The Genetics of Psoriasis and Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA) is an inflammatory arthritis that manifests in 20–30% of patients diagnosed with psoriasis. Epidemiologic studies suggest a substantial genetic contribution to PsA. There is a strong need for genome-wide association studies on patients with PsA, including PsA-weighted or specific variants, and a need for a better understanding of the relevance of HLA alleles in disease expression. Interferon signaling and the nuclear factor-κB cascade are involved in PsA, and there are genetic differences between purely cutaneous psoriasis (PsC) and PsA. Psoriasis susceptibility genes for which putative functional coding variants in *TYK2* and *TRAF3IP2* are strongly associated with PsC and PsA, and neutrophil extracellular traps promote Th17 induction in an Act1 D10N-dependent fashion. Genomics and serological factors may also predict treatment response in tumor necrosis factor inhibitors (TNFi) in PsA, and genetics may play a role in treatment response to TNFi. Collaborations through the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) are essential to increase study population size, which will enhance the ability to detect the genetic variants that create a predisposition to psoriatic disease and to predict response to biological therapy. (J Rheumatol Suppl. 2019 June;95:46–50; doi:10.3899/jrheum.190119)

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Psoriatic arthritis (PsA) is an inflammatory arthritis that manifests in 20-30% of patients diagnosed with psoriasis[1]. PsA is attributed to genetic, immunologic, and environmental factors[2], and epidemiologic studies suggest a strong genetic basis to PsA. The genetic contribution to PsA is substantial with a recurrence rate in siblings and first-degree relatives that is between 30–55%[3,4,5,6].

Genetic association studies initially focused on targeted case-control investigations of candidate genes with limited success. It was not until the advent of genome-wide association studies (GWAS), including the Immunochip[7], that our understanding of disease pathogenesis took a major step forward. GWAS scans and metaanalyses (over 15,000 psoriasis cases and 27,000 healthy controls) have identified over 60 confirmed risk loci. They have also revealed pathways that are involved in the pathogenesis of psoriasis, specifically the innate immune system, antigen presentation, and the acquired or adaptive immune response[8,9,10,11,12,13,14,15,16,17,18].

Because PsA frequently accompanies psoriasis with an estimated prevalence of 30% among patients with psoriasis, it is not surprising that GWAS in PsA have identified variants that include those that are also identified in psoriasis. In contrast to psoriasis, GWAS scans and metaanalyses in PsA (over 3000 PsA cases and 13,000 controls) have yielded fewer variants achieving a genome-wide level of significance. In excess of 20 variants have reached a genome-wide level of significance in PsA, including *HLA-A*[19], *HLA-B*[8,9,13,19], *HLA-C*[8,9,13,19], *IL-12B*[9,13,19], *IL-23R*[19], *IL-23A*[19], *TNIP1*[9,19], *TRAF3IP2*[12,13,19], *CSF2/P4HA2*[19], *HCP5*[8], *FBXL19*[20], *REL*[16], *TYK2*[19], *NOS2*[21], *PTPN22*[21], *TNFAIP3*[18], *IFNLR1*[18], *IFIH1*[18], and *NFKBIA*[18]. Similar to psoriasis, GWAS scans and metaanalyses have identified pathways involved in the pathogenesis of PsA, especially the innate immune system, antigen presentation, and the acquired or adaptive immune response[8,9,12,13,16,18,19,20,22]. These genetic markers have illuminated key signaling pathways involved in PsA pathogenesis that can be broadly classified into those involved in epidermal differentiation, innate immunity, antigen presentation and processing, and acquired/adaptive immunity.

To determine whether there are PsA-weighted or -specific variants, the results of GWAS from PsA were compared with those from cutaneous psoriasis (PsC) without joint involvement. The identification of risk loci that are specific for the development of PsA in patients with psoriasis has been more challenging, but evidence is emerging of loci associated at genome-wide significance thresholds with PsA and not psoriasis, including loci at *CSF2*, *PTPN22*, *TNFAIP3*,

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and *HLA-B*[18,19,23]. Again, most of the genetic hits exhibited modest OR, with the exception of the HLA region. *HLA-B*08*, *HLA-B*27*, *HLA-B*38*, and *HLA-B*39* have been associated with the highest increased risk of PsA, with *HLA-C*06* being associated with a decreased risk of PsA (i.e., a PsA protective effect) when compared to patients with PsC.

As mentioned, more than 60 genetic signals have reached a GWAS level of significance in psoriasis, whereas about 20 genetic signals have achieved the same in PsA cohorts. So why is there a paucity of PsA-specific genes? We know that PsA is a disease of remarkable clinical, imaging, prognostic, and functional heterogeneity. Misclassification of clinical phenotypes, incomplete penetrance, variable expression, and genetic heterogeneity complicates the detection of a gene(s) specific for PsA. It is likely that additional variants will be identified using a GWAS approach for PsA (similar to psoriasis), because there are currently about 3000 PsA samples that have been tested and analyzed (compared with over 17,000 for psoriasis). Therefore, performing additional GWAS on larger PsA cohorts followed by metaanalyses should identify additional PsA variants. On the other hand, it could be that the genetic burden (or variance) for PsA is just not as high as originally thought.

Regarding approximate OR for genetic variants identified in PsA GWAS scans, it has become evident that the HLA region, specifically *HLA-C* and *HLA-B* loci, exhibit the strongest OR, whereas most of the other genetic signals that are significantly different from controls are associated with a relatively modest OR (< 1.50)[8,13,16,18,19,20,22]. These data suggest that additional dynamic biomarkers (as opposed to genetic biomarkers, which are static) may be required to develop risk algorithms for PsA because genotype risk alone appears insufficient. Machine learning offers an efficient method to combine the various biomarkers into a utilitarian clinical test.

Given that these SNP associations occur mainly in regulatory regions of genes or in intergenic regions, fine-mapping may be required to tease out the causative genetic variants. It was reported that the risk heterogeneity between PsA and PsC might be driven by HLA-B amino acid position 45[24], but another recent study argues that amino acid position 97 of *HLA-B* differentiates PsA from PsC, especially when controlling for the age of psoriasis onset[25]. These studies depend crucially on the accuracy of methods for inferring HLA types from GWAS data. These methods continue to evolve, and this important question is probably best viewed as being in flux at the present time. However, it seems likely that differences in the antigen-binding grooves of the closely related *HLA-B* and *HLA-C* genes will ultimately provide important insights into triggering antigens for PsC versus PsA.

There is sufficient evidence to suggest that disease expression of PsA is affected by the carriage of specific HLA-B alleles. In sacroiliitis, genetic investigations indicate that the pattern of sacroiliitis is influenced by the type of HLA-B allele present. *HLA-B*27:05:02* is strongly associated with symmetrical sacroiliitis. In contrast, asymmetric sacroiliitis, the more prevalent form of sacroiliitis in PsA, was not significantly associated with *HLA-B*27:05*, but instead exhibited a strong association with the more prevalent *HLA-B*08:01*[26]. In PsA, the presence of certain HLA-B alleles (especially *HLA-B*08*, *B*27*, *B*38*, and *B*39*) has been associated with subphenotypes. Asymmetrical sacroiliitis is associated with *HLA-B*08*, *HLA-B*38*, and *HLA-B*55*, whereas symmetrical sacroiliitis is positively correlated with *HLA-B*27*[23]. Dactylitis is positively correlated with *HLA-B*08* and *HLA-B*27*. *HLA-B*27* is also positively correlated with axial involvement (ankylosis), enthesitis, and uveitis, whereas peripheral polyarthritis is positively correlated with *HLA-B*38* and *HLA-B*39*. These findings suggest that considering only 2 HLA alleles, *HLA-B*27* and *HLA-B*08*, might offer advantages in identifying the most appropriate treatment because they are associated with phenotypically different diseases (*HLA-B*27*: increased prevalence of spondylitis, symmetrical sacroiliitis, enthesitis, dactylitis, and uveitis; *HLA-B*08*: peripheral arthritis, erosive arthritis, unilateral sacroiliitis, dactylitis, and nail pitting).

Genetics of Psoriasis

Psoriasis is a common, inflammatory, and hyperproliferative skin disease that is associated with arthritis[27] and cardiovascular and metabolic comorbidities[28,29,30]. GWAS of psoriasis have identified 86 psoriasis susceptibility loci[9,11,12,13,14,15,20,31,32], as well as genetic differences between purely PsC and PsA in the MHC[24] and across the genome[18]. A recent collaborative GWAS of psoriasis involving about 40,000 subjects identified 16 new susceptibility regions. This study highlighted the involvement of interferon signaling and the nuclear factor-κB (NF-κB) cascade and demonstrated strong enrichment for psoriasis genetic signals in T cell regulatory elements[31]. Despite these successes, fine-mapping studies indicate that most of these genetic signals (about 80–90%) do not encode "traditional" deleterious changes in protein structure. To address this challenge, we are studying the effects of psoriasis-related genetic variation on chromatin accessibility (by ATAC-seq) and gene expression (by RNA-seq) in blood-derived myeloid dendritic cells and skin-homing T cells from hundreds of psoriasis cases and controls. These studies are revealing excellent overlap between our ATAC-seq, as well as publicly available chromatin accessibility and transcription factor binding site data.

Other research in the Psoriasis Genetics Laboratory at the University of Michigan focuses on psoriasis susceptibility genes for which putative functional coding variants have been identified. In this regard, the cytokines interleukin

(IL)-23 and IL-17 play central roles in psoriasis pathogenesis[33,34,35], as well as many other autoimmune and inflammatory disorders[36]. *TYK2* and *TRAF3IP2* encode major downstream mediators of IL-23 and IL-17 signaling through STAT and TRAF, respectively[15,37]. Coding variants of *TYK2* and *TRAF3IP2* are strongly associated with PsC and PsA[18]. We[38] and others[39] have reported that psoriasis-protective TYK2 variants inhibit STAT3/4 phosphorylation in IL-12–stimulated Th1 cells. We have shown that the psoriasis-associated *TRAF3IP2* D10N variant inhibits NF-κB, p38, and extracellular signal-regulated kinase signaling in response to CD40 ligand[40]. Other research from the laboratory has shown that shRNA-mediated silencing of *TRAF3IP2* inhibits responses to inflammatory cytokines in keratinocytes[41]. Why this putative loss-of-function variant appears to increase inflammatory responses in the *in vivo* setting remains to be determined, but a recent paper from Xiaoxia Li's group suggests that Act1 may inhibit STAT3, which in turn exerts multifaceted effects on Th17 biology as a downstream mediator of IL-23 signaling[42].

Using an assay based on CD3/CD28 activation of peripheral blood mononuclear cells (PBMC), with analysis by flow cytometry, qPCR, and RNA-seq, the Elder laboratory found that (1) neutrophil extracellular traps (NET) augment the induction of Th17 cells from memory T cell precursors; (2) monocyte depletion abrogates this Th17 induction; and (3) remarkably, the *TRAF3IP2* D10N variant has a significant stimulatory effect on the induction of Th17 cells in CD3/CD28-activated PBMC that is enhanced in the presence of NET[43]. Together, these findings support the concept that NET promote Th17 induction in an Act1 D10N-dependent fashion. Blood is an ideal bioresource for functional genetic studies, because it is readily available by re-contacting individuals whose genotype status is known. Ongoing work is taking advantage of this practical resource by analyzing the components of NET that lead to Th17 induction, the signal transduction requirements involved, and the involvement of *TYK2* genetic variation in this process.

Prediction of Treatment Response in Tumor Necrosis Factor Inhibitors (TNFi) in PsA Using Genomics and Serological Factors

While the last 10 years have seen several paradigm changes in PsA, including TNFi, treatment response in individual patients is highly variable. TNFi medications are highly effective, but costs per patient per year are considerable despite the introduction of biosimilars. Additionally, 40–45% of patients do not respond to these drugs[44], and prescribers are currently reliant on a trial-and-error approach. There is a clear need for a precision evidence approach in PsA, ideally incorporating genetic, clinical, and serological factors of individual patients.

Few consistent clinical predictors of response to TNFi exist in the literature to date[45]. A limited number of studies to assess genetic predictors of treatment response to TNFi in patients with PsA have been conducted. These studies have mainly used a candidate gene approach, where the choice of genes is based on existing knowledge of the biological pathways and the treatment agent to which their response is being analyzed. TNF promoter region polymorphisms have been most commonly evaluated. In a heterogeneous cohort including both patients with rheumatoid arthritis (RA) and PsA, the -308 G/G (rs1800629) genotype conferred a better response to treatment than A/A or A/G genotypes[46]. In a metaanalysis that evaluated the -308 polymorphism, which included 692 patients with RA treated with etanercept (ETN), adalimumab, and infliximab (IFX), the -308 A variant was a negative predictor of TNFi treatment response[47].

Polymorphisms of *TNFAIP3*, a gene encoding for a zinc finger protein (A20) that negatively regulates TNF-induced pathways, have been reported to be associated with TNFi treatment response in psoriasis[48]. Both the G allele of rs610604 and haplotype rs2230926 T-rs610604 G were found to be associated with a good response to ETN or all TNFi. The proportion of responders was significantly higher for patients carrying 2 copies of this allele compared to non-carriers. The effect was observed in ETN-treated patients (90.7% vs 70.3%, p = 0.0027) and for all TNFi-combined patients (88.1% vs 70.7%, p = 0.0075). To a lesser degree, the same held true for heterozygous carriers of the G risk allele compared with carriers of no copies (79.1% vs 70.3%, p = 0.067 for ETN, and 80.1% vs 70.7%, p = 0.034 for all TNFi)[48]. The TNF receptor 1A (*TNFR1A*) variant rs767455/G36A in patients with PsA treated with IFX has been associated with a better European League Against Rheumatism (EULAR) response at 3 months as compared to RA, both with the AA genotype (AA 85% vs AG/GG 58.9%, p = 0.04) and with the A allele (A 76.7% vs G 58.3%, p = 0.03)[49].

Variants such as those in the *PDE3A-SLCO1C1* locus located on chromosome 12p12 are also associated with treatment response to TNFi[50]. As in RA, the minor allele G of SNP rs3794271 is linked with a worse response to TNFi in PsA (p = 0.0036). Others include TNF-related apoptosis-inducing ligand receptor 1 (*TRAIL-R1*) rs20575 and the presence of the high-affinity *FCGR2A-131H* allele associated with EULAR response to IFX and ETN, respectively[51]. While these results hold promise, homogeneous cohorts of large sample sizes are needed to more accurately evaluate and replicate these results before they can be robustly used to predict treatment response and inform therapeutic stratification.

DISCUSSION

The remarkable accumulation of knowledge gained from genetic/genomic studies of psoriasis and PsA has advanced our understanding of disease pathogenesis. Important signaling pathways have been identified, highlighting the

importance of innate immunity, antigen presentation and processing, and acquired/adaptive immunity, with the most notable being the emergence of the Th17 signaling pathway. While these investigations have yielded important insights, several key messages were delivered at the 2018 annual Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) meeting, including the need (1) to properly phenotype patients; (2) to considerably increase sample size for GWAS, particularly with PsA; (3) for a strategy to enhance fine mapping and functional studies of identified genetic variants; and (4) to apply multiple omics (e.g., genome, exome, transcriptome, and methylome) that focus on specific cell types of relevance to psoriatic disease. GRAPPA is essential to the success of advancing the genomics of psoriatic disease because of its ability to facilitate collaborations for the collection of clinical information and appropriate biospecimens to address the aforementioned issues and to provide an effective venue for the dissemination of findings.

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