# Genomic Influences on Susceptibility and Severity of Rheumatoid Arthritis

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**KEYWORDS**

• Genomics • Genetics • Rheumatoid arthritis • Severity • Phenotype

**KEY POINTS**

- Genetic studies have increased our understanding of rheumatoid arthritis (RA), pointing out the importance of HLA-DRB1 HLA-B and HLA-DPB1, JAK-STAT signaling, NF-kB, and T-cell receptor signaling.
- The genetics of RA severity is challenging because of the variability of the phenotype, the large amount of data needed, and the interactions with environment.
- The heterogeneity within RA hampers the findings of strong genetic associations.
- The combination of genetic risk factors into a Genetic Risk Scores creates a fairly good predictive model, but its clinical applicability is yet limited.
- Future studies are needed that focus on the functional understanding of the found genetic variants as well as on the development of methods that can encompass with the complexity of RA development.

## INTRODUCTION

Rheumatoid arthritis (RA) is widely considered the most common chronic inflammatory arthritis. RA is characterized by symmetric polyarthritis of the small hand and feet joints, which leads to irreversible destruction of joints and subsequently to significant morbidity, disability for patients, and costs for society.

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Current treatment options are such that the decreased life expectancy as well as the severe joint destruction can substantially be reduced. Still, a high degree of variability in disease outcome and treatment response is observed among the group of RA patients. A problem in the treatment and diagnosis of RA is that the underlying abnormality is incompletely understood and patients are diagnosed with RA if they fulfill a subset of a list of criteria. Typically, treatment is targeted against inflammatory processes in general.

Therefore, an important aim in RA research is to improve the knowledge of the abnormality. The current understanding of RA is that it follows a multiple hit model that includes different preclinical phases, eventually crossing a threshold leading to the manifestation of clinical symptoms and ultimately joint damage. Likely, genetic predisposition combined with environmental factors influence the transition from one disease stage to another. The importance of genetics in understanding RA is underlined by the observation that RA heritability is ~40% to 65% for seropositive RA and ~20% for seronegative RA.[1,2] A family history of RA confers a 3- to 5-fold increased risk of developing RA.[1] These findings have fueled genetic studies and improved the understanding of RA.

After decades of genetic research in RA, the question arises whether this information has changed the clinical care. In this review, the authors aim to give the reader an overview of the major findings and issues in the field of RA genomics from a clinical perspective.

## GENETICS OF RHEUMATOID ARTHRITIS SUSCEPTIBILITY

Most genetic studies explored RA susceptibility by comparing the prevalence of genetic variants between cases and controls. These studies have led to a large number of discoveries, especially after the introduction of genome-wide association studies. Still, the major genetic risk region, the HLA region, was discovered decades ago (see Vincent van Drongelen and Joseph Holoshitz's article, "HLA-Disease Associations in Rheumatoid Arthritis," in this issue).

### *Human Leukocyte Antigen in Rheumatoid Arthritis Susceptibility*

HLA is a region of greater than 200 genes that encodes the major histocompatibility complex (MHC), which plays a crucial role in immune regulation. MHC molecules are located on the surface of many immune cells (such as macrophages, B cells, and especially dendritic cells), where they recognize pathogens and present them to T cells.

The fact that this genetic region is highly variable, spans a large region with many immune genes, and is characterized by strong linkage disequilibrium makes it a challenging region to study. The increasing insight into the region and methods to study this region has led to a repeatedly changing nomenclature and improved the precision of its association with RA. The dominant RA association within the HLA region is with the HLA-DRB1 locus. Until recently, the major association of this gene with RA was considered to be the HLA-Shared Epitope (HLA-SE), a 5-position amino acid motif at position 70 to 74 at the HLA-DRB1 gene encoding the amino acid sequences QKRAA, QRRAA, or RRRAA.[3]

Recent studies were able to study the region more precisely by the availability of highly dense genome-wide association studies (GWAS) and the development of imputation methods to more precisely define the highly polymorphic HLA region from single nucleotide polymorphism (SNP) data. These studies showed that the most significant associations within the HLA region are a combination of amino acid residues encoded