Genetics of Psoriasis and Psoriatic Arthritis: Update and Future Direction

KRISTINA CALLIS DUFFIN, VINOD CHANDRAN, DAFNA D. GLADMAN, GERALD G. KRUEGER, JAMES T. ELDER, and PROTON RAHMAN

ABSTRACT. Psoriasis and psoriatic arthritis (PsA) both have substantive genetic determinants. Numerous candidate regions and genes have now been replicated in disease susceptibility, and to a lesser extent in disease expression, in both disease entities. Intensive efforts are now under way or are being planned to perform genome-wide association scans (GWAS) in psoriasis and PsA. A major determinant of success for GWAS is likely to be accumulation of multiple large well-phenotyped cohorts, sophisticated data management, and verification of the findings. At the 2007 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members of the GRAPPA genetics committee presented a discussion of the genetics of psoriasis and PsA, including future trends. This article is a summary of that presentation and a review of the literature. (J Rheumatol 2008;35:1449–53)

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GENETICS OF PSORIASIS

Genetic factors have long been recognized to play an important role in psoriasis. The heritability of psoriasis was first described 200 years ago, evidenced by familial clustering of disease and later by demonstrating increased concordance in monozygotic twins versus dizygotic twins[1,2]. Psoriasis has a complex, multifactorial genetic basis, and this concept has only been strengthened by the discoveries of over 20 candidate loci, using linkage analysis, and more recently, genome-wide association scans (GWAS).

From the Department of Dermatology, University of Utah, Salt Lake City, Utah, USA; University of Toronto Psoriatic Arthritis Clinic, University Health Network, Toronto Western Research Institute, University of Toronto, Toronto, Ontario, Canada; University of Michigan and Ann Arbor Veterans Affairs Health System, Ann Arbor, Michigan, USA; Department of Medicine, Division of Rheumatology, Memorial University, St. John's, Newfoundland, Canada.

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K.C. Duffin, MD, Department of Dermatology, University of Utah; V. Chandran, MBBS, MD, DM, University of Toronto Psoriatic Arthritis Clinic, University Health Network, University of Toronto; D.D. Gladman, MD, FRCPC, University of Toronto and Toronto Western Research Institute, University of Toronto; G.G. Krueger, MD, Department of Dermatology, University of Utah; J.T. Elder, MD, PhD, University of Michigan and Ann Arbor Veterans Affairs Health System; P. Rahman, MD, MSc, Department of Medicine, Division of Rheumatology, Memorial University.

Address reprint requests to Dr. P. Rahman, Department of Medicine, Division of Rheumatology, Memorial University, 154 LeMarchant Road, St. John's, Newfoundland, Canada. E-mail: prahman@mun.ca

Major Histocompatibility Complex (MHC) and Psoriasis Susceptibility

PSORS1 and HLA-C. The major genetic determinant of psoriasis is believed to reside in an approximately 300-kb segment in the MHC I region on chromosome 6p21.3 known as PSORS1. Over 30 years ago, this region was found to harbor human leukocyte antigen (HLA) genes that associated with autoimmune diseases. Psoriasis was found to be associated with HLA-C and several HLA-B alleles[3]; however, the association with HLA-B was later determined to be due to strong extended haplotypes and linkage disequilibrium with HLA-C[4]. This region was subsequently identified by linkage analysis in 1997[5,6] and replicated in numerous populations. Candidate genes just telomeric to HLA-C were appealing since several (CDSN, HCR, and PSORS1C3) are expressed in skin. However, none of the candidates are convincingly associated with psoriasis independent of HLA-C. Extensive study of this segment has been led by Elder and colleagues using recombinant ancestral haplotypes[7]. Although a 70-kb risk segment telomeric to (and excluding) HLA-C initially was believed to confer the most risk[8], an international collaborative study extended the risk segment to a 300-kb span from just telomeric to HLA-B to beyond CDSN, thus including HLA-C[7]. After sequencing this segment in 2 risk and 5 non-risk chromosomes, then examining recombinant haplotypes retaining HLA-Cw6 but lacking risk alleles in CDSN, Nair, *et al* concluded that HLA-Cw6 is the PSORS1 risk variant that confers susceptibility to psoriasis[9].

HLA-C and disease expression. A specific allele of the HLA-C region, HLA-Cw*0602, is also the only genetic variant repeatedly observed to associate with phenotypic

features of psoriasis. Patients carrying this allele typically have early onset, higher incidence of guttate or streptococcal-induced flares of disease[10], koebnerization, and a more severe course. Homozygosity for HLA-Cw*0602 predisposes to the likelihood of development of psoriasis and to earlier onset, but it otherwise does not influence clinical course[11]. Women carrying HLA-Cw*0602 are more likely to experience remission with pregnancy[12]. HLA-Cw*0602 is less frequent in patients with PsA (20%)[13] and does not appear to be a risk factor for later onset of psoriasis (type II), palmar-plantar pustular disease, nail disease, or scalp disease[10,14,15].

Functional role of HLA-C. Despite its repeated genetic association with psoriasis, limited data exist to explain the functional role of HLA-C in psoriasis pathogenesis. *In vitro* studies have suggested that compared to the CD8+ T cells from HLA-Cw6-negative individuals, CD8+ T cells from HLA-Cw6-positive individuals are more responsive to peptides found in both the hyperproliferative keratin K17 and streptococcal M protein, suggesting that HLA-Cw6 may predispose individuals to recognize keratin self-antigens[16]. Responses were 10-fold higher in T cells expressing cutaneous lymphocyte-associated (CLA)-positive skin-homing receptors than in CLA-negative T cells, demonstrating that these responses are targeted to the skin.

HLA-C also serves as a ligand for killer immunoglobulin-like receptors (KIR) on natural killer (NK) and natural killer T (NK T) cells, which may also have a role in psoriasis[17]. Inheritance of activating KIR, encoded on chromosome 19q13.4, particularly KIR2DS1 and KIR2DS2, has been associated with psoriasis[18], and lack of inhibitory KIR or their corresponding HLA-C ligand has been associated with the development of PsA[19]. However, this function of HLA-C appears unlikely to account for the strong associations between psoriasis and HLA-Cw6, as several other HLA-C alleles manifest the same binding specificity for KIR.

Susceptibility Loci Outside the MHC

Although the PSORS1 locus is generally understood to confer the most risk for psoriasis, numerous susceptibility loci also have been identified outside of the MHC region. Linkage scans were used to identify and replicate the intervals designated PSORS2-PSORS9, as reviewed[20]. Although dense microsatellite markers and sequencing within these loci have identified candidates, lack of replication of the specific risk variants, and lack of a clear role of variants that do not lie within functional genes, has slowed our understanding of the magnitude of the contribution and the relevance of these loci. GWAS using single-nucleotide polymorphism (SNP) technology have identified new candidates within and outside of linkage peaks. The PSORS intervals and their candidate genes are summarized in Table 1.

Results of Genome-wide Association Studies

Interleukin 12 (IL-12) and IL-23. Perhaps the most compelling new gene candidates for psoriasis to date, IL12B and IL23R, have been identified using GWAS rather than linkage analysis[21]. Using a 25,215 gene-centric SNP platform for discovery and followup tag SNP and sequencing, this study confirmed a reported psoriasis-associated SNP in the IL12B 3' untranslated region (rs3212227)[22] and found a second SNP (rs6887695) located 60 kb upstream[21]. This study also identified 2 missense SNP in IL23R that associated with psoriasis, one of which (rs11209026, Arg381Gln) is also associated with Crohn's disease[23]. Both the IL12B and IL23R SNP have since been replicated in 2 UK psoriasis populations and in a study of US and German families and cases and controls (see Table 1). The functional relevance of these SNP remains unclear, but IL-12 and IL-23, a complex of the p19 and p40 subunits, have a key role in the pathogenesis of psoriasis: IL-12 stimulates interferon-γ (IFN-γ) in naive Th cells, and IL-23 stimulates IFN-γ production and proliferation of memory Th1 cells, and has a role in the recently described Th17 pathway. The p40 subunit is increased in psoriatic lesions[24], and neutralization of p40 with a human monoclonal antibody causes marked improvement of psoriasis[25].

GENETICS OF PSORIATIC ARTHRITIS

Epidemiological evidence implicates a strong genetic basis in PsA. Moll and Wright were the first to demonstrate familial aggregation of PsA, and estimated the recurrence risk ratio in first-degree relatives (λ_1) to be 55[26], compared with estimates ranging from 5 to 10 in cutaneous psoriasis. More recent studies have estimated the λ_1 to be 47 in a British population[27] and 30[4] in a Canadian population[28].

PsA and Genes within the MHC Region

Polymorphisms in the genes coded in the HLA region on chromosome 6p have been shown to be associated with PsA. Class I antigens (HLA-B13, HLA-B57, HLA-B39, HLA-Cw6, HLA-Cw7) have consistently shown a positive association with psoriasis and PsA in population studies, with the strongest association being with HLA-Cw6[29]. HLA antigens may also identify patients with a particular pattern of PsA: HLA-B27 with spinal involvement, B38, and B39 with peripheral polyarthritis.

HLA antigens were identified as prognostic factors in patients with PsA[29]. HLA-B39 alone, HLA-B27 in the presence of HLA-DR7, and HLA-DQw3 in the absence of HLA-DR7 each conferred an increased risk for disease progression. HLA-B22 was found to be protective for disease progression[29]. The "rheumatoid arthritis (RA) shared epitope" was found to be associated with radiological erosions among patients with PsA[30]. Recently, patients with PsA carrying both HLA-Cw6 and HLA-DRB1*07 alleles were found to have a less severe course of arthritis[31].

Table 1. Psoriasis susceptibility loci and gene candidates.

Locus	Region	Gene Candidates/Function	Lead Author and Year of Publication of Psoriasis Susceptibility Studies*
PSORS1	6p21.3	*HLA-Cw6; CDSN, HCR, HERV-K, HCG2, 7PS04S1C3, POU5F1, TCF19, CCHCR1, LMP, SEEK1, SPR1.*	Samuelsson L, 1999; Lee YA, 2000; Elder JT, 2001; Veal CD, 2001; Zhang XJ, 2002; Foerster J, 2004; Sagoo GS, 2004
PSORS2	17q25	*RUNX1; RAPTOR; SLC9A3R1; NAT9; TBCD*	Tomfohrde J, 1994; Nair RP, 1997; Enlund F, 1999; Samuelsson L, 1999; Helms C, 2003; Zheng Y, 2003; Capon F, 2004; Stuart P, 2006; Capon F, 2007
PSORS3	4q34	*IRF-2#*	Matthews D, 1996; Hida S, 2000; Foerster J, 2004
PSORS4	1q21	*Loricrin#; Filaggrin#; Pglyrp3,4#; S100 genes within epidermal differentiation complex*	Bhalerao J, 1998; Capon F, 1999; Semprini S, 2002; Giardina E, 2004; Giardina E, 2006; Sun C, 2006; Zhao Y, 2007
PSORS5	3q	*SLC12A8; Cystatin A#; Zn finger protein 148#*	Enlund F, 1999; Samuelsson L, 1999; Hewett, 2002; Samuelsson L, 2004; Huffmeier U, 2005
PSORS6	19p13	*JunB*	Lee YA, 2000; Zenz R, 2005
PSORS7	1p	*PTPN22# (1p13); IL-23R (1p32.1–31.2)*	Veal CD, 2001; Tsunemi Y, 2002; Nistor I, 2005; Duerr RH, 2006; Huffmeier U, 2006; Capon F, 2007; Cargill M, 2007
PSORS8	16q	*CX3CL1, CX3R1; NOD2/CARD15#*	Nair RP, 1997; Karason A, 2003; Young C, 2003; Plant D, 2006
PSORS9	4q31	*IL-15*	Bhalerao J, 1998; Samuelsson L, 1999; Zhang XJ, 2002; Bowcock AM, 2004; Sagoo GS, 2004; Sun LD, 2007; Zhang XJ, 2007
PSORS10	18p11		Veal CD, 2001; Asumalahti K, 2003
—	5q31.1–33.1	*IL-12B; SLC22A4#; SLC22A5#; IL-13; IL3, IL4, IL5, CSF2 and IRF1*	Tsunemi Y, 2002; Duerr RH, 2006; Friberg C, 2006; Capon F, 2007; Cargill M, 2007, Nair et al, 2008
—	9q33-34		Zhang XJ, 2002; Yan KL, 2007
—	6p22	*CDKALI*	Wolf N, 2007
	19q34	*KIR2DS1, KIR2DL1, KIR2DL5*	Suzuki Y, 2004; Luszczek W, 2004

* Full citations not included in References; # candidate genes investigated and not believed to confer risk of psoriasis.

There are conflicting reports on the associations of tumor necrosis factor-α (TNF-α) polymorphisms located on chromosome 6p with PsA[32]. A metaanalysis confirmed an association between TNF-α-238G/A polymorphism and PsA with an odds ratio of 2.29 (95% confidence interval 1.48–3.55)[32]. A recent study reported that TNF-α-857C/T may represent a risk factor for PsA (but not for psoriasis) that is independent of the PSORS1 allele[33].

Class I MHC chain-related gene A (MICA) located 47 kb upstream of HLA-B also has been shown to be associated with PsA[34,35]. In a Spanish population, MICA A9 polymorphism corresponding to the MICA 002 allele was associated with PsA (but not psoriasis), independent of HLA-Cw*0602 ($p < 0.00035$, relative risk 3.2)[34]. Similar associations have been shown with Jewish[35], Croatian[36], and British patients[37] with PsA.

Susceptibility Loci for PsA Outside the MHC Region

Only one genome-wide linkage study in PsA has been published[38]. With respect to PsA-association studies outside the MHC region, a large number of candidate genes have been tested[39,40]. However, only a few genes have been independently replicated and are reviewed below.

Chromosome 16q (via genome-wide linkage study). The study was conducted in Iceland, where 178 patients with PsA were identified from 906 patients included in a genetic study of psoriasis[38]. A linkage with a LOD score of 2.17 was observed on 16q. When the linkage analysis was conditioned on paternal transmission to affected individuals, a LOD score of 4.19 was obtained, whereas a LOD score of only 1.03 was obtained when conditioned on maternal transmission. This locus is close to the PSORS8 locus identified for psoriasis[41].

Chromosome 2q (IL-1 gene cluster). The interleukin 1 gene cluster on chromosome 2q also has been investigated for association with PsA. An association has been reported with the IL-1α-889 SNP variant[42]. A recent study of 29 SNP at the IL-1 cluster also revealed 2 regions contributing independently to risk of PsA: a region spanned by markers rs3783547, rs3783543, and rs17561 in IL1A, and a region

near the end of IL1B, through IL1F7, IL1F8, and into IL1F10[43].

Chromosome 19q13.4 (KIR genes). The activating KIR, KIR2DS1 and KIR2DS2, have been associated with PsA, particularly in the absence of the HLA ligands for the corresponding inhibitory KIR (KIR2DL1 and KIR2DL2/3)[19,44]. Further, it was shown that the susceptibility to PsA may be determined by the overall balance of activating and inhibitory composite KIR-HLA genotypes[45].

PRESENT DIRECTION OF GENETIC STUDIES IN PSORIASIS AND PsA

At present, genetic association studies are at the forefront of genetic analysis. This is a result of the high density SNP arrays, markedly enhanced sample sizes, and more affordable cost of high-throughput genotyping. The international HapMap project has also been instrumental in limiting the number of markers to be typed as a result of well characterized linkage disequilibrium between the markers. Further, as evidenced by Cargill, *et al*, genome-wide pooling studies have been developed that decrease the cost of these investigations[21]. GWAS appear to be bearing fruit as novel SNP have been identified in multiple common diseases including Crohn's disease, obesity, and prostate cancer.

Despite the recent success, many limitations still exist with genetic association studies. As evidenced by recent SNP associations with the IL-12 p40 subunit (IL12B) and the IL-23 receptor (IL23R), the genotype relative risk for these high-priority genes is quite modest, and these variants account for only a small proportion of the genetic risk[21]. Much larger sample sizes are required for discovery of novel variants, and new findings should be replicated in numerous large independent cohorts such as the Genetics Association Information Network (GAIN), a public-private partnership created to facilitate GWAS of common human disease. The first phase of GAIN includes genotyping of 1500 psoriasis cases and 1500 controls for 600,000 SNP. De-identified phenotype information from this study has been deposited in a database managed by the National Center for Biotechnology Information for access by the general research community, with access to genotypes restricted to authorized users who have applied for access and agreed to GAIN guidelines regarding confidentiality, intellectual property, and publication (available from http://www.fnih.org/GAIN2/home_new.shtml).

Once a genetic variant has been identified and replicated, however, the pathogenesis of the respective disease is not necessarily illuminated. In fact, most of the variants being identified are in noncoding regions or belong to genes with unknown function. Functional verification of these results is likely to have the most meaningful influence and is of central importance. Other complexities that require further investigations are genotype/phenotype correlations and gene/environment interactions. For these studies, detailed clinical characterization is required along with sophisticated genetic analysis, due to the extensive data likely to be generated from testing of numerous clinical and environmental variables.

CONCLUSION

As in other multifactorial genetic disorders, the genetics of psoriasis and PsA are now coming into focus, powered by the collection of large case-control samples, advances in genotyping technology, and advanced statistical analysis. The emerging results are complemented by recent advances in immunology and therapeutics. While much remains to be done, the integration of genetics and immunology is becoming a reality for both psoriasis and PsA.

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