Genetic, Epigenetic and Pharmacogenetic Aspects of Psoriasis and Psoriatic Arthritis

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KEYWORDS

• Genetics • Candidate genes • GWAS • Psoriasis • Psoriatic arthritis
• Pharmacogenetics • Epigenetics

KEY POINTS

- Despite the large number of genes identified in psoriatic disease, the genetic contribution identified by genome-wide association studies (GWAS) accounts for less than 25% of heritability.
- This "missing heritability" is attributed to inherent limitations of this technology and limits searches to common variants, neglecting rare variants.
- No clinically actionable information can be gleaned by a single variant from GWAS studies owing to the very low odds ratio for the individual variants.
- A genetic risk score combining multiple loci associated with psoriasis/psoriatic arthritis may hold more clinical promise.

GENETICS OF PSORIATIC DISEASE

Clinicians have long recognized a strong familial component to psoriatic disease, and this observation has been substantiated in population and cohort-based studies. Epidemiologic studies suggest that psoriatic arthritis (PsA) has a higher heritability than psoriasis vulgaris (PsV).[1] However, many of the genes identified to date are related to psoriasis, whereas genes specific to PsA remain elusive.

Initial genetic studies in psoriatic disease involved interrogation of *HLA* alleles, which was subsequently followed by candidate gene studies within and outside the major histocompatibility complex (MHC) region. With the emergence of genome-wide microarrays, multiple genome-wide linkage studies were performed using either

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large multiplex families or sibling pairs. These strategies were followed by genome-wide association studies (GWAS), which also included metaanalyses. These large, international, single nucleotide polymorphism–based studies have identified numerous additional genes reaching genome-wide significance, which can be broadly classified into those involved in maintaining skin barrier functions, innate immunity, and acquired immunity. New technologies are being used to investigate the genetic basis of psoriatic disease using next-generation sequencing, copy number variation (CNV) analysis, and epigenetics.

Major Histocompatibility Complex Associations in Psoriatic Disease

The MHC region located on the short arm of chromosome 6 continues to be the dominant susceptibility region in psoriatic disease. Recent estimates suggest that at least one-third of the entire genetic contribution of psoriasis and PsA resides within this region. The major genetic determinant of psoriasis was initially localized to ~300 kb segment in the MHC I region, known as *PSORS1*; subsequent resequencing studies concluded that *HLA-Cw6* is the *PSORS1* risk variant that confers susceptibility to PsV.[2] There is also consistent association between *HLA-Cw0602* and PsA; however, the magnitude of the association with PsA is lower compared with PsV.[3] The *HLA-C*0602* allele seems to be associated with subphenotypes of PsV and PsA. In patients with PsV, *HLA-C*0602* is associated with type 1 psoriasis, guttate psoriasis, Koebner phenomenon, and amelioration of psoriasis during pregnancy.[4] Among patients with PsA, the *HLA-C*0602* allele is associated with delayed onset of arthritis and there is an inverse correlation with psoriatic nail disease, as summarized elswhere.[5]

The *HLA-B*27* allele seems to be a specific genetic marker for PsA; however, its magnitude is not as strong as in ankylosing spondylitis.[6] The prevalence of *HLA-B*27* is only about 20% compared with 70% to 90% in ankylosing spondylitis. The *HLA-B*27* allele is also associated with selected subphenotypes of PsA, including axial involvement, dactylitis, and greater burden of articular damage.[7] Thus, the presence of the *HLA-B*27* allele in PsA may lead to a more severe form of disease.

The 3 most consistently reported *HLA-B* alleles that are specific to PsA are *HLA-B*38*, *HLA-B*08*, and *HLA-B*39*.[6,8] A recent large fine-mapping study of psoriatic disease within the MHC region using an HLA-variant imputation approach, has shed new light regarding HLA associations within this region for PsV and PsA.[9] In this elegant study, Okada and colleagues[9] defined the 4-digit *HLA* allele and amino acid resolutions. This study included 9247 affected individuals (3038 PsA subjects, 3098 cutaneous psoriasis (PsC) subjects, and 3111 subjects of unknown PsA or PsC status) and 13,589 control individuals of European ancestry. They found that the *HLA-B*27* allele was the most discriminative allele separating PsA from PsC. A more refined analysis revealed that the presence of glutamine in position 45 of the *HLA-B* antigen conferred the strongest risk for PsA. This polymorphic site is located in the binding groove of HLA-B and can influence the binding of a peptide to the HLA molecule. The PsA-specific alleles noted (*HLA-B*27*, *B*39*, and *B*38*) all encode proteins that contain Glu at position 45.

Non–Major Histocompatibility Complex Candidate Genes Studies in Psoriatic Arthritis

Multiple association studies of non-MHC genes have been conducted in PsA. Most association studies reporting an initial association have not been replicated and the majority have failed to demonstrate independence from association with known *HLA* alleles. *MICA* represents the non-*HLA* gene within the MHC region that has received the most interest. This gene is in close proximity to the *HLA-B* locus and,