Genetics, Environment, and Gene-Environment Interactions in the Development of Systemic Rheumatic Diseases

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KEYWORDS

• Rheumatoid arthritis • Systemic lupus erythematosus • Ankylosing spondylitis
• Environment • Genetics • Interaction • Smoking

KEY POINTS

- Genetic and environmental risk factors have been identified for rheumatic diseases using case-control, cohort, and genome-wide association studies.
- The identification of gene-environment interactions (GEIs) may elucidate biological mechanisms for rheumatic diseases by causally linking established genetic and environmental risk factors.
- The most well studied example of GEIs in rheumatic disease susceptibility is for cigarette smoking and the *HLA-DRB1* for seropositive rheumatoid arthritis (RA); the presence of both risk factors greatly increases the risk for RA development.
- Owing to the relative rarity of systemic lupus erythematosus (SLE), comprehensive studies of GEIs have not yet been performed for SLE. However, there is some evidence that genes may interact with smoking and ultraviolet-B radiation exposure in increasing the risk for SLE.
- *HLA-B27* is the most potent genetic risk factor for ankylosing spondylitis, and there are suggestions that molecular mimicry by gut microbes might stimulate autoimmunity through GEIs with *HLA-B27*.
- Emerging research frontiers such as epigenetics, metabolomics, and the study of the oral, respiratory, and gastrointestinal microbiome may provide new biological mechanisms to link genetic and environmental risk factors in the pathogenesis of rheumatic diseases.

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INTRODUCTION

The current paradigm for the etiology of autoimmune rheumatic disease is that several preclinical stages precede the onset of clinically apparent disease. When individuals at increased genetic risk are exposed to environmental or lifestyle factors, early alterations in the immune system and the breakdown of self-tolerance ensue, eventually leading to the presentation of overt disease (**Fig. 1**).[1,2] Indeed, several genetic and environmental risk factors have been strongly associated with the risk of incident rheumatic diseases, and many more are weakly associated or hypothesized to be related.[3,4] However, the pathogenesis and biological mechanisms for the development of autoimmune rheumatic diseases remain poorly understood.

Interactions between genetic and environmental factors may elucidate biological mechanisms for rheumatic disease susceptibility and bridge findings in several fields of research. Greater understanding of the etiology of rheumatic disease may provide important insights into prevention, screening, and treatment options. Therefore, researchers in rheumatic disease are motivated to explore the intersection of genetic and environmental risk factors. However, rheumatic diseases present distinct challenges for the identification of gene-environment interactions (GEIs). These challenges include heterogeneous phenotypes, low disease incidence and prevalence, geographic variation in epidemiology, and the difficulty in identifying individuals at elevated risk for disease before clinical diagnosis.

This article serves as an overview to contextualize genetic and environmental risk factors in the development of rheumatic diseases, and highlights future research directions according to study designs and molecular approaches. Specific successes and challenges concerning rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) are addressed.

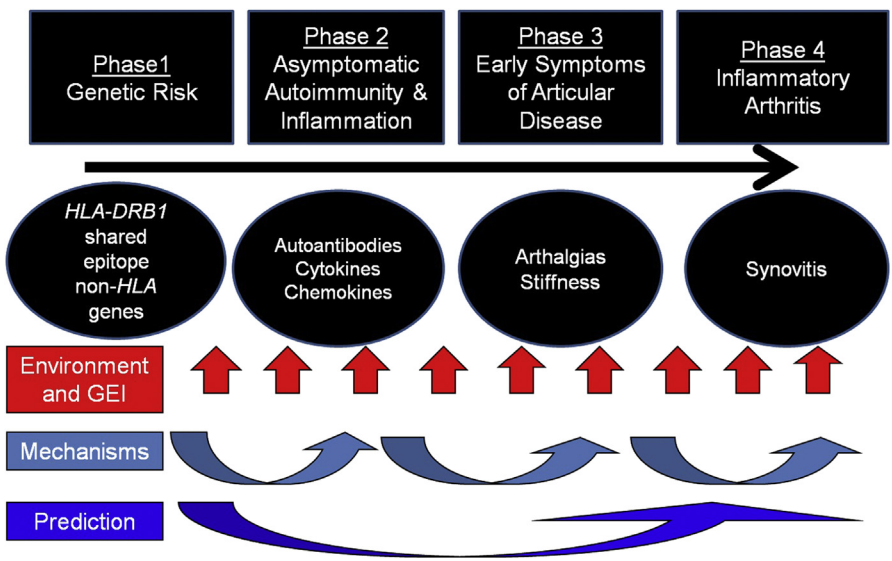

Fig. 1. The preclinical phases of rheumatoid arthritis. Other rheumatic diseases likely follow similar phases of progression from genetic susceptibility, immune dysregulation, and subclinical disease to classifiable disease. Environmental factors and gene-environment interactions likely occur throughout this process of disease pathogenesis. (*From* Karlson EW, Deane K. Environmental and gene-environment interactions and risk of rheumatoid arthritis. Rheum Dis Clin North Am 2012;38(2):406; with permission.)