Future Directions of Genomics Research in Rheumatic Diseases

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KEYWORDS

• Human genetics • Statistical genetics • Genome-wide association study
• Next-generation sequencing • Human leukocyte antigen

KEY POINTS

- Recent developments in human genome genotyping and sequencing technologies have successfully identified several risk genes of rheumatic diseases.
- Fine-mapping studies using the HLA imputation method revealed that both classic and nonclassic HLA genes contribute to the risk of rheumatic diseases.
- Integration of human disease genomics with biological, medical, and clinical databases should contribute to the elucidation of disease pathogenicity and novel drug discovery.
- Disease risk genes identified by large-scale genetic studies are considered to be promising resources for novel drug discovery, including drug repositioning (eg, CDK4/6 inhibitors), and biomarker microRNA screening (miR-4728-5p and its target gene of PADI2) for rheumatoid arthritis.

BACKGROUND

Rheumatic diseases are autoimmune diseases that are characterized by inflammation and destruction of joints, muscles, blood vessels, and organs. Both genetic and environmental factors typically contribute to the onset of rheumatic diseases. For example, familial and epidemiologic studies have demonstrated that approximately

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50% of the disease risk of rheumatoid arthritis (RA), one of the most common rheumatic diseases that affect synovial joints, is explained by genetic factors.[1] Recent developments in human genome sequencing technologies, such as high-density single nucleotide polymorphism (SNP) microarrays and next-generation sequencing (NGS), have substantially contributed to the elucidation of the genetic architecture of human complex traits. In particular, genome-wide association studies (GWAS), a method of statistical genetics that massively evaluates the disease risk of genome-wide SNPs, has successfully identified several human disease risk genes.[2] Specifically for RA, a large-scale transethnic GWAS identified more than 100 risk genetic loci, with implications for novel drug discovery.[3,4] In this review, the authors highlight recent findings on genomics of rheumatic diseases and their application to translational research.

ROLES OF THE MAJOR HISTOCOMPATIBILITY REGION TO RISK OF RHEUMATIC DISEASES

The major histocompatibility complex (MHC) region, a genetic locus located at chromosome 6p23, is known to have a strong impact on the genetic risk of rheumatic diseases. Although this region is only 0.1% of the length of the human genome, the MHC region confers most of the risk for most rheumatic diseases. The initial identification of the genetic risk loci was reported to be associated with the HLA genes located in the MHC region, such as *HLA-DRB1* for RA,[5] *HLA-C* for psoriasis,[6] *HLA-B* for ankylosing spondylitis,[7] and *HLA-DPB1* for Graves disease.[6] However, delineation of the detailed disease risk of HLA alleles has been challenging and controversial owing to the complex structures of the polymorphisms in the MHC region. For RA, the *HLA-DRB1* alleles, which share a conserved amino acid sequences at positions 70 to 74 and are called shared epitope (SE) alleles, confer strong risk in multiple populations,[5,8,9] but non-SE *HLA-DRB1* alleles contribute risk as well.[9]

Recently, the method of statistical genetics called HLA imputation was developed.[10] This approach computationally imputes (ie, estimates) HLA alleles of the individuals using SNP genotyping data and, therefore, allows comprehensive HLA allele risk assessment using existing large-scale GWAS data without additional genotyping costs.[10] Application of the HLA imputation method to GWAS data had facilitated successful fine-mapping of the risk HLA variants of multiple diseases.[11–21] HLA imputation-based analysis of GWAS data in autoantibody-positive RA revealed that most of the MHC risk was explained by amino acid sequence polymorphisms at positions 11 and 13 of HLA-DRβ1 molecule in multiple populations, including Europeans,[11,12] East Asians,[13] Japanese,[14] and African Americans (**Fig. 1**).[15] The

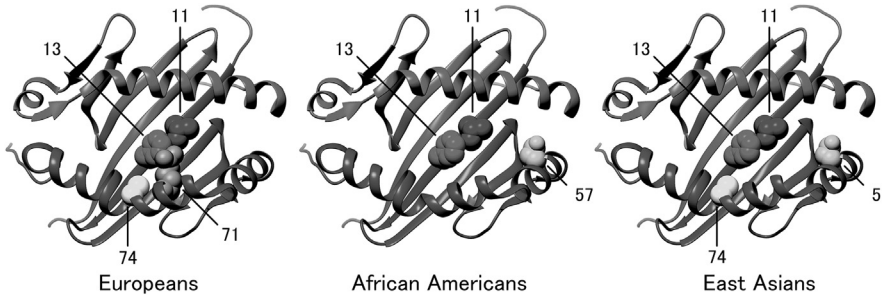

Fig. 1. Amino acid positions of RA risk on 3-dimensional structure of the HLA-DRβ1 molecule. HLA-DRβ1 amino acid sequence alterations at positions 11 and 13 confer strong risk of RA in multiple populations.[11–15]

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