Population Genetics and Natural Selection in Rheumatic Disease

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KEYWORDS

• Rheumatic diseases • Population genetics • Natural selection • Genetic variation
• Genetic disease association • Genetic diversity • Adaptation • Genetic disease risk

KEY POINTS

- If untreated, rheumatic diseases can diminish reproductive potential and impair the ability to raise offspring that successfully reproduce. Thus, it is likely that the frequency of disease-risk alleles seen in populations around the world is influenced by population-specific natural selection.
- Both autoimmune and nonautoimmune rheumatic disorders show genetic associations in regions with signatures of selection.
- The prevalence of rheumatic disease may result, at least partially, from past events of selection that increased host resistance to infection.
- Many of the complexities of gene effects in different rheumatic diseases can be explained by population genetics phenomena.

INTRODUCTION

Rheumatic diseases are a family of more than 100 chronic, and often disabling, illnesses characterized by inflammation and loss of function, especially in the joints, tendons, ligaments, bones, and muscles. They collectively affect more than 20% of US adults, with osteoarthritis, rheumatoid arthritis (RA), spondylarthritides, gout,

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and fibromyalgia being the most prevalent.[1,2] Patients often endure lifelong debilitating symptoms, reduced productivity at work, and high medical expenses. Arthritis and related illnesses, as well as back or spine problems, are major causes of disability.[3] Importantly, because many rheumatic diseases present before or during a woman's reproductive years, they can have effects on fetal and maternal outcomes,[4] such as pregnancy loss in women with systemic lupus erythematosus (SLE)[4,5] and vasculitis,[4] and infertility in women with RA.[5]

Most rheumatic diseases exhibit marked gender and ethnic disparities. Most predominately afflict women (eg, RA, SLE, systemic sclerosis, fibromyalgia), but spondyloarthropathies and gout are more common in men.[6] African American individuals are at higher risk than European American individuals for SLE and systemic sclerosis, which they tend to develop earlier in life and experience more severe disease.[7] Despite the variation in prevalence, incidence, and disease severity that are known to vary among ethnic groups, little is known about the genetic etiology of these diseases in the different populations and the reasons for the ethnic disparities remain elusive.

Left untreated, most rheumatic diseases can affect the ability to raise offspring that successfully reproduce and result in reduced reproductive fitness. Thus, alternative forces must exist that permit the relative high frequency of risk alleles. Because immune and inflammatory responses can be highly sensitive to environmental change,[8] evolutionary adaptation to specific environments might have driven selection on immune-related genetic variants, impacting variant frequencies and leaving signatures of selection in the genome. Given that infectious organisms are strong agents of natural selection,[9,10] it is plausible that alleles selected for protection against infection confer increased risk of autoimmune and inflammatory diseases, as the "hygiene hypothesis"[11] postulates. It is thought that the adaptation to pathogen pressure through functional variation in immune-related genes conferred a specific selective advantage for host survival, including protection from pathogens and tolerance to microbiota.[12] However, the emergence of such variation conferring resistance to pathogens is also influencing immune and inflammatory disease risk in specific populations.

In the past decade, multiple genome scans for signatures of selection on common variation have identified many immune-related loci.[13–17] Similarly, 90 genome-wide association studies (GWAS) (**Table 1**) have established rheumatic disease–associated alleles. There is also growing evidence that autoimmune and inflammatory disease–associated variants are under selection.[17–21] This review expands on our previous work[22] and summarizes the evidence for rheumatic disease–associated loci under selection and the candidate selective pressures. Given that genomic variation can have clinically important consequences,[23] elucidating the patterns of variation and the functional role of the selective pressure might contribute to a better understanding of disease etiology and the development of new therapies for improved disease management.

SHARED GENETIC ETIOLOGY IN RHEUMATIC DISEASES

The family of rheumatic diseases is remarkable for its heterogeneity and similar underlying mechanisms. The genetic heritability of rheumatic diseases is extremely variable, ranging from very high in ankylosing spondylitis (AS) to almost negligible in systemic sclerosis.[24] GWAS have proved particularly powerful for autoimmune diseases,[25] including many autoimmune rheumatic diseases, which might be due to their immune and inflammatory genetic etiology. **Table 1** summarizes the rheumatic diseases with published GWAS and the number of disease-associated loci uncovered from these GWAS.

The common genetic etiology is exemplified by the sharing of associated loci among rheumatic diseases, such as the Human Leukocyte Antigen (*HLA*), *STAT4*,