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Psoriasis risk SNPs and their association with HIV-1 control

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Abstract

Human evolution has resulted in selection for genetic polymorphisms beneficial in the defense against pathogens. However, such polymorphisms may have the potential to heighten the risk of autoimmune disease. Here, we investigated whether psoriasis-associated single nucleotide polymorphisms influence host control of HIV-1 infection. We studied psoriasis and viral immune response variants in three HIV-positive cohorts: (1) HIV-1 controllers and non-controllers in the Study of the Consequences of the Protease Inhibitor Era (SCOPE) cohort (n=366), (2) Individuals with primary HIV infection in the Options cohort (n=675), and (3) HIV-positive injection drug users from the Urban Health Study (UHS) (n=987). We found a strong association of two psoriasis MHC variants, rs9264942 and rs3021366, with both HIV-1 controller status and viral load, and identified another Class III MHC variant rs9368699 to be strongly associated with viral load. A number of genetic variants outside the MHC (*SOX5*, *TLR9*, *SDC4*, *PROX1*, *IL12B*, *TLR4*, *MBL-2*, *TYK2*, *IFIH1*) demonstrated nominal significance. Overall, our data suggest that several psoriasis variants within the MHC have a robust impact on HIV-1 control, while variants outside the MHC require further investigation.

Keywords

psoriasis; HIV; genetics; immunogenetics; MHC; viral control; viral load; primary infection

1. Introduction

Psoriasis is an immune-mediated inflammatory condition where the excessive immune activation results in inflammation of the skin and raised red scaly patches. Psoriasis has a worldwide prevalence of 2–4%. [1] Previous segregation and linkage analysis show psoriasis

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to be a heritable condition as evidenced by a twin concordance rate of 70% and a sibling recurrence risk λ_s between 4–11. [2]

HIV-1 control is a rare immunologic phenotype in approximately 1% of HIV-1 infected individuals in which patients who are infected with the HIV-1 virus spontaneously maintain low viral loads in the absence of anti-retroviral therapy (ART). HIV-1 control has been observed across all ethnicities and modes of viral transmission and it has been shown to be associated with certain genetic and immunologic characteristics.[3]

Our previous work analyzing genetic variants in the major histocompatibility (MHC) region in psoriasis cases versus controls revealed that psoriasis patients are enriched for several human leukocyte antigen (HLA) class I alleles that are also associated with HIV-1 control. [4] A follow-up study demonstrated that there is a significant increase in antiviral gene expression in psoriasis lesional skin compared to healthy controls.[5] Another study showed that *HLA-C* alleles associated with higher HLA-C surface expression contribute to viral control in HIV but lead to an increase in risk of another immune-mediated disease, Crohn's disease.[6] Together, these studies suggest that some genetic variants that protect the human host against viral pathogens may also increase the risk of autoimmune disease.

Here, to further understand the genetic relationship between psoriasis and HIV-1 control, we genotyped a more comprehensive panel of psoriasis risk single nucleotide polymorphisms (SNPs) in HIV cohorts to determine if viral control is associated with psoriasis susceptibility SNPs. We also genotyped a number of known viral control SNPs to evaluate whether they were associated with HIV-1 control.

2. Materials and Methods

2.1 Subjects

Three HIV cohorts were examined in this study: Study of the Consequences of the Protease Inhibitor Era (SCOPE) and Options as discovery cohorts and the Urban Health Study (UHS) as a replication cohort.

The SCOPE cohort is an ongoing prospective cohort study at the University of California San Francisco (UCSF) where HIV-positive participants are seen at 4-month intervals to complete questionnaires and provide a blood sample to determine HIV plasma RNA level and CD4+ T cell count. A subset of SCOPE participants are classified into two groups: (1) virologic "controllers" who were defined individuals maintaining at least one year duration of steady-state HIV RNA plasma levels below 2,000 copies RNA/ml in the absence of antiretroviral drugs; and (2) virologic "non-controllers" who are defined as antiretroviral drug-treated and untreated individuals with at least one documented plasma HIV RNA level of more than 10,000 copies/ml. [7] For this study, we genotyped 139 controllers and 227 non-controllers in the SCOPE cohort. Of the 366 individuals genotyped, 61 controllers and 115 non-controllers were Caucasian and 40 controllers and 50 non-controllers were African-American.

The UCSF Options cohort consisted of individuals with either potential acute retroviral syndrome or potential recent HIV antibody seroconversion, together representing individuals with possible primary HIV infection.[8] We genotyped 675 HIV-positive individuals in the Options cohort for this study, all of whom had known dates of seroconversion and for whom viral load measurements were taken prior to the start of anti-retroviral therapy. Of the 675 individuals in the Options cohort, 454 were Caucasian and 32 were African American. Both the SCOPE and Options studies were approved by the Institutional Review Board of UCSF.

Participants in UHS were part of a cross-sectional study of injection drug users in the San Francisco area recruited in 1986–2005. To qualify for the study, participants 18 years of age and older had to have injected an illicit drug in the past 30 days and had to be able to provide informed consent. A subset of HIV+ and HIV− cases with an available blood sample were then selected for genotyping. For this study, we used the dataset of 366 HIV+ cases of European descent and the 621 HIV+ cases of African American descent that was available through the database of Genotypes and Phenotypes dbGaP. [9]

2.2 SNP selection

We performed a literature search to identify known psoriasis susceptibility SNPs and SNPs previously reported to be associated with control of several viruses including HIV. We chose 43 psoriasis risk SNPs, 39 viral control SNPs, and 2 associated with both psoriasis and viral control. Details are shown in Table 1 and Supplementary Table 1.

2.3 Genotyping

Frozen PBMCs were obtained from 415 SCOPE patients and 696 Options patients. DNA was extracted using Qiagen DNeasy tissue kit. The quality and quantity of DNA was assessed using a Nanodrop-8000. The DNA samples were mixed with a TaqMan OpenArray (ThermoFisher Scientific, Waltham, MA) master mix and loaded onto the genotyping plate containing 256 TaqMan assays of which 179 were used for this study (Supplemental Table 3). The genotypes were called using TaqMan Genotyper software from Life Technologies (Applied Biosciences, Foster City, CA). Genotype data on the HumanOmni1-Quad_v1-0_B platform and the dataset imputed up to the 1000 Genomes for the UHS was acquired through dbGaP. For the UHS cohort, we acquired directly genotyped data and imputed data through dbGaP accession number phs000454.v1.p1. The UHS cohort was genotyped on the HumanOmni1-Quad_v1-0_B platform and then imputed in IMPUTE2 using 1000 Genomes phase 1 version 3 as the reference panel by the original authors in Hancock et al. [10].

2.4 Quality control

In both the SCOPE and Options cohorts, SNPs were excluded if missing more than 20% genotyping data and if the minor allele frequency (MAF) was less than 1%. Individuals were removed if missing more than 20% genotyping data. Principal components analysis (PCA) was performed in EIGENSTRAT using 95 ancestry informative markers (AIMs) in both the European and African American cohort in SCOPE and the European cohort in the Options project.[11, 12] These 95 AIMs are listed in Supplementary Table 4. None of the individuals were excluded as ancestry outliers upon visual inspection of the clusters from the PCA.

For the UHS cohort acquired through dbGap, the directly genotyped data, imputed data and principal components already had quality control metrics applied as previously described. [10]

2.5 Statistical Analysis

In the SCOPE cohort, we performed logistic regression analysis adjusting for sex and PCs in HIV-infected patients classified as controllers versus non-controllers stratified by ethnicity. HIV-controllers were coded as the cases and the non-controllers were coded as the controls for the logistic regression model. Conditional analyses were then performed on the top hits.

In the Options cohort, we performed linear regression analyses adjusting for sex and PCs on log-transformed median viral load in three different time periods after seroconversion (all before treatment with antiretroviral therapy). The three pre-treatment windows were: viral load between 0–3 months from time of seroconversion representing very early immune response, viral load between 0–6 months representing early immune response, and viral load measured after 6 months representing late immune response. We then performed conditional analysis on the top SNPs in the each of the pre-treatment windows.

To test for replication, we tested 18 SNPs that scored $p<0.1$ in any of the pre-treatment windows in the Options cohort and used a Bonferroni threshold of less than 0.003. We performed PC-adjusted linear regression analyses on log-transformed median viral load. Additional covariates that we adjusted for include age, sex and survey year. Conditional analyses were then performed on the top results. All genetic analyses were performed separately for Caucasian and African-American groups.

3. Results

We evaluated 43 psoriasis risk SNPs, 39 viral control SNPs and 2 SNPs associated with both psoriasis and viral control in the SCOPE and Options cohort and then tested the top SNPs in the UHS dataset for replication.

In the Caucasian population of SCOPE, the SNPs passing the Bonferroni correction (p-value less than 0.000658) were rs9264942, which is 35 kb upstream from *HLA-C* (OR=2.61, p=0.00062), and rs3021366 which tags the *HLA-B*5701* allele (OR=5.99, p=0.000497) as shown in Table 2. For both of those SNPs, individuals with one copy of the minor allele are more likely to be virologic controllers. When we conditioned on rs9264942, rs3021366 remained statistically significant (OR=3.64, p=0.019) but did not pass a multiple testing threshold (Table 5).

In the African American population of SCOPE, the top SNPs were rs27524 (OR=2.33, p=0.016) in the *ERAP1* region and rs13196377 (OR=11.38, p=0.04) in the *TRAF3IP2* region. Both of these SNPs were statistically significant but did not pass multiple testing thresholds (data not shown).

Since controller status was not available for the Options dataset, we tested genetic risk factors for association with early viremia using log-transformed median viral load measurements. For the Caucasian Options cohort of individuals with primary HIV infection,

the top genetic associations are shown in Table 3. The most significant result in the Options cohort across all three pre-treatment windows is SNP rs9264942 (<3 month: β=−0.39, $p=2.8\times10^{-6}$, <6 month: β=−0.32, $p=3.35\times10^{-6}$, ≥6 month: β=−0.36, $p=1.53\times10^{-5}$) which was also one of the top SNPs in the SCOPE cohort. The rs9264942 minor allele is associated with a decreased viral load in the three pre-treatment windows. Additional SNPs that were highly significant in the early pre-treatment windows of less than three months and less than six months were rs3021366 which tags the *HLA-B*5701* allele (<3 month: β=−0.94, $p=7.19\times10^{-5}$, <6 month: β=−0.91, $p=1.5\times10^{-5}$) as well as rs9368699 in the *C6orf48* region (<3 month: β=−0.99, $p=7.1\times10^{-5}$, <6 month: β=−0.78, $p=2.3\times10^{-4}$). The *HLA-B*5701* SNP was also strongly associated in the SCOPE cohort and the *C6orf48* SNP rs9368699 showed suggestive association in the SCOPE cohort (OR=2.43, p=0.08). When these genetic associations were conditioned on the top SNP rs9264942, both rs3021366 and rs9368699 remained statistically significant suggesting independent effects, although only rs3021366 remained significant after adjustment for multiple testing using a Bonferroni threshold (Table 5).

To replicate findings regarding viral load in the Options cohort and to provide complementary data to our SCOPE results, we examined the UHS dataset which also studied viral load. The two SNPs that replicated at or below the multiple testing threshold in the UHS study were rs3021366 (*HLA-B*5701*; β =−0.45, p=0.003) and rs9368699 (*C6orf48*; β =−0.54, p=0.0003) as shown in Table 4. SNP rs9264942 (*-35HLAC*) bordered nominal significance in the UHS dataset. In the conditional analysis, *C6orf48* SNP rs9368699 remained significant after conditioning on rs9264942 which was the top SNP from discovery. The direction of the β coefficient indicating decreased viral loads with the minor allele is consistent with the results from the Caucasian Options cohort.

4. Discussion

In this study, we investigated a set of psoriasis risk SNPs and viral control SNPs in HIV cohorts to examine whether these SNPs influence HIV-1 control or viral load. We observed two strong hits in the MHC class I region. The rs3021366 SNP tagging the *HLA-B*5701* allele had a strong effect in the SCOPE, Options, and UHS cohorts which affirms previous findings that the *HLA-B*5701* allele is protective in HIV-1 disease.[13],[14],[15] The *HLA-B*5701* allele has also been strongly associated with increased risk in psoriasis. Another top hit in SCOPE, Options, and UHS was the rs9264942 variant 35 kb upstream from *HLA-C* locus. This variant has been shown to correlate with increased cell surface expression of *HLA-C* and is also associated with both psoriasis and HIV-1 control.[6] These SNPs represent the two SNPs we identified as associated with both psoriasis and HIV viral control when selecting genetic loci for this study. Interestingly, we also identified a strong hit with variant rs9368699 upstream of *C6orf48* in the MHC Class III region. This variant showed a strong effect on lower viral load in the Options and UHS cohorts, but was only suggestively associated with HIV-1 controller status in SCOPE. This SNP has been shown to be associated with the HIV long-term nonprogressor (LTNP) phenotype; individuals who can immunologically maintain a stable amount of $CD4^+$ T cells for approximately 7–10 years.[16–18] LTNPs and controllers both experience a longer progression to AIDS but while LTNPs can maintain higher $CD4^+$ T cell counts, they may still have detectable viral loads.

Similarly, controllers can immunologically control viral loads but may still experience a loss of $CD4^+$ T cells.[19] Our study demonstrated a novel association between rs9368699 and lower viral load in early viremia in Options and replicated the association in the UHS cohort. The suggestive association with a higher odds of being a controller in SCOPE complemented the association between low viral loads and the minor allele of rs9368699 in both Options and UHS.

Outside of the MHC region, we observed several nominally significant associations ($p<0.05$) such as *SOX5*, *TLR9*, *SDC4*, and *PROX1* in SCOPE (Table 2) and *PROX1*, *IL12B*, *TLR4*, *MBL-2*, and *TYK2* in Options (Table 3). However, these were not significant after strict Bonferroni correction for multiple testing, possibly due to limited power of our sample size. One gene of note is the psoriasis-associated gene *IFIH1* (rs17716942) which showed a suggestive association in the Options cohort (Table 3) and which showed nominal replication in the UHS dataset (Table 4). This SNP demonstrated a consistent direction of effect in both cohorts with the minor allele associating with higher viral loads. The *IFIH1* gene is known to be part of the innate immune and antiviral response and encodes the MDA5 protein which detects viral infection.[20, 21] This SNP has not previously been reported to be associated with HIV viral control. It is possible that the suggested association between the *IFIH1* SNP and an increased viral load may be a modest effect thus requiring a larger sample size to detect a statistically significant effect. Nevertheless, the biology of *IFIH1* is promising and warrants further research.

In summary, we examined a set of known psoriasis and virologic risk SNPs to determine if these SNPs were associated with the ability to spontaneously control viral load in HIV patients. We found strong associations with variants in MHC Class I and Class III regions, as well as several suggestive signals outside the MHC. Our study further highlights the similar genetic architecture in psoriasis and HIV-1 control in the MHC region and suggests the *IFIH1* locus as a potential region of interest for follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

List of SNPs associated with psoriasis risk and viral control

SNP Category	GENE	SNPs
Psoriasis risk and viral control	B*5701	rs3021366[13],[22]
	-35HLAC	rs9264942[13], [23]
Psoriasis risk	CARD14	rs11652075
	ERAP1	rs27524; rs30187
	FBXL19	rs12924903
	HLA-C	rs10484554[24]
	IFIH1	rs2111485[25]; rs1990760[26],[27],[28]; rs17716942[29]
	IL12B	rs2082412[30]; rs3213094[29]; rs2546890[31]; rs953861[31]; rs12188300[32]
	IL13	rs1800925; rs20541; rs848
	IL23A/STAT2	rs2066808
	IL23R	rs1004819; rs7530511; rs2201841; rs11209026
	IL28RA	rs4649203
	LCE3D Del	rs4112788
	NFKBIA	rs8016947[29]
	NOS2	rs4795067
	PTPN22	rs3765598
	REL	rs702873
	RPS26	rs12580100
	SDC4	rs1008953[33]; rs2743403[33]
	SATB1 - KCNH8	rs6809854
	TNFAIP3	rs610604
	TNIP1	rs17728338
	TRAF3IP2	rs240993; rs458017; rs13196377; rs13190932; rs33980500; rs13210247
	TYK2	rs12720356[29]; rs280497[29]; rs753859[29]
	ZNF313	rs495337
Viral control	AGR3	rs152363[34]
	APH1B	rs1047552
	APOBEC	rs139316
	C6orf48	rs9368699[16, 17]
	CXCR6	rs2234358
	CYP7B1	rs6996198
	DC-SiGN	rs4804803[35],[36]; rs2287886[37]
	DEFB-1	rs1799946; rs1800972
	DYRK1A	rs12483205
	IFNg	rs2069709
	IL-10	rs1800872
	IL1B	rs1143634
	IL28B	rs4803222; rs8099917
	IL-4	rs2243250

SNP Category	GENE	SNPs
	IL7RA	rs987106
	MBL-2	rs5030737[38],[39]
	NALP3	rs10754558[40]
	PARD3B	rs11884476
	PRMT6	rs4118325[41]
	PROX1	rs17762192[42]
	PSORS1C3	rs3131018[43]
	SOX5	rs1522232[41]
	TLR3	rs3775291
	TLR4	rs4986790[44]; rs4986791[44]
	TLR8	rs3764880
	TLR9	rs352139[44],[45],[46]; rs352140[47]; rs5743836[44]
	TRIM5	rs10838525; rs3824949; rs3740996; rs11038628; rs11601507; rs28381981
	ZNRD1	rs7746866[13]

Table 2

SNP association results in the SCOPE cohort

CHR	SNP	GENE	Frequency in cases (n=53)	Frequency in controls (n=97)	OR	95% CI	P-value
6	rs3021366	B*5701	0.2	0.04	5.99	(2.19 – 16.4)	**0.000497**†
6	rs9264942	-35HLAC	0.6	0.4	2.61	(1.51 – 4.51)	**0.00062**†
12	rs1522232	SOX5	0.58	0.42	2.02	(1.16 – 3.51)	0.01
3	rs5743836	TLR9	0.18	0.08	2.48	(1.11 – 5.54)	0.027
6	rs3131018	PSORS1C3	0.23	0.36	0.51	(0.27 – 0.93)	0.029
20	rs2743403	SDC4	0.32	0.22	1.91	(1.05 – 3.49)	0.035
1	rs17762192	PROX1	0.51	0.39	1.78	(1.03 – 3.08)	0.04
6	rs610604	TNFAIP3	0.29	0.39	0.55	(0.31 – 0.99)	0.047
11	rs28381981	TRIM5	0.08	0.04	2.99	(0.97 – 9.2)	0.057
1	rs10754558	NALP3	0.40	0.29	1.65	(0.97 – 2.82)	0.065
6	rs9368699	C6orf48	0.12	0.04	2.43	(0.90 – 6.58)	0.08

†Indicates that the p-value adjusted for the number of tests performed is p<0.05. The Bonferroni threshold for 76 tests is p=0.0007.

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Table 3

SNP associations in the Options cohort in where p<0.1 in at least one of the three pre-treatment windows

			< 3 months infection		<6 months infection		>6 months infection	
CHR	**SNP**	**GENE**	**BETA**	**P**	**BETA**	**P**	**BETA**	**P**
1	rs4118325	PRMT6	0.19	0.05	0.14	0.10	0.02	0.86
1	rs17762192	PROX1	0.23	0.0048	0.11	0.11	0.09	0.30
2	rs17716942	IFIH1	0.12	0.32	0.085	0.37	0.20	0.08
5	rs2546890	IL12B	−0.04	0.59	0.004	0.95	0.20	0.02
6	rs7746866	ZNRD1	−0.23	0.06	−0.25	0.01	−0.25	0.02
6	rs3131018	PSORS1C3	0.27	0.0009	0.21	0.002	0.16	0.07
6	rs9264942	-35HLAC	−0.39	**2.68E-06**†	−0.32	**3.35E-06**†	−0.36	**1.53E-05**†
6	rs10484554	HLA-C	−0.30	0.009	−0.23	0.02	−0.28	0.02
6	rs3021366	B*5701	−0.94	**7.19E-05**†	−0.91	**1.50E-05**†	−0.49	0.04
6	rs9368699	C6orf48	−0.99	**7.10E-05**†	−0.78	**0.00023**†	−0.26	0.25
9	rs4986790	TLR4	−0.18	0.06	−0.16	0.04	−0.11	0.29
9	rs4986791	TLR4	−0.30	0.07	−0.35	0.01	−0.35	0.04
10	rs5030737	MBL-2	−0.36	0.01	−0.34	0.005	−0.21	0.14
14	rs8016947	NFKBIA	−0.01	0.89	0.03	0.66	0.15	0.09
19	rs2287886	DC-SIGN	0.14	0.08	0.08	0.27	0.06	0.55
19	rs4804803	DC-SiGN	−0.07	0.47	0.02	0.82	0.20	0.07
19	rs280497	TYK2	−0.19	0.01	−0.17	0.007	−0.09	0.25
20	rs1008953	SDC4	−0.12	0.21	−0.08	0.33	−0.18	0.07

†Indicates that the p-value adjusted for the number of tests performed is p<0.05. The Bonferroni threshold for 77 tests is p=0.0006.

Table 4

SNP associations in UHS replication dataset

CHR	SNP	BP	SNP_Status‡	GENE	BETA	P
6	rs9368699	31802541	g	C6orf48	−0.54	**0.0003**†
6	rs3021366	31445771	g	B*5701	−0.45	**0.003**†
2	rs17716942	163260691	i	IFIH1	0.23	0.046
6	rs9264942	31274380	i	-35HLAC	−0.15	0.059

†Indicates that the p-value adjusted for the number of tests perfomed is p<0.05. The Bonferroni threshold for 18 tests is p=0.003

Table 5

Conditional analysis on top SNP rs9264942 in the MHC region

CHR	SNP	Gene	Cohort	Treatment window (Options)	Effect Size[¥]		P-value
6	rs3021366	B*5701	SCOPE	-	OR	3.64	0.019
			Options	<3 mos	β	−0.77	0.001
				<6 mos	β	−0.78	**0.00015**[†]
			UHS	-	β	−0.52	0.003
6	rs9368699	C6orf48	Options	<3 mos	β	−0.81	0.0012
				<6 mos	β	−0.66	0.0016
			UHS	-	β	−0.57	**0.0007**[≠]
6	rs3131018	PSOR1C3	Options	<3 mos	β	0.20	0.017

[†]Indicates that the p-value adjusted for the number of tests perfomed is p<0.05. The Bonferroni threshold for 77 tests in Options is p=0.0006

[≠]Bonferroni correction for 18 tests is 0.003 in replication dataset

[¥]OR=odds ratio; β=beta coefficient