocyte antigen (HLA) gene region. The genetic contribution to RA is evidenced most convincingly by the association of certain class II major histocompatibility complex (MHC) gene products (e.g., HLA-DR) with the development and/or severity of RA, approximately one third arises from the MHC at 6p21.3. (3,4).

The number of established RA susceptibility loci has now grown to 13. An association between HLA-DR4 and RA was already documented almost 30 years ago. Research into functional defects of gene products of genetic risk variants will increase the understanding of the pathogenesis of RA (5-7).

RA patients with two disease associated alleles tend to have more extra-articular manifestations as well as more destructive joint involvement than those with only one allele.

A large body of work has shown that there is a strong association between RA and the presence of DR4 alleles. An other association has been observed between RA and other MHC class II
gene products. RA has been associated with DR1 (DRB1*0101) (8-10). The discovery of risk variants suggests immunological processes that are involved in disease pathogenesis. The protection is mediated by regulatory T cells reactive. RA is reported to be subclassified into two subsets by anti-citrullinated peptide antibody. A lot of reported susceptibility genes to RA (i.e., HLA-DRB1(*04, PTPN22, TRAF1/C5, CTLA4) are found to be associated only with anti-CCP positive RA but not with anti-CCP negative RA. The contribution of specific DRB1 alleles encoding the shared epitope has been well described. Several studies have suggested that additional telomeric genetic influences may exist. The HLA-DRB1 locus within the major histocompatibility complex (MHC) at 6p21.3 has been identified as a susceptibility gene for RA (11-14). The polygenic contribution of the MHC to RA implicates 2 additional non-DRB1 susceptibility loci. Anti-CCP antibody positive RA tends to develop more severe arthritis than negative RA. DRB1*03 was exclusively associated with anti-CCP negative RA. The DRB1*13 allele plays a dual role in the development of RA, by protecting against anti-CCP positive RA but, in combination with DRB1*03, increasing the risk of anti-CCP-negative RA. Protection against anti-CCP-positive RA is predominately associated with HLA-DRB1*1301 (15-17).

It has also been suggested that HLA-DQ alleles in linkage dysequilibrium with HLA-DR4 may be involved in the predisposition to disease. It is possible that HLA-DR derived peptides may modulate the development of arthritis through presentation by HLA-DQ molecules. A deletion polymorphism in glutathione S-transferase Mu-1 (GSTM1-null) has been implicated to play a role in RA risk and progression (18). About 5 years ago it reported that certain HLA-DR1 alleles are associated with protection both against developing RA and a severe course of the disease The role of the HLA-DQ in RA has been a subject of controversy. The description of the new genetic risk factors and the interaction with environmental triggers as well as phenotypic features are gradually expanding the ability to predict disease susceptibility and course (19). Those with one at-risk allele, in turn, tend to have more severe disease than those patients with RA who inherit no disease-associated MHC type. The investigation of genetic factors affecting the development or severity of RA may give new insights into the pathways involved in disease pathogenesis and lead to the identification of novel therapeutic targets. Nevertheless, additional larger genomic and functional studies are required to further define their role in RA.

**Conclusion**

Recent groundbreaking advances have expanded our knowledge about the genetic factors that contribute to the susceptibility and severity of RA. The genetic basis of RA can be explained by known risk loci. There is a difference in genetic risk factors for RA in patients with or without antibodies against cyclic citrullinated peptides. Explanation for these HLA associations comes from molecular analysis of the MHC class II molecules. The main genetic contribution comes from the HLA complex. No gene other that HLA-DRB1 has been clearly demonstrated to be involved in the disease. The findings indicate that there might be a role of variations in genes involved in the immune response and in tissue repair in RA pathogenesis.

**References**


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