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A Role for *KIR* Gene Variants Other Than *KIR2DS1* in Conferring Susceptibility to Psoriasis

Rafal Płoski,[1] Wioleta Łuszczek,[1] Piotr Kuśnierczyk, Piotr Nockowski, Maria Cisło, Paweł Krajewski, and Jacek Malejczyk

ABSTRACT: Recently we described an association between psoriasis and *KIR2DS1,* a gene for a stimulatory natural killer cell receptor, in a Polish population. The association was independently reported among Japanese and confirmed in a U.S. population. Prompted by these findings, we reanalyzed data by a multivariate approach in search of possible effects of *KIR* genes other than *KIR2DS1* (non-*KIR2DS1*). The methodology was based on a stratified analysis and multiple logistic regression. We found that the non-*KIR2DS1* genes had joint effects comparable to or stronger than the effects of *KIR2DS1* in both the fraction of explained variance (0.174 vs 0.204, respectively, for *KIR2DS1* and non-*KIR2DS1*) and the statistical significance ($p = 0.000008$ vs $p = 0.000001$, respectively). When individual genes were considered, a decrease in *KIR2DS5* among patients vs controls (OR = 0.2, $p_{cor} = 0.0005$) and a decrease in *KIR2DS3* restricted to *KIR2DS1*-positive individuals (OR = 0.2, $p_{cor} = 0.005$) were evident. We also performed a multivariate analysis of the *HLA-Cw* genotypes but failed to demonstrate any effects in addition to the known association with *HLA-Cw*06.* We conclude that the effect of the *KIR* genes on psoriasis susceptibility is complex, extending beyond the association with *KIR2DS1* and involving protective effects and interactions. *Human Immunology 67, 521–526 (2006).* © American Society for Histocompatibility and Immunogenetics, 2006. Published by Elsevier Inc.

KEYWORDS: KIR; KIR2DS1; psoriasis susceptibility; protective effects

ABBREVIATIONS

HLA human leukocyte antigen
KIR killer cell immunoglobulinlike receptor
PsA psoriatic arthritis patient

INTRODUCTION

Psoriasis is a common autoimmune disease partially determined by genetic factors. The genes most consistently implicated in the pathogenesis of this disorder are alleles of the human leukocyte antigen (*HLA*) loci, in particular *HLA-Cw*06* [1]. Recently we demonstrated an association between susceptibility to psoriasis and presence of a gene for a stimulatory killer cell immunoglobulinlike receptor (*KIR*), *KIR2DS1,* in a Polish population [2]. KIRs are a family of cell surface receptors that exert inhibitory or stimulatory functions and are expressed by natural killer cells and a subset of T cells. Whereas a number of KIRs with inhibitory roles were demonstrated to bind certain HLA-C and -B molecules, the physiological ligands for the stimulatory KIRs are largely unknown [3]. The *KIR* genes are encoded by a tightly linked complex on chromosome 19 [4] and display extensive polymorphism, whose characteristic feature is large variation in the repertoire of the individual genes present [5]. Although the functional significance of the association between *KIR2DS1* and psoriasis is not clear, it was independently observed by Japanese authors [6]

From the Department of Medical Genetics (R.P.), Department of Forensic Medicine (P.K.), and Department of Histology and Embryology, Center of Biostructure (J.M.), Medical University in Warsaw, Warsaw, Poland; the Laboratory of Immunogenetics, Department of Clinical Immunology, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, (W.ŁŁ., P.Ku.); and the Clinic of Veneorology, Dermatology, and Allergology, Medical University of Wroclaw, Wroclaw, Poland (P.N., M.C.).

Address reprint requests to: Rafal Ploski, M.D., Ph.D., Department of Medical Genetics, Medical University in Warsaw, ul. Oczki 1, 02-007 Warsaw, Poland; Tel: + 48 22 628 39 00; Fax: + 48 22 628 63 04; E-mail: rploski@wp.pl.

[1] R. P. and W. L. contributed equally to this work.

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and subsequently confirmed by a study on a U.S. population [7]. Further credibility for a role of *KIR2DS1* in psoriasis comes from findings of increased frequency of this gene among psoriatic arthritis patients (PsA) [8–10].

The association between psoriasis and *KIR2DS1* in the Polish population was relatively strong (OR = 5.6). Such an increase in one gene variant among patients vs controls may have a confounding effect in the analysis of other variants; for example, it may cause a decrease in the frequencies of some genes, especially those which are (or behave as if they were) allelic to the associated variant. The issue is further complicated by strong linkage disequilibrium across the *KIR* locus [2–4]. In the presence of an association with one variant, linkage disequilibrium may influence the distribution of other variants, causing secondary increases or decreases in their frequencies compared with controls. Thus, in the univariate analysis performed in the original study [2], the association with *KIR2DS1* may have rendered difficult the detection of weaker positive or negative associations between other *KIR* genes and disease.

Given the reproducibility of the association of *KIR2DS1* with psoriasis/PsA [2, 6–10], we were prompted to reanalyze our results [2] by a multivariate approach allowing adjustment for the increase in *KIR2DS1* frequency among patients and thus helping to reveal possible effects on disease susceptibility of other *KIR* genes, their combinations, and/or combinations of *KIR* and *HLA-Cw* genotypes.

MATERIALS AND METHODS

The studied individuals and the typing methods were described previously [2]. Briefly, the investigated cohort consisted of 116 patients with psoriasis vulgaris diagnosed and treated at the Clinic of Venereology and Dermatology and 123 healthy unrelated blood donors from a regional blood bank in whom psoriasis was specifically excluded. Typing for *KIR* and *HLA-C* polymorphism was performed by sequence-specific primers. Based on the distribution of *HLA-Cw* subtypes in Caucasians (http://www.ncbi.nlm.nih.gov/projects/mhc/ihwg.cgi), the *HLA-Cw* alleles were assigned to C1 (Asn80) and C2 (Lys80) groups as follows: HLA-C1 (Cw1, 3, 7, 8, 12, 13, 14, 16) and HLA-C2 (Cw2, 4, 5, 6, 15, 17). The study was approved by the Bioethics Committee of the Medical University of Wroclaw.

Statistical analysis was performed with the SPSS software package (SPSS Inc., Chicago, IL, USA). Pairwise comparisons between proportions were done by the χ^2 or Fisher's exact test, as appropriate. The heterogeneity of risk conferred by a given *KIR* variant in the presence and absence of a potentially interacting factor (another *KIR* or *HLA* genotype) was assessed by the Breslow–Day test. The statistical significance of *KIR-HLA* interactions with the *HLA* effect modeled as codominant was done by logistic regression [11]. The *HLA* genotype was encoded as 0, 1, or 2 according to the number of respective alleles. For each *KIR* variant, a model including this variant, the *HLA* genotype, and the appropriate interaction factor as the independent variables was compared with the model without the interaction by the likelihood ratio test, thus allowing an estimation of the statistical significance of the interaction[11].

The p values were corrected for the number of comparisons. The following correction factors were used: 16, the number of tested genes (8) multiplied by number of groups (2), in the analysis of the distribution of *KIR* gene variants among patients and controls stratified according to the presence of *KIR2DS1* (Table 1); 9, the number of variables without *KIR2DS1,* in the analysis of effects of individual variables by logistic regression; 512, the number of all possible subsets of a nine-element set, in the analysis of the reduced logistic regression model; and 40, the number of comparisons with the Breslow–Day test, in the analysis of non-*KIR2DS1 KIR-HLA* interactions. The fraction of total variance of the dependent variable (*i.e.,* the presence of psoriasis) explained by the independent variables (*i.e.,* the *KIR* genes) in a logistic model was calculated as the Nagelkerke R^2 [12].

TABLE 1 Distribution of *KIR* gene variants among patients and controls stratified according to the presence of *KIR2DS1*

	KIR2DS1 (−)		KIR2DS1 (+)	
KIR	Patients (N = 17) n (%)	Controls (N = 60) n (%)	Patients (N = 99) n (%)	Controls (N = 63) n (%)
2DL1	15 (88.2)	53 (88.3)	91 (91.9)	56 (88.9)
2DL2	11 (64.7)	30 (50.0)	59 (59.6)	38 (60.3)
2DL3	14 (82.4)	57 (95.0)	84 (84.8)	53 (84.1)
2DS2	11 (64.7)	25 (41.7)	55 (55.6)	35 (55.6)
2DS3	3 (17.6)	5 (8.3)	19 (19.2)[1]	29 (46.0)
2DS4	2 (11.8)	17 (28.3)	21 (21.2)	18 (28.6)
1D	16 (94.1)	53 (88.3)	82 (82.8)[2]	38 (60.3)
2DS5	1 (5.9)	5 (8.3)	32 (32.3)[3]	37 (58.7)

N, number of individuals in a group; *n,* number of individuals with a given *KIR* variant. In all analyses, correction factor = 16.

[1] OR = 0.278, χ^2 = 13.302, 1*df,* $p < 0.0003$, $p_{cor} = 0.005$, comparison vs *KIR2DS1* (+) controls, Breslow–Day homogeneity of OR among *KIR2DS1* (+) vs *KIR2DS1* (−): $p = 0.007$.

[2] OR = 3.173, χ^2 = 10.159, 1*df,* $p < 0.0014$, $p_{cor} < 0.023$, comparison vs *KIR2DS1* (+) controls,

[3] OR = 0.336, $p = 0.001$ (Fisher exact test), $p_{cor} = 0.016$, comparison vs *KIR2DS1* (+) controls.