

Integrative Approaches to Understanding the Pathogenic Role of Genetic Variation in Rheumatic Diseases



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KEYWORDS

- Rheumatic disease • Integrative genomics • Systems biology • Precision medicine
- Genetics • GWAS

KEY POINTS

- Large genetic studies of rheumatic diseases have implicated many risk loci.
- Within risk loci, the identity and function of the pathogenic variants that underlie rheumatic diseases remain largely unknown, but methods in development will address these gaps in knowledge.
- Integrative analysis of omics datasets will yield new insights into the molecules, cells, tissues, and pathways that initiate and perpetuate rheumatic diseases.
- Functional characterization of prioritized genetic variants will pave the way for better diagnosis, treatment, and prevention of rheumatic diseases.

Disclosure Statement: J.Y. Chen discloses that he is also the founder of MedeoLinx, LLC, an Indianapolis startup biotech company providing novel drug discovery products and services based on translational systems biology. Other authors have nothing to disclose.

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Rheum Dis Clin N Am 43 (2017) 449–466
<http://dx.doi.org/10.1016/j.rdc.2017.04.012>

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INTRODUCTION

The study of rheumatic diseases draws on many genome-scale technologies. **Box 1** defines relevant terms that will be used in this discussion. Genome-wide association studies (GWAS) and other genetic studies have identified and replicated numerous loci associated with rheumatic diseases. Although these findings have led to increased awareness of particular pathogenetic pathways, there are multiple impediments to the translation of these results to the clinic. First, and as expected, the variants identified thus far do not account for the entirety of the heritable basis of any given rheumatic disease. Second, genetic variants in close physical proximity tend to be inherited together (linkage disequilibrium, or LD, see **Box 1**). As a result, a rheumatic disease risk locus usually contains multiple associated variants, from which the actual pathogenic variants are difficult to separate. This is most pronounced in the major histocompatibility complex region, where there are hundreds of associated variants, many of which are in strong LD. However, new techniques that leverage transethnic and annotation data will help narrow the search for single-nucleotide polymorphisms (SNPs) that are directly pathogenic. Finally, determining the mechanisms of action of pathogenic variants is challenging, due to interaction effects, cell type-specific gene expression, the local tissue milieu, the temporal course of gene expression, and complicating environmental factors.

There is hope, however. Although rheumatic diseases are complex and have considerable differences in etiology, clinical presentation, and treatment, there is overlap in the pathogenic mechanisms involved. For example, pathobiology involving the adaptive immune system (eg, autoantibodies) is similar among rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory myositis, and Sjögren syndrome. In these conditions, failure of adaptive immune cells (B and T lymphocytes) to maintain self-tolerance opens the way to several aspects of autoimmune pathogenesis, such as autoantibody production. These commonalities stem in part from genetic variants that affect multiple rheumatic diseases and similar conditions; for instance, dysregulation of autoantibody production characterizes patients with a risk variant in *PTPN22*, and this variant is associated with many rheumatic conditions, including RA, SLE, type 1 diabetes, and others.¹ Identifying such shared risk factors may provide insights into causes of rheumatic diseases. Furthermore, ongoing technological and bioinformatic advancements have enabled increasingly accurate and sensitive characterization of cells, tissues, organisms, and diseases through analyses of the genome, transcriptome, epigenome, proteome, and metabolome (see **Box 1** for definitions). This review discusses how integration of data can help characterize and prioritize genetic variants for laboratory-based studies of their functional and biological consequences that will lead to better understanding of the mechanisms of human rheumatic diseases.

HERITABILITY OF RHEUMATIC DISEASES

Historical evidence for the heritability of rheumatic diseases comes from studies of familial clustering, sibling recurrence risk ratios, twin studies, and parent-child trio studies.² More recently, a large number of advanced methodologies based on genome-wide assays for estimating heritability have been devised.^{3–5} Heritability estimates for rheumatic diseases are often approximately 0.5,² but this is highly variable. GWAS (see **Box 1**) conducted to date have identified hundreds of risk loci for autoimmune diseases and thousands of associations with disease and traits.^{1,2}

Although in aggregate these studies explain a meaningful proportion of disease risk, much of the heritable basis of rheumatic disease remains unexplained. There are

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