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Genetics of psoriatic arthritis

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A B S T R A C T

Spondyloarthritis (SpA) represents a group of inflammatory rheumatic diseases that cluster within families and possess overlapping clinical features. The pathogenesis of SpA encompasses a complex array of genetic, immunological and environmental factors. In this article, we will briefly review the genetics of PsA, and then focus on the genes that may be potentially linked either directly or indirectly to the immunopathology of the Th-17 pathway. The most consistent and dominant genetic effect of PsV and PsA is located on chromosome 6p21.3 within the major histocompatibility complex (MHC) region, which accounts for approximately one-third of the genetic contribution of PsV and PsA. To date, 36 genes have reached genome-wide significance, accounting for approximately 22% of psoriasis (PsV) heritability. Prominent genes identified via GWAS include *HLA-Cw6, IL12B, IL23R, IL23A, TNIP1, TNFAIP3, LCE3B-LCE3C, TRAF3IP2, NFkBIA, FBXL19, TYK2, IFIH1, REL, and ERAP1*. Genes identified in psoriatic arthritis (PsA) has largely echoed those in PsV and include *HLA-B/C, HLA-B, IL-12B, IL-23R, TNIP1, TRAF3IP2, FBXL19, and REL*. The lack of identified genetic susceptibility loci is largely attributed to the much smaller number of PsA patients and the greater clinical heterogeneity of PsA. Searching for different types of genetic variants such as small CNVs and/or insertions/deletions has also led to the identification of several genes with a function relative to PsV in particular including *DEFB4*, *LCE3C_LCE3B*, and *IL-22* gene (exon 1). The candidate genes identified in PsV/PsA have highlighted pathways of critical importance to psoriatic disease including distinct signaling pathways comprised of barrier integrity, innate immune response and adaptive immune response, mediated primarily by Th-

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17 and Th-1 signalling. While GWAS studies have yielded great insights into the genes that contribute to the pathogenesis of PsV and PsA, replication in large cohorts, fine-mapping and resequencing efforts, together with functional studies of genetic variants identified, are warranted to better understand susceptibility to and progression of these diseases. That searching solely for common variants by GWAS will identify only a fraction of the entire genetic burden of disease, a concerted effort is underway to search for highly penetrant but rare disease alleles in families with PsV and PsA, using next-generation sequencing and through epigenetic investigations.

Introduction

Spondyloarthritis (SpA) represents a group of inflammatory rheumatic diseases that cluster within families, have overlapping clinical features, and share common pathogenesis, particularly with respect to the critical role of the T helper (Th)-17 axis in initiating and propagating inflammation in ankylosing spondylitis (AS) and psoriatic arthritis (PsA). In this section, we briefly review the genetics of PsA, and then focus on the genes that may be potentially linked either directly or indirectly to the immunopathology of the Th-17 pathway.

The pathogenesis of SpA encompasses a complex array of genetic, immunological, and environmental factors. Population-based studies suggest a strong genetic basis to PsA given the impressive magnitude of familial aggregation. The recurrence ratio of PsA among first-degree relatives (λ_1) ranges from 30 to 55, which ranks second only behind AS, and this value is considerably higher than what is estimated in psoriasis [1,2]. Additional evidence regarding the genetic basis of PsA arises from class I human leukocyte antigen (HLA) associations, non-HLA major histocompatibility complex (MHC) genes, and validated genetic associations outside the MHC region [3]. Additionally, there is a robust genetic association for psoriasis vulgaris (PsV). Much of what has been identified regarding the genetics of PsA has originated from studies in PsV, as the genetics of PsV have been more thoroughly investigated. Genetic associations in PsV are relevant to PsA as the two diseases are interrelated epidemiologically and share similar immunopathology. Almost all patients with PsA either have or will develop PsV, and approximately 30% of patients with PsV have PsA [4]. Therefore, PsA and PsV will undoubtedly share common genetic variants.

Genetic associations within the MHC region (directed genetic studies)

All genetic investigations to date have revealed that the most consistent and dominant genetic effect of PsV and PsA is located on chromosome 6p21.3 within the MHC region, accounting for approximately one-third of the genetic contribution of PsV and PsA [3]. The genetic variants identified to date involve class I HLA alleles and, to a lesser extent, non-HLA genes within the MHC region.

The major effect in the MHC region is located within an ~300-kb segment known as psoriasis susceptibility region 1 (*PSORS1*). Elegant resequencing studies have confirmed that *HLA-Cw*0602* is the *PSORS1* risk variant in PsV [5]. This is a reproducible finding among all type 1 PsV cohorts. Potential genotype–phenotype correlations with *HLA-Cw*0602* include early age of onset, higher likelihood of familial psoriasis, guttate psoriasis, and presence of the Koebner phenomenon [6]. The presence of *HLA-Cw*0602* may also lead to improvement of psoriasis during pregnancy [6].

*HLA-Cw*0602* is also associated with PsA; however, the magnitude of association is lower than in PsV [7]. In fact, among PsV patients, individuals who carry the *HLA-Cw*0602* allele have a delayed onset of PsA and also are less likely to develop PsA. Other *HLA* antigens associated with PsA include *HLA-B13*, *HLA-B27*, *HLA-B38/39*, *HLA-B57*, and *HLA-DRB1*04* [7]. The most recent case–control and family-based association study by Chandran et al. demonstrated that HLA-C*12/B*38, HLA-B*27, and HLA-C*06/B*57 are haplotypes (alleles) robustly associated with PsA [8].