

# Psoriasis Bench to Bedside

## Genetics Meets Immunology

**M**ORE THAN 25 years of accumulating evidence strongly implicates the immune system in the pathogenesis of psoriasis, including both acquired immunity (T cells) and innate host defense (macrophages, antigen-presenting cells, and keratinocytes). Psoriasis also has a strong genetic component, but the identity of the genes involved has largely remained obscure. In a study recently published in *Nature Genetics*,<sup>1</sup> these 2 themes of psoriasis—genetics and immunology—come together in a coherent and clinically relevant way.

The genetic makeup of psoriasis is multifactorial: multiple genes and the environment conspire to increase one's risk of developing psoriasis. Like several other multifactorial autoimmune disorders, psoriasis manifests strong HLA associations. In 2006, *HLA-Cw6* was found to be the likely cause of these HLA associations in psoriasis.<sup>2</sup> However, previous searches for psoriasis genes outside the HLA region yielded no consistent, reproducible evidence of linkage (ie, consistent transmission of a genetic marker with psoriasis through families<sup>3</sup>). The same problem has been encountered in other multifactorial disorders.<sup>4</sup> We now appreciate that while linkage studies are very good for finding genes that make large contributions to risk, they are less powerful in multifactorial disorders, in which individual genes typically make only modest contributions to risk. In this setting, tests of association are much more powerful than tests of linkage.<sup>5</sup> Association studies are also easier to execute, as there is no need to collect family members. However, association studies require approximately 500 000 ge-

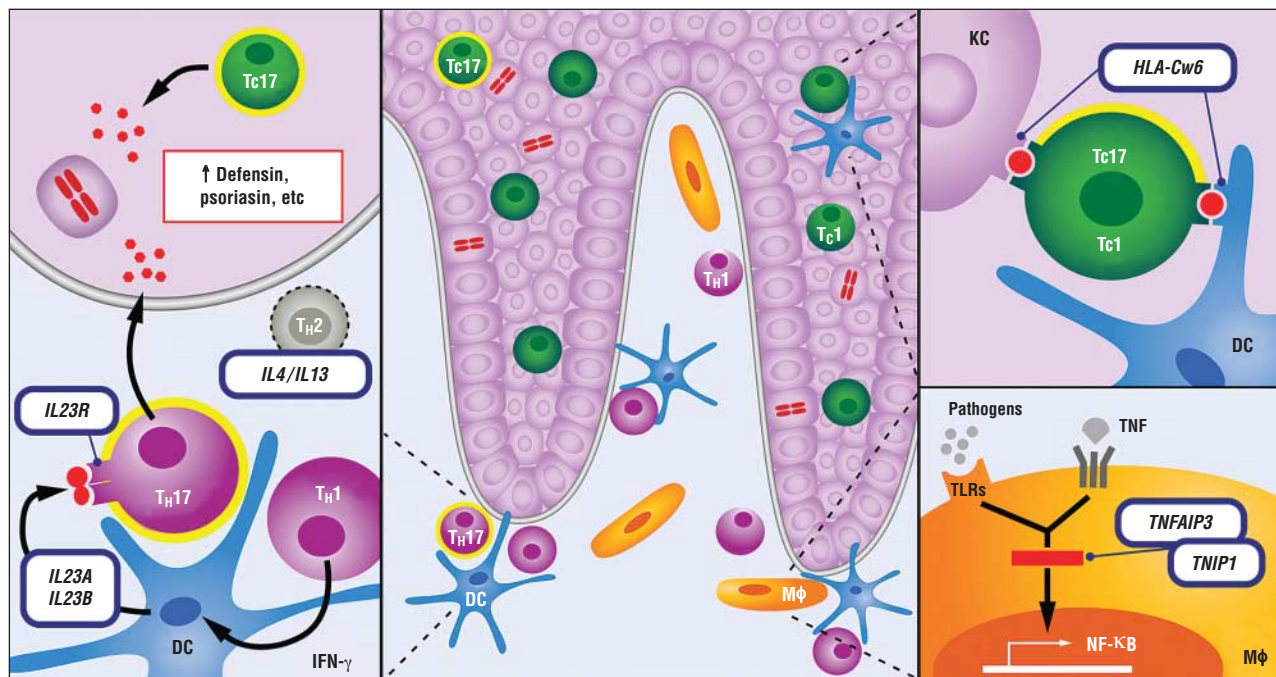
netic markers to survey the genome comprehensively compared with the approximately 300 markers needed to perform a linkage scan.

With the dawning of the new millennium, sequencing of the human genome provided the needed markers. Called *single nucleotide polymorphisms* (SNPs), these markers represent subtle differences in the DNA code that normally exist between individuals. With the advent of the HapMap,<sup>6</sup> which provides a dense map of millions of SNPs, along with the development of microarray-based genotyping technologies that allow up to 1 million SNPs to be tested at once, the impossible became possible. To take advantage of these developments, in 2006 we initiated the Collaborative Association Study of Psoriasis, whose objective was to carry out a genome-wide association scan.<sup>1</sup> In the initial scan, we tested 438 670 SNPs in 1359 psoriasis cases and 1400 healthy controls. We found significant associations at 3 genetic regions that had previously been associated with psoriasis (*HLA-C*, *IL12B*, and *IL23R*).<sup>2,7</sup> As expected from earlier studies,<sup>2,8-10</sup> *HLA-C* produced by far the strongest genetic signal. While its precise role in psoriasis remains unknown, it has been postulated that it may be involved in antigen presentation to CD8<sup>+</sup> T cells, whose migration into the epidermis appears to be required for the development of psoriatic lesions<sup>11</sup> (**Figure**).

Besides *HLA-C*, *IL12B*, and *IL23R*, there were many other interesting signals requiring confirmation. Working with 5 additional groups in the United States, Canada, Germany, and France, we studied 18 of the most interesting genetic regions in an additional 5048 cases and 5051 controls. Seven of the 18 regions showed consistently strong as-

sociation with the development of psoriasis, and 4 of the associations were novel. One of these was *IL23A*, which encodes the p19 subunit of the cytokine interleukin (IL)-23. This study is the first to find a disease association with *IL23A* in any human disorder. Notably, 2 of the previously identified psoriasis genes encode proteins that bind to p19. *IL23R* encodes a component of the IL-23 receptor, and *IL12B* encodes p40, a component of both IL-12 and IL-23 (Figure). Interleukin 12 supports T<sub>H</sub>1 cells, whereas IL-23 supports the expansion of a novel subset of T cells, called T<sub>H</sub>17 cells, which protect the skin and other epithelial-lined organs, such as the gut<sup>12</sup> (Figure). Notably, one of the *IL23R* variants also confers risk for Crohn disease,<sup>13</sup> which has long been known to be clinically associated with psoriasis.<sup>14</sup> Moreover, 2 other reported psoriasis genetic "hotspots" contain epidermal defense genes that are highly overexpressed in psoriasis: *DEFB4* (encoding human  $\beta$ -defensin 2),<sup>15</sup> and *LCE3C/3D* (encoding late cornified envelope proteins 3B and 3C).<sup>16,17</sup>

Antibodies targeting p40 are highly effective against psoriasis.<sup>18</sup> Because p40 is common to IL-12 and IL-23, anti-p40 antibodies block both cytokines. Interleukin 23 is elevated in psoriasis lesions, but IL-12 is not,<sup>19</sup> suggesting that IL-23 is the primary target. Biological agents targeting tumor necrosis factor (TNF) are also highly effective against psoriasis.<sup>20</sup> Notably, 2 of the novel genetic signals that we found are involved in the regulation of TNF signaling: *TNFAIP3* and *TNIP1* (Figure). Together, the products of these genes function as a "brake" on immune responses triggered by TNF and by toll-like receptors, which recognize microbial agents through the innate immune system. Consistent



**Figure.** Model of psoriasis integrating genetics and immunology. The majority of dermal T cells are CD4<sup>+</sup> (purple circles). Of these, most are T<sub>H</sub>1, and approximately 5% express interleukin (IL)-17 (T<sub>H</sub>17, yellow halo). Most of the T cells in the epidermis are CD8<sup>+</sup> (green circles), and about 5% of these express IL-17 (Tc17, yellow halo). HLA-Cw6 may be involved in the activation of CD8<sup>+</sup> T cells by dendritic cells (DC, blue), and activated CD8<sup>+</sup> T cells may recognize keratinocyte (KC) antigens presented in the context of HLA-Cw6. Some of these T cells are likely to be Tc17 cells. *IL23A* and *IL23B* encode the subunits of IL-23. *IL23R* encodes a subunit of the receptor for IL-23. *IL4* and *IL13* may participate in tipping the balance of CD4<sup>+</sup> T cells toward T<sub>H</sub>2. T<sub>H</sub>1 cells stimulate the production of IL-23 by DC. In turn, IL-23 stimulates the production of IL-17 (and other cytokines such as IL-22) by T<sub>H</sub>17 cells. These cytokines stimulate KC proliferation (mitotic figures) and upregulate KC innate immune defense mechanisms, including defensin, psoriasin, and other proteins that are highly expressed in psoriasis lesions (etc). Macrophages (Mφ, orange) express tumor necrosis factor (TNF) receptors and toll-like receptors (TLRs), which signal to NF-κB in the nucleus. The proteins encoded by *TNFAIP3* and *TNIP1* bind to each other and block this signaling. Similar signaling pathways may also be active in other types of skin cells. IFN-γ indicates interferon gamma. Genetic regions implicated by this study are italicized and outlined in purple.

with a role in the control of autoimmunity, different genetic variants near *TNFAIP3* have been associated with rheumatoid arthritis and lupus.<sup>21,22</sup> Given that psoriasis increases risk of myocardial infarction,<sup>23</sup> it is notable that *Tnfaip3* influences the risk of coronary artery disease in mice.<sup>24</sup> These 2 genes provide novel targets for therapeutic intervention. Moreover, as our genetic toolbox of psoriasis risk markers expands, we may be able to predict which patients will respond best to various therapies and, even if imperfectly, begin to predict who is at risk for the development of skin and joint disease as well as cardiovascular complications.

The final novel genetic hotspot implicates 2 “next-door neighbor” genes—*IL4* and *IL13*—genes whose products support development of T<sub>H</sub>2 cells. Psoriasis has traditionally been viewed as a “T<sub>H</sub>1 disease,”<sup>25</sup> and genetic defects in this region may help tip the normal T<sub>H</sub>1/T<sub>H</sub>2 balance toward T<sub>H</sub>1. Interestingly, interferon gamma, a major product of T<sub>H</sub>1 cells, supports the produc-

tion of IL-23 by antigen-presenting cells.<sup>26</sup> Together, these studies link all of these psoriasis loci together in a plausible functional pathway (Figure).

With the likely exception of *HLA-Cw6*, the causative genetic changes responsible for the association signals that we have observed remain to be determined. Our current efforts focus on pinpointing these lesions as well as on finding other associated regions in our current sample. However, further enrollment is critical. Our study involved approximately 6400 cases and 6400 controls. Research in other multifactorial autoimmune disorders has shown that the number of associated regions increases dramatically by a 2- to 3-fold increase in subjects. Potential participants can learn more about psoriasis genetics research in several ways. The Psoriasis Genetics Laboratory maintains a Web site ([www.psoriasis.umich.edu](http://www.psoriasis.umich.edu)) and a toll-free number (800-356-2840). Other resources include the Utah Psoriasis Initiative (<http://uuhsc.utah.edu/psoriasis/>)

and the National Psoriasis Foundation ([www.psoriasis.org](http://www.psoriasis.org)).

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## REFERENCES

1. Nair RP, Duffin KC, Helms C, et al; Collaborative Association Study of Psoriasis. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet.* 2009;41(2):199-204.
2. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet.* 2006;78(5):827-851.
3. Capon F, Trembath RC, Barker JN. An update on the genetics of psoriasis. *Dermatol Clin.* 2004;22(4):339-347, vii.
4. Altmüller J, Palmer LJ, Fischer G, Scherb H, Wjst M. Genomewide scans of complex human diseases: true linkage is hard to find. *Am J Hum Genet.* 2001;69(5):936-950.
5. Botstein D, Risch N. Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nat Genet.* 2003;33(suppl):228-237.
6. International HapMap Consortium. A haplotype map of the human genome. *Nature.* 2005;437(7063):1299-1320.
7. Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet.* 2007;80(2):273-290.
8. Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet.* 1997;6(5):813-820.
9. Nair RP, Henseler T, Jenisch S, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. *Hum Mol Genet.* 1997;6(8):1349-1356.
10. Liu Y, Helms C, Liao W, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet.* 2008;4(3):e1000041.
11. Conrad C, Boyman O, Tonel G, et al. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. *Nat Med.* 2007;13(7):836-842.
12. Bettelli E, Oukka M, Kuchroo VKT. (H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol.* 2007;8(4):345-350.
13. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science.* 2006;314(5804):1461-1463.
14. Najarian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. *J Am Acad Dermatol.* 2003;48(6):805-824.
15. Hollox EJ, Huffmeier U, Zeeuwen PL, et al. Psoriasis is associated with increased beta-defensin genomic copy number. *Nat Genet.* 2008;40(1):23-25.
16. de Cid R, Riveira-Munoz E, Zeeuwen PL, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet.* 2009;41(2):211-215.
17. Zhang XJ, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet.* 2009;41(2):205-210.
18. Krueger GG, Langley RG, Leonardi C, et al; CNTO 1275 Psoriasis Study Group. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med.* 2007;356(6):580-592.
19. Lee E, Trecicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med.* 2004;199(1):125-130.
20. Leonardi CL, Powers JL, Matheson RT, et al; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med.* 2003;349(21):2014-2022.
21. Plenge RM, Cotsapas C, Davies L, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet.* 2007;39(12):1477-1482.
22. Graham RR, Cotsapas C, Davies L, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. *Nat Genet.* 2008;40(9):1059-1061.
23. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA.* 2006;296(14):1735-1741.
24. Idel S, Dansky HM, Breslow JL. A20, a regulator of NFkappaB, maps to an atherosclerosis locus and differs between parental sensitive C57BL/6J and resistant FVB/N strains. *Proc Natl Acad Sci U S A.* 2003;100(24):14235-14240.
25. Uyemura K, Yamamura M, Finson D, Modlin R, Nickoloff B. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. *J Invest Dermatol.* 1993;101(5):701-705.
26. Kryczek I, Bruce AT, Gudjonsson JE, et al. Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. *J Immunol.* 2008;181(7):4733-4741.