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The Interaction of LILRB2 with HLA-B is Associated with Psoriasis Susceptibility

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TO THE EDITOR:

The strongest signal for genetic susceptibility to psoriasis resides within the major histocompatibility complex (MHC) near class I loci (Okada et al., 2014). However, the mechanistic basis for how MHC associations confer psoriasis risk has yet to be fully elucidated (Prinz, 2018). Fine-mapping studies have identified specific amino acids in the peptide binding groove of HLA-B and HLA-C as conferring risk (Chen et al., 2012, Okada et al., 2014). This suggests that psoriasis risk may be mediated through HLA presentation of autoantigens. However, MHC I have other immunoregulatory functions, including binding and regulation of natural killer (NK) cells through killer cell immunoglobulin-like receptors (KIRs) or regulation of antigen presenting cells (APCs) through leukocyte immunoglobulin-

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DATA AVAILABILITY

The GAIN dataset used for the analyses described in this manuscript was obtained from the database of Genotypes and Phenotypes (dbGaP) found at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000019.v1.p1. Samples and associated phenotype data for the Collaborative Association Study of Psoriasis were provided by Drs. James T. Elder (University of Michigan, Ann Arbor, MI), Gerald G. Krueger (University of Utah, Salt Lake City, UT), Anne Bowcock (Washington University, St. Louis, MO), and Goncalo R. Abecasis (University of Michigan, Ann Arbor, MI). This study makes use of data generated by the Wellcome Trust Case-Control Consortium. The Wellcome Trust Case-Control Consortium data were obtained from the WTCCC official website (http://www.wtccc.org.uk/). A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk.

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like receptors (LILR). We have shown that HLA-B can mediate psoriasis risk through interaction with KIRs (Ahn et al., 2016). Here, we demonstrate that HLA-B can also mediate psoriasis susceptibility through differential binding to LILRs.

LILRs are a cousin of KIRs, closely located on chromosome 19, but are primarily found on APCs such as dendritic cells and macrophages, as well as subsets of B-cells, T-cells, and NK cells (Jones et al., 2011). LILRs participate in regulation of APC function through engagement of either activating receptors (LILRA) or inhibitory receptors (LILRB) (Hudson and Allen, 2016). LILRA increase secretion of inflammatory cytokines and basophil degranulation by increasing monocyte activation. Conversely, LILRB inhibit co-stimulatory proteins on APCs, may reduce antigen presentation on these cells, and facilitate an increased regulatory T cell response. LILR have been associated with several autoimmune and infectious diseases (Zhang et al., 2017). Here, we examined the distribution of binding affinities of LILRB1 and LILRB2 to HLA-A, -B, and -C in two large psoriasis genome-wide association study (GWAS) cohorts totaling 10,069 subjects.

To code the binding affinity of LILRB1 and LILRB2 to various HLA alleles as a genetic variable, we utilized published binding scores of LILRB1/2 to 31 alleles of HLA-A, 50 alleles of HLA-B, and 16 alleles of HLA-C (Bashirova et al., 2014, Jones et al., 2011) (Table S1). These scores were determined by incubating LILRB1-Fc or LILRB2-Fc fusion proteins with LABScreen HLA class I single antigen beads and measuring the median fluorescence intensity of each LILRB-HLA pairing. Each individual was assigned a LILRB1 or LILRB2 binding score for HLA-A, -B, and -C that was the sum of the binding scores of that individual's two HLA-A, -B, or -C alleles to LILRB1 or LILRB2 (Bashirova et al., 2014, Chen et al., 2012). These six variables (LILRB1-A, LILRB1-B, LILRB1-C, LILRB2-A, LILRB2-B, and LILRB2-C) were then used for association testing utilizing stepwise additive logistic regression models in PLINK, adjusted for individual imputed HLA class I and class II alleles, gender, and the first ten principal components of ancestry. Additional details of imputation and association testing are provided (Supplementary Methods).

Analysis of the Wellcome Trust Case-Control Consortium (WTCCC) discovery cohort revealed a number of independently associated variables (Table 1). As expected, the strongest signal was for HLA-C*06:02. However, we also identified an independent effect for LILRB2-B with an OR [95% CI] of 0.44 [0.28-0.68], p = 2.33E-04. This OR < 1 implies stronger LILRB2-B binding decreases psoriasis risk; alternatively stated, weaker binding increases risk for psoriasis. None of the other five LILRB variables demonstrated significance of $p<0.01$. In a second, independent cohort (Genetic Association Information Network (GAIN)), we validated that reduced binding of LILRB2 to HLA-B allotypes promotes psoriasis (p=3.43E-03, OR 0.50 [0.32-0.80]), (Table 1). Joint analysis of the WTCCC and GAIN cohorts indicated a significant effect of LILRB2-B binding level in both stepwise regression analysis (p=2.20E-09, OR 0.41 [0.30-0.55]) and multivariate analysis (p=2.34E-09, OR 0.41 [0.30-0.55])(Table 2).

We found that LILRB2 is robustly expressed in cutaneous dendritic cells and negligibly expressed in keratinocytes and T cells (Figure S1). We also found that LILRB2 is significantly overexpressed ($p<5.0E-08$, fold change=2.2) in psoriasis lesional skin

compared to healthy skin (Table S2), consistent with the known increased number of dendritic cells in psoriatic skin. We have shown that the ability of dendritic cells to induce proliferation of allogeneic CD4+ T cells after exposure to a panel of recombinant class I molecules is inversely proportional to binding scores of the HLA allotype to LILRB2 (Bashirova et al., 2014). Addition of LILRB2 siRNA to this mixed leukocyte reaction enhanced CD4+ T cell proliferation (Bashirova et al., 2014).

Our results indicate that psoriasis patients, on average, harbor HLA-B alleles with decreased binding affinity to LILRB2, which may lead to a reduction in APC inhibition that results in more potent T cell reactivity. HLA-B*57:01 and HLA-B*27:05 have been strongly associated with psoriasis (Chen et al., 2012, Okada et al., 2014) and these two alleles are among those with the lowest LILRB2 binding affinities (Table S1). The signal observed in our study for LILRB2-B but not HLA-C or HLA-A may be explained by the fact that HLA-C is expressed on the cell surface at roughly one-tenth the level of HLA-A and HLA-B (Apps et al., 2015), and by the observation that there is a much smaller range of variation for LILRB2 binding to HLA-A compared to HLA-B.

The role of LILR molecules in the pathogenesis of diseases is becoming more recognized. The binding affinity of LILRB2 to HLA-B has been associated with HIV-1 viral control (Bashirova et al., 2014); genetic epistasis has been demonstrated between LILRA3 and HLA-B*52 in Takayasu's Arteritis (Terao et al., 2018); and LILRB1 has been demonstrated to be protective in ankylosis spondylitis (Majorczyk et al., 2019). A paradigm in evolutionary genetics is the balance between a potent immune system and overshooting towards autoimmune pathogenesis (Kulkarni et al., 2008). For example, HLA Class I alleles protective against HIV-1 are enriched in psoriasis patients (Chen et al., 2012). The differential binding of HLA-B and LILRB2 demonstrate another example of this evolutionary balance.

To our knowledge, our work is the first to identify a role for LILRB2 in psoriasis susceptibility. Our finding, supported by two independent datasets, expands our mechanistic understanding of the role of HLA in immune-mediated diseases, highlighting the importance of APC regulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MHC	major histocompatibility complex
NK	natural killer cells
APC	antigen presenting cells
LILR	leukocyte immunoglobulin-like receptors
KIR	killer cell immunoglobulin-like receptors
GWAS	genome-wide association study

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Table 1.

Stepwise regression analysis of the association of LILRB binding and individual HLA alleles with psoriasis in the WTCCC and GAIN cohorts

WTCCC (Discovery Cohort) 2,178 cases, 5,175 controls			GAIN (Replication Cohort) 1,368 cases, 1,348 controls		
Variable	**p-value**	**OR (95% CI)**	**Variable**	**p-value**	**OR (95% CI)**
C0602	3.32E-26	4.20 (3.22-5.47)	C0602	5.27E-35	4.41 (3.49-5.58)
A0201	1.83E-13	1.70 (1.47-1.95)	DQB0604	2.65E-06	0.37 (0.25-0.56)
A0101	4.64E-08	1.62 (1.36-1.92)	B5001	2.24E-03	0.43 (0.25-0.74)
B3801	2.78E-02	1.82 (1.07-3.11)	B3801	3.37E-04	2.20 (1.43-3.39)
B5501	5.41E-05	1.93 (1.40-2.65)	A0201	1.32E-03	1.34 (1.12-1.61)
LILRB2-B	**2.33E-04**	**0.44 (0.28-0.68)**	B3901	3.17E-03	2.08 (1.28-3.37)
DQB0604	1.30E-02	0.64 (0.45-0.91)	DRB0801	6.81E-03	0.56 (0.37-0.85)
A1101	1.64E-02	1.31 (1.05-1.62)	B5501	3.47E-03	1.91 (1.24-2.95)
C1203	2.66E-02	1.54 (1.05-2.26)	B0801	2.10E-03	1.45 (1.14-1.83)
B1302	6.15E-04	1.74 (1.27-2.38)	**LILRB2-B**	**3.43E-03**	**0.50 (0.32-0.80)**
B5701	1.41E-02	1.49 (1.08-2.04)			
B4001	2.69E-02	0.75 (0.58-0.97)			
DQA0501	1.88E-03	0.77 (0.65-0.91)			
B0801	7.66E-03	1.36 (1.08-1.70)			
B4403	4.09E-02	0.77 (0.59-0.99)			

Abbreviations: GWAS, Genome Wide Association Studies; WTCCC, Wellcome Trust Case-Control Consortium.

Table 2.

Stepwise regression and multivariate association analysis of LILRB binding and individual HLA alleles with psoriasis in the combined WTCCC and GAIN cohorts. All variables from the stepwise analysis were included in the multivariate analysis.

	Stepwise Univariate Analysis		Multivariate Analysis	
Variable	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
C0602	1.71E-123	5.29 (4.61-6.08)	1.33E-123	5.30 (4.62-6.09)
B5001	1.71E-06	0.45 (0.33-0.62)	1.83E-06	0.45 (0.33-0.63)
A0201	2.51E-15	1.57 (1.40-1.75)	2.32E-15	1.57 (1.40-1.75)
A0101	3.68E-07	1.43 (1.24-1.63)	4.45E-07	1.42 (1.24-1.63)
DQB0604	5.53E-06	0.53 (0.40-0.70)	4.94E-06	0.53 (0.40-0.69)
B5501	2.39E-06	1.84 (1.43-2.37)	2.57E-06	1.84 (1.43-2.37)
LILRB2-B	**2.20E-09**	**0.41 (0.30-0.55)**	**2.34E-09**	**0.41 (0.30-0.55)**
B4001	3.58E-03	0.75 (0.62-0.91)	3.53E-03	0.75 (0.62-0.91)
B4403	1.81E-03	0.73 (0.60-0.89)	1.83E-03	0.73 (0.60-0.89)
C1203	4.29E-07	1.72 (1.40-2.13)	3.59E-07	1.73 (1.40-2.14)
B0801	5.40E-05	1.75 (1.34-2.30)	6.54E-05	1.74 (1.33-2.29)
DQA0501	1.35E-02	0.85 (0.75-0.97)	1.44E-02	0.85 (0.75-0.97)
A1101	3.61E-02	1.20 (1.01-1.43)	3.87E-02	1.20 (1.01-1.43)
C0701	3.09E-02	0.76 (0.60-0.98)	3.42E-02	0.77 (0.60-0.98)
DRB0801	4.76E-02	0.75 (0.56-1.00)	5.47E-02	0.75 (0.56-1.01)

Abbreviations: GWAS, Genome Wide Association Studies; WTCCC, Wellcome Trust Case-Control Consortium.