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Inhibitory KIR3DL1 Alleles are Associated with Psoriasis

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DEAR EDITOR

Genetic association studies have implicated over 40 genetic loci in the pathogenesis of psoriasis, with the largest signal observed at the MHC Class I locus for HLA-C; however, recent data also suggest a lesser but significant pathogenic role for HLA-B^{1,2}. Although both of these molecules participate in adaptive immunity through antigen presentation, they can also regulate the innate immune response through interaction with killer cell immunoglobulin-like receptors (KIR) expressed on the surface of both natural killer (NK) and a subset of T cells. KIRs are a family of receptors encoded by a cluster of 14 genes on chromosome 19q13.4. KIRs may encode activating or inhibitory receptors that bind the Bw4 motif on HLA-B or C1/C2 motif on HLA-C³.

Previous studies have shown that the presence of activating KIR3DS1⁴ and KIR2DS1⁵ are associated with increased susceptibility for psoriasis and psoriatic arthritis^{6,7}, results consistent with a model wherein expression of activating KIRs increases risk of developing immune-mediated diseases³. However, whether decreased expression of inhibitory KIRs is also associated with increased risk of psoriasis has not been fully explored.

The inhibitory KIR3DL1 is among the most polymorphic of all *KIR* loci (<http://www.ebi.ac.uk/ipd/kir/stats.html>). Cell surface expression of KIR3DL1 varies greatly between alleles and alleles can be classified into three allotypes: *KIR3DL1*NULL* (no cell surface expression: *004 and *019), *KIR3DL1*LOW* (low-expression: *005, *007, and *053), and *KIR3DL1*HIGH* (high-expression: *001, *002, *008, *009, *015, *020, *029, and *035)^{8,9}. The ligand for KIR3DL1 is the Bw4 epitope present on several HLA-B molecules such as HLA-B*57 and HLA-B*27, as well as HLA-A*24¹⁰.

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Conflict of Interest

The authors state no conflict of interest.

To investigate the association of *KIR3DL1* and *HLA-Bw4* with psoriasis, we carried out genotyping of *KIR3DL1* and *HLA-B* in a cohort of 314 subjects (203 psoriasis cases and 111 healthy controls) of European descent recruited from the United States. Diagnosis of psoriasis was established by a dermatologist. The average age of onset of psoriasis was 19 years, 54% were female, and approximately 23% were diagnosed with psoriatic arthritis. Controls were healthy volunteers without a history of autoimmune disease, with an average age of 39.0 and were 51.4% female.

KIR3DL1 typing was performed by sequencing exons 3, 4, 5, and 9 of *KIR3DL1*. Primers and PCR conditions are shown in Supplementary Table 3. *KIR3DL1* alleles were called from the sequencing data using Assign software (Conexio Genomics, Fremantle, Australia). HLA typing of cases was performed as previously described¹¹. HLA typing of controls was performed with the PCR-sequence based typing (PCR-SBT) method recommended by the 13th International Histocompatibility Workshop (available at: <http://www.ihwg.org>). HLA sequences were analyzed using Assign software (Conexio Genomics). In a minority of cases with missing *HLA-B* typing (n = 18), *HLA-B* genotypes were imputed with genome-wide association data (Supplementary Materials online).

Based on our previous work¹² and empirical data measuring cell surface expression of *KIR3DL1*¹³, individuals carrying at least one **HIGH* allele but no **LOW* allele were considered *KIR3DL1*HIGH* carriers, while individuals carrying at least one **LOW* allele were considered *KIR3DL1*LOW* carriers. If an individual carried at least one **NULL* allele and no copy of either a **LOW* or **HIGH* allele, they were considered a **NULL* carrier. 32 individuals homozygous for *KIR3DS1* (who do not carry any copies of *KIR3DL1*) were excluded from analysis. *HLA-B* genotypes were grouped into either *HLA-Bw4* or *HLA-Bw6*.

First, we tested *KIR3DL1*LOW*, *KIR3DL1*HIGH*, and *KIR3DL1*NULL* functional genotypes for association with psoriasis using a univariate logistic regression model (Supplementary Materials online). All p-values were adjusted for multiple tests by the Benjamini-Hochberg false discovery rate (FDR) procedure. Statistically significant associations were observed with the *KIR3DL1*LOW* (FDR = 0.05) and **NULL* (FDR = 0.04) genotypes (Table 1A). The **LOW* genotype associated with increased risk of psoriasis (OR = 1.68) while the **NULL* genotype associated with a protective effect (OR = 0.41).

Next, we tested the ligand for *KIR3DL1*, *HLA-Bw4*, for association with psoriasis with and without adjustment for *HLA-C*0602*, the strongest known psoriasis risk allele in the MHC region¹. In the unadjusted analysis, *Bw4*-positive genotypes were associated with increase in risk for psoriasis (OR = 1.79, FDR = 0.05), while *Bw6* genotypes (those lacking *Bw4*) were associated with reduced risk of psoriasis (OR = 0.56, FDR = 0.05). However, after adjustment for *HLA-C*0602*, which is commonly found on the same haplotype as the *Bw4*-positive allele *HLA-B*5701*⁴, neither *Bw4* nor *Bw6* were significantly associated with psoriasis (Table 1B).

Finally, we performed association testing of the compound genotypes *3DL1*LOW* + *HLA-Bw4*, *3DL1*HIGH* + *HLA-Bw4*, and *3DL1*NULL* + *HLA-Bw4* with adjustment for *HLA-C*0602*. This revealed a statistically significant association with the *3DL1*LOW* + *HLA-*

Bw4 compound genotype, with a significant increase in risk for psoriasis (OR = 2.50, FDR = 0.02) (Table 1C). A multivariate logistic regression model was used to test for evidence of multiplicative interaction between the *3DL1* genotypes and the *HLA-Bw4* genotypes and found suggestive evidence for epistasis between *3DL1* *LOW and *-Bw4* ($\beta = 1.14$, $p = 0.07$).

Overall, our results suggest that low cell-surface expression of KIR3DL1 in the presence of the HLA-Bw4 epitope is associated with an increased risk for developing psoriasis. This result is consistent with a model whereby a reduction in inhibitory signal in NK or T cells results in a heightened immune cell response³. We also found that individuals with the *KIR3DL1* *NULL genotype were protected from psoriasis irrespective of HLA-Bw4 status, suggesting that *NULL alleles may have intracellular effects independent of cell surface expression. A genetic study of ankylosing spondylitis also found that *KIR3DL1* *NULL alleles were protective of disease development¹⁴. While our sample size is relatively small, a power calculation revealed that our study has 80% power to detect an odds ratio of 2.0 or higher under a dominant model (see Supplementary Materials online). Our work—while requiring replication—provides additional evidence that NK cell receptors and ligands may be important in psoriasis susceptibility, adding to a body of literature that has suggested the importance of other NK cell receptors such as KIR2DS1 and KIR3DS1, as well as ligands such as MICA¹⁵.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

A. Association analysis of <i>KIR3DL1</i> genotypes						
Genotype	OR (95% CI)	P value	FDR	N_{cases} (%) ¹	$N_{controls}$ (%) ²	
<i>3DL1*LOW</i>	1.68 (1.02–2.79)	0.04	0.05	78/203 (38.4%)	30/111 (27.0%)	
<i>3DL1*HIGH</i>	0.92 (1.02–2.79)	0.71	0.71	109/203 (53.7%)	62/111 (55.9%)	
<i>3DL1*NULL</i>	0.41 (1.02–2.79)	0.01	0.04	16/203 (7.9%)	19/111 (17.1%)	
B. Association analysis of <i>HLA-B</i> genotypes (adjusted for <i>HLA-C*0602</i>)						
Genotype	OR (95% CI)	P value	FDR	N_{cases} (%) ¹	$N_{controls}$ (%) ²	
<i>HLA-Bw4</i>	1.27 (0.70–2.27)	0.43	0.57	140/178 (78.7%)	68/102 (66.7%)	
<i>HLA-Bw6</i>	0.79 (0.44–1.42)	0.43	0.57	38/178 (21.3%)	34/102 (33.3%)	
C. Association analysis of compound <i>KIR3DL1</i> and <i>HLA-Bw4</i> genotypes (adjusted for <i>HLA-C*0602</i>)						
Genotype	OR (95% CI)	P value	FDR	N_{cases} (%) ¹	$N_{controls}$ (%) ²	
<i>3DL1*LOW + Bw4</i>	2.50 (1.32–5.00)	6.80×10^{-3}	0.02	56/178 (31.5%)	14/102 (13.7%)	
<i>3DL1*HIGH + Bw4</i>	0.73 (0.43–1.22)	0.23	0.48	72/178 (40.4%)	45/102 (44.1%)	
<i>3DL1*NULL + Bw4</i>	0.65 (0.25–1.71)	0.37	0.48	12/178 (6.7%)	9/102 (8.8%)	

Abbreviations: OR, odds ratio; CI, confidence interval.

¹ Proportion of cases carrying given genotype.

² Proportion of controls carrying given genotype.