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Carriers of rare missense variants in IFIH1 are protected from psoriasis

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Abstract

Testing of ~25,000 putative functional single nucleotide polymorphisms (SNPs) across the human genome in a genetic association study has identified three psoriasis genes, *IL12B, IL23R* and *IL13*. We now report evidence for the association of psoriasis risk with missense SNPs in the interferon induced with helicase C domain 1 gene (*IFIH1*). The rare alleles of two independent SNPs were associated with decreased risk of psoriasis - rs35667974 (Ile923Val): OR=0.45, P=4.09×10^{-5} (2,098 cases *vs*. 1,748 controls) and rs10930046 (His460Arg): OR=0.52, P=5.70×10^{-4} (2,098 cases *vs*. 1,744 controls). Compared to noncarriers, carriers of the 923Val and/or 460Arg variants were protected from psoriasis (OR=0.48, P=7.31×10^{-8}). These results suggest that *IFIH1* is a novel psoriasis gene.

Keywords

IFIH1; psoriasis; SNP; genetic association

INTRODUCTION

Psoriasis is a common, chronic, T-cell mediated inflammatory disease of the skin (Nestle *et al.*, 2009) affecting 2-3% of whites of European descent but fewer Asians and Africans (Campalani and Barker, 2005). It is considered a multi-factorial, complex disease involving both genetic and environmental factors (Bowcock and Krueger, 2005; Smith *et al.*, 2009). Genetic contribution to the disease is demonstrated by increased concordance in monozygotic compared to dizygotic twins (72% vs 15-23%, respectively, for northern European individuals) and the observation that upwards of 71% of patients with childhood psoriasis have a positive family history (Bowcock and Krueger, 2005). Indeed, the human leukocyte antigen (HLA) variant HLA-Cw*0602 strongly predisposes to psoriasis (Nair et

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CONFLICT OF INTEREST
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al., 2006; Fan et al., 2008), and multiple single nucleotide polymorphisms (SNPs) in at least 7 genes including *IL12B, IL13, IL23R, STAT2/IL23A, TNFAIP3, TNIP1*, and *LCE*, have been convincingly associated with psoriasis risk (Cargill et al., 2007; Chang et al., 2008; Liu et al., 2008; de Cid et al., 2009; Nair et al., 2009; Zhang et al., 2009). Variants in β-defensin, *CDKAL1* and other genes may also affect risk of psoriasis (Lesueur *et al.*, 2007; Capon *et al.*, 2008; Hollox *et al.*, 2008; Wolf *et al.*, 2008; Li *et al.*, 2009). However, these variants do not fully account for the genetic contribution to psoriasis, underscoring the necessity of further search for other genetic variants.

RESULTS

We recently conducted a large-scale genetic association study testing 25,215 putative functional SNPs across the genome in three independent psoriasis case-control sample sets. Based on these data, we reported results that validated *IL12B* and provided the first evidence for *IL23R* and *IL13* as psoriasis risk genes (Cargill *et al.*, 2007; Chang *et al.*, 2008).

To continue the search for psoriasis genes, we prioritized the remaining markers from our genetic study for additional genotyping and association testing. Excluding markers in the *HLA, IL12B, IL23R*, and *IL13* loci, we individually genotyped and analyzed 337 autosomal markers in one or more of the three sample sets (all markers had Hardy Weinberg equilibrium $P>0.001$ in controls). An association test showed that 113 markers were associated with psoriasis risk (allelic $P<0.05$ in all samples combined) (Supplementary Table 1); these markers include those in *PADI4*, which is involved in the genetics of rheumatoid arthritis (Suzuki *et al.*, 2003), and *FNDC1*, which is highly expressed in the epidermis of psoriatic skin but barely detectable in normal skin (Anderegg *et al.*, 2005).

The most significant marker was rs35667964 in the *IFIH1* gene on chromosome 2 (allelic $P=1.74\times10^{-5}$). Another SNP in *IFIH1*, rs10930046, was also significantly associated with psoriasis risk (allelic $P=0.0055$). Further testing of these two polymorphisms in a fourth sample set replicated rs10930046 (replication allelic $P=0.031$, combined allelic $P=5.70\times10^{-4}$; Table 1), and the odds ratio of rs35667964 was the same direction as in the other three sample sets (replication allelic $P=0.42$, combined allelic $P=4.09\times10^{-5}$; Table 1). Both markers were missense polymorphisms, resulting in Ile923Val and His460Arg variants, respectively, in the IFIH1 polypeptide. The minor allele frequencies of both the 923Val and 460Arg variants were low: 2.17% and 2.09% in the combined control population, respectively. Because of the low allele frequency, very few individuals carried two copies of either of the protective variants; therefore, testing the carrier status of the protective alleles did not substantially alter the association results (Table 1). Compared with noncarriers, carriers of 923Val variant or 460Arg variant were protected from psoriasis.

These two *IFIH1* markers are not correlated with each other ($r^2=0.001$ in the control samples). As shown in Table 2, only one case and two control individuals carried both the rare variants. Regression analyses showed that both markers remained significant when adjusted for the other (adjusted $P<0.05$), suggesting that the two rare missense variants independently protect from psoriasis. Because of these findings, we further tested the combined effect of these two variants on psoriasis risk. Compared with noncarriers (i.e. individuals with 460His and 923Ile variant of the IFIH1 polypeptide), carriers of the protective variants 460Arg and/or 923Val were significantly associated with lower risk of psoriasis (OR=0.48, $P=7.31\times10^{-8}$ in all sample sets combined, Breslow-Day $P=0.068$ for OR heterogeneity). As expected, carriers with at least one protective allele (460Arg, 923Val or both) were more common than carriers of either of the variants alone (460Arg or 923Val), comprising 8.1% of the combined control sample sets.

DISCUSSION

The above results suggest that missense variants in *IFIH1* may modulate risk of psoriasis in the white, North American population. The observed statistical evidence are at the level of $P=4.09\times10^{-5}$ and 5.70×10^{-4} for the two independent SNPs individually and 7.31×10^{-8} for the carrier status of the protective variants. In the context of our study that tested ~25,000 putative functional SNPs, the carrier association remained significant after adjustment for multiple testing (Bonferroni corrected $P=0.0018$), supporting that variants in *IFIH1* are genuinely associated with psoriasis risk.

Pleiotropic effect of IFIH1 in modulating autoimmunity

A role for *IFIH1* in the etiology of psoriasis is bolstered by *a priori* genetic connection between this gene and other autoimmune and inflammatory diseases and the observation that distinct autoimmune and inflammatory diseases share overlapping genetic factors (Li and Begovich, 2009). Definitive evidence for a role of *IFIH1* in autoimmunity comes from T1D, where genome wide significance was observed for at least two distinct *IFIH1* SNPs: a common missense polymorphism rs1990760 (Ala946Thr; risk allele frequency=0.60 in whites) (Smyth *et al.*, 2006) and the rare missense polymorphism rs35667974 tested in our study (Nejentsev *et al.*, 2009). The effect of the common SNP in T1D is weak (OR=0.86), a phenomena that has also been observed in other common complex diseases, while that of the rare SNP is stronger (OR=0.51). There is also strong evidence for a role of rs1990760 in systemic lupus erythematosus (SLE) (Gateva *et al.*, 2009), inconsistent evidence in multiple sclerosis (Martinez *et al.*, 2008; Couturier *et al.*, 2009; Enevold *et al.*, 2009) and Graves' disease (Sutherland *et al.*, 2007; Penna-Martinez *et al.*, 2009), and no evidence for celiac disease (Smyth *et al.*, 2008) or rheumatoid arthritis (Marinou *et al.*, 2007).

SNP rs1990760 was not tested in our psoriasis sample sets for technical reasons. Another missense SNP, rs3747517 (His843Arg), in linkage disequilibrium with rs1990760 (Ala946Thr) ($r^2=0.61$) and associated with T1D (Smyth *et al.*, 2006), was tested in the pools of our Sample Set 1 but was not significant ($P=0.25$). However, assuming that the frequency of rs1990760 risk allele in the unrelated controls is 60% and an allelic odds ratio of 1.15, as observed in the T1D and SLE studies (Smyth *et al.*, 2006; Gateva *et al.*, 2009), one would require 1,701 case patients and 1,701 controls to observe an association with disease status with 80% power at a *P*-value of 0.05. Thus, our first three sample sets may lack sufficient power to determine whether rs1990760 is associated with psoriasis, even at the nominal significance level.

Rare genetic variants and risk of psoriasis

The effect of the rare missense variant rs35667974 (Ile923Val) on risk of psoriasis and T1D is in the same direction and of similar magnitude (OR=0.45 (this study) and 0.51 (Nejentsev *et al.*, 2009)). Carriers of the protective allele 923Val comprised 4.5% of the control population, and, when the other rare missense SNP is also considered, carriers of either the protective alleles accounted for 8.1% of the controls. These observations underscore the important contribution of rare variants to disease susceptibility of common complex diseases such as psoriasis. They also have implications in not only further validating *IFIH1* as a psoriasis risk gene but also suggesting variants in this gene be re-evaluated in appropriately powered studies of other autoimmune diseases. Assuming that the minor allele frequency of rs35667974 (Ile923Val) in controls is 0.022 (as observed in this study and the T1D study) and effect size of 0.50, the number of samples required to achieve 80% power is estimated to be 1,080 cases with an equal number of controls. Interestingly, under the above assumptions, a given case-control sample set is predicted to have more power to detect the rare SNP (Ile923Val) with its stronger effect than the common SNP (Ala946Thr) with its

weak effect. Therefore, this and the other rare SNPs warrant testing in the other autoimmune studies to further clarify its role in modulating autoimmune and inflammatory disease risk.

The other psoriasis-associated SNP, rs10930046 (His460Arg), was not associated with T1D (Nejentsev *et al.*, 2009). It is possible that distinct variants of the same risk factor may differentially affect individual diseases. Alternatively, our finding may be a result of type I error. We noticed that unlike rs35667974, which had the same frequency in our controls and the T1D controls, the minor allele frequency of rs10930046 was different between our white, North American controls and the UK T1D controls (2.1% vs. 1.0%). Therefore, further testing of this marker in other psoriasis sample sets is required. Interestingly, residue 460 lies in the helicase ATP binding domain of the IFIH1 protein, although it remains to be determined whether a change from a histidine residue to an arginine residue (blosum score=0) affects the activity of the protein.

Biological evidence for a role of IFIH1 in psoriasis

The known biological function of IFIH1 supports a role for this gene in autoimmune and inflammatory diseases including psoriasis. IFIH1 is an interferon-induced putative RNA helicase that affects cell growth, differentiation and death (Kang *et al.*, 2002; Besch *et al.*, 2009) and has been implicated in the recognition of RNA virus (Kato *et al.*, 2006). Virus infection may be one of the environment factors that trigger and/or exacerbate psoriasis, and human endogenous retroviruses have been detected in psoriatic skins (Fry and Baker, 2007). In addition, *IFIH1* expression is increased in epidermal cells and tissues from psoriatic plaques compared to normal controls (Prens *et al.*, 2008); increased *IFIH1* expression may account for some *IFIH1* risk variants in T1D (Liu *et al.*, 2009). Together with this and other biological evidence, our genetic results suggest that investigation of how the identified missense variants differentially affect IFIH1 protein function is important, particularly the conserved 923Ile *vs.* 923Val (blosum score=3). Understanding their functional differences will provide insights into the role(s) for IFIH1 in the pathogenesis of psoriasis and may guide the design of pharmacological interventions either directly or indirectly targeting IFIH1 for the treatment of psoriasis and other autoimmune and inflammatory diseases.

MATERIALS AND METHODS

Samples and Strategy

Samples from dermatologist-confirmed psoriasis cases and controls were collected from the University of Utah (Sample Set 1: 467 cases and 460 controls), from the Genomics Collaborative Division of SeraCare Life Sciences (Sample Set 2: 498 cases and 498 controls) and Genomics Collaborative and BioCollections Worldwide (Sample Set 3: 483 cases and 427 controls). All individuals were white, North Americans and were 18 years or older at the time they were enrolled in the sample collections. A detailed description of clinical and demographic information can be found in a previous publication (Cargill et al. 2007). A fourth sample set contained 660 cases and 365 controls: psoriasis cases were Caucasians with plaque-type psoriasis recruited at the University of California, San Francisco and Washington University, St. Louis. Controls were healthy Caucasians with no history of autoimmune or inflammatory disease recruited from San Francisco. All protocols were approved by national and/or local institutional review boards, and informed written consent was obtained from all subjects.

The initial testing of 25,215 SNPs was carried out in DNA pools of Sample Set 1. Markers that had allelic $P<0.05$ were then tested in replication DNA pools of Sample Set 2. Replicated markers (allelic $P<0.05$) were then sequentially individually genotyped in these and a third sample sets. For this report, a total of 62 SNPs were individually genotyped in all

three sample sets, 189 other markers in 2 sample sets, and 86 other markers in 1 sample set. Two markers in *IFIH1* were further genotyped in Sample Set 4.

Genotyping

For Sample Sets 1 to 3, individual genotyping was performed using allele-specific kinetic PCR on 0.3ng of DNA at the Celera Genotyping Lab. Data were hand curated before statistical analysis, without knowledge of case-control status. Genotyping calls were made on >95% of samples. Previous analyses suggest a genotyping accuracy of >99% (Cargill et al. 2007). For the fourth sample set, genotyping was performed at a laboratory at the University of California, San Francisco via Applied Biosystems Taqman assay.

Statistics

Deviation from Hardy-Weinberg equilibrium (HWE) was examined in the control samples using the exact test of Weir (Weir, 1996). Allelic association of a marker with disease status was determined by the χ^2-test; a meta-analysis in all three sample sets was carried out using fixed effects of the Mantel-Haenszel method to combine odds ratios across the sample sets. *P*-values were two sided in all samples combined. Odds ratios and 95% confidence intervals (95%CI) were estimated from the allele or genotype counts. Assessment of OR heterogeneity across sample sets was done by the Breslow-Day test. Testing of the independence of two markers was carried out by the logistical regression. The linkage disequilibrium measure r^2 was calculated from unphased data with use of the LDMAX program in the GOLD package (Abecasis et al., 2000). Power and sample size for an association study in a case control study were estimated using the program “PS: Power and Sample Size Calculation” (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize). For the estimation, independent cases and controls with 1 control per case was assumed. The Type I error probability associated with the test of a null hypothesis was set at 0.05. An uncorrected χ^2 statistic was used too evaluate this null hypothesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SNP	single nucleotide polymorphism
T1D	type I diabetes
SLE	systemic lupus erythematosus
HWE	Hardy-Weinberg equilibrium
OR	odds ratio
CI	confidence interval

Table 1

Association of missense variants in *IFIH1* with psoriasis

			Count[2]					Allelic Test[4]		Genotypic Test[5]	
RS Number	**Variation[1]**	**Samples**	**CC**	**CT**	**TT**	**Sum**	**MAF[3]**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
rs35667974	Ile923Val	Case	3	37	2,058	2,098	0.0102	0.45 (0.31 - 0.67)	4.09×10^{-5}	0.43 (0.29 - 0.64)	2.36×10^{-5}
		Control	2	72	1,674	1,748	0.0217				
rs10930046	His460Arg	Case	3	39	2,056	2,098	0.0107	0.52 (0.36 - 0.76)	5.70×10^{-4}	0.51 (0.35 - 0.76)	6.47×10^{-4}
		Control	4	65	1,675	1,744	0.0209				

[1] C allele corresponds to 923 Val and 460 Arg variants

[2] HWE $P>0.05$ (exact test) in controls of individual sample sets for both SNPs

[3] minor allele frequency

[4] adjusted for sample set

[5] dominant model, adjusted for sample set

Table 2

Association of psoriasis with carriers of either the IFIH1 460Arg and/or 923Val variants.

		IFIH1 Variant[2]				Carriers vs. Noncarriers[3]	
Status of Protective Alleles[1]		**Residue 460**	**Residue 923**	**Case Count (%)**	**Control Count (%)**	**OR (95% CI)**	**P**
Carriers	Sub-Group	**Arg**	Ile	41 (1.96)	67 (3.85)	0.48 (0.37 - 0.63)	7.31×10^{-8}
		His	**Val**	39 (1.86)	72 (4.13)		
		Arg	**Val**	1 (0.05)	2 (0.11)		
	Combined			81 (3.87)	141 (8.09)		
Noncarriers		His	Ile	2011 (96.13)	1601 (91.91)		

[1] Carriers of protective IFIH1 alleles have at least one copy of the arginine residue at position 460 or a valine residue at position 923. Noncarriers are homozygous for the histidine residue at position 460 and the isoleucine residue at position 923.

[2] Protective alleles in boldface

[3] chi-square test, adjusted for sample set