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Risk variants for psoriasis vulgaris in a large case–control collection and association with clinical subphenotypes

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Recent genome-wide association studies (GWASs) have identified >20 new loci associated with the susceptibility to psoriasis vulgaris (PsV) risk. We investigated the association of PsV and its main clinical

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subphenotypes with 32 loci having previous genome-wide evidence of association with PsV ($P < 5e-8$) or strong GWAS evidence ($P < 5e-5$ in discovery and $P < 0.05$ in replication sample) in a large cohort of PsV patients ($n = 2005$) and controls ($n = 1497$). We provide the first independent replication for *COG6* ($P = 0.00079$) and *SERPINB8* ($P = 0.048$) loci with PsV. In those patients having developed psoriatic arthritis ($n = 955$), we found, for the first time, a strong association with *IFIH1* ($P = 0.013$). Analyses of clinically relevant PsV subtypes yielded a significant association of severity of cutaneous disease with variation at *LCE3D* locus ($P = 0.0005$) in PsV and nail involvement with *IL1RN* in purely cutaneous psoriasis (PsC, $P = 0.007$). In an exploratory analysis of epistasis, we replicated the previously described *HLA-C–ERAP1* interaction with PsC. Our findings show that common genetic variants associated with a complex phenotype like PsV influence different subphenotypes of high clinical relevance.

INTRODUCTION

Psoriasis vulgaris (PsV) is a chronic inflammatory disease of the skin that affects 2–3% of the worldwide population (1). In PsV, immune cells infiltrate the dermis and epidermis and promote inflammation, which can be visible as red, raised and scaly plaque like lesions. It is a genetically complex disease with an estimated sibling recurrence risk (λ_s) between 4 and 11 (2). Within PsV, there is a wide range of phenotypic variation, which can have an important implication in daily clinical practice. Thus, in order to advance in the understanding of PsV's complex etiology, it is of paramount importance to identify the genetic basis of its phenotypic variation.

The study of genetic associations with PsV clinical subphenotypes has been limited to our ability to identify genomic loci consistently associated with PsV susceptibility itself. Before the advent of genome-wide association studies (GWASs), only three loci, *HLA-C* (3), *IL12B* and *IL23R* (4) had been robustly associated with PsV etiology. Together, they did not explain the full heritability of the disease and additional risk loci remained to be identified. Recently, GWAS have markedly expanded the group of genomic loci associated with the susceptibility to develop PsV (5–9). To date, more than 20 new loci have been convincingly associated with PsV. However, there is still a lack of a comprehensive analysis of each individual risk allele with PsV clinical subphenotypes.

One of the most clinically relevant PsV subphenotypes is the development in 10–30% patients of a chronic arthritis called psoriatic arthritis (PsA). PsA has distinct clinical features ranging from arthritis of the distal interphalangeal joints to spondylitis and sacroiliitis (10,11). Patients with PsA, generally, are treated with a different therapeutical approach than those patients without arthritis (herein purely cutaneous psoriasis or PsC) (12). From a genetic perspective, there is also evidence that PsA has a higher recurrence risk than PsV (λ_s ~27–47) (13). Thus, the presence of PsA could be considered the most influential clinical PsV subphenotype both for its treatment implications and for its specific genetic risk background.

Variation at the *HLA-C* locus is one of the clearest examples that the variation of a risk factor also influences relevant clinical subphenotypes. The association of *HLA-C* with PsV risk has been long known. This has allowed to investigate its association with several PsV clinical subphenotypes. *HLA-C* has been shown to be more strongly associated with PsC susceptibility than PsA (5). *HLA-C* risk haplotype, *HLACw*0602*, has also been associated with an earlier age at onset of PsV, suggesting that it is not a risk factor for late onset (>40 years) PsV (14). Very recently, *HLA-C* has been found to statistically interact with risk loci *ERAP1* in the susceptibility of PsV, one of the yet few convincing examples of epistasis in a complex disease (6). Like variation at *HLA-C*, we hypothesize that variation in recently identified risk loci can be highly relevant factors in the genetic basis of PsV clinical subphenotypes.

In the present study, we have used a large case–control cohort ($n = 3502$) to test the association of 32 risk alleles with PsV and its main clinical subphenotypes. Using a large PsA cohort ($n = 955$), we have been able to directly test the genetic basis of this disease compared with the PsV group without arthritis (PsC, $n = 1050$) and identify common and differential risk factors for other relevant disease subphenotypes. The results in this study improve our knowledge of genetic variation within the complexity of PsV.

RESULTS

Statistical power and clinical cohorts

The 3502 individual case–control cohort of this study provides good power to identify genetic variants of high-to-moderate effect. Using previously reported risk estimates, we had >80% power to replicate 19 loci.

We found several of the clinical features to be differentially distributed between the two main PsV subphenotypes (Table 1). The PsA cohort had a higher female percentage ($P = 0.02$), later age at onset of cutaneous affection ($P = 0.0004$), lower percentage of moderate-to-severe skin disease ($P < 0.0001$) and lower percentage of the guttate type of psoriasis ($P = 0.0002$). According to a later age at onset of PsA disease compared with PsC ($P < 0.0001$), disease duration was significantly lower ($P < 0.0001$). The remaining clinical subphenotypes (nail affection, erythrodermic and pustular PsV and family PsV) showed no statistically significant difference between the two cohorts.

Control for population stratification

Our analysis of population substructure, based on 90 highly informative ancestry informative markers (AIMs) revealed the existence of a unique population, without any outlier

Table 1. Clinical characteristics of the PsA and PsC cohorts analyzed in this study

Characteristic	PsC	PsA
Number of cases	1050	955
Geographic ancestry	European	European
Country of origin	Spain	Spain
Female sex (%)	40.6	45.6
Age at onset (mean ± SD years)	29.6 ± 17.4	41.5 ± 14.1
Age onset cutaneous affection (mean ± SD years)	29.6 ± 17.4	32.3 ± 16.4
Disease duration (mean ± SD years)	20.3 ± 14.3	11.4 ± 9.7
Moderate–severe cutaneous involvement (%)	64.1	31.9
Nail involvement (%)	45.7	48.3
Guttate Ps (%)	8.2	4.7
Erythrodermic Ps (%)	2.9	2.4
Pustular Ps (%)	1.7	1.1
Family Ps (%)	51.1	47
HLA-B27-positive (%)	NA	14.1

NA, not available.

individual (probability that the sample belongs to the same population >99%).

Replication study of association with PsV risk

Comparing all PsV cases ($n = 2005$) against all controls ($n = 1497$), we positively replicated the association in 19 of the 32 tested loci (Table 2). From these, we replicated, for the first time, the association of PsV with *COG6* locus ($P = 0.00079$). Also, we provide the first independent replication of *SERPINB8* ($P = 0.048$) association in a Caucasian European population. Within the set of positively replicated loci, *NOS2*, *IFIH1*, *REL*, *SDC4*, *FBXL19*, *DPP6* and *RYR2* had not been tested in an independent replication sample rather than the original GWAS. Two other genes, *RPS26* and *PTTG1*, show a trend of association ($P = 0.052$ and $P = 0.098$, respectively), which is reinforced by the fact that they have the same direction of the originally identified effect.

Association with PsA and PsC subphenotypes

Comparing 1050 PsC cases against all controls ($n = 1497$), we found significant association for five loci (Table 2). Analyzing the allele frequencies in the PsA cohort ($n = 955$) compared with all controls ($n = 1497$), we found a significant association for six loci. A total of four loci were found to be significative in both PsA and PsC analyses; *IFIH1* and *NOS2* were significative in the PsA subgroup but not in the PsC subgroup and *IL13* was significative only in the PsC subgroup.

Within the four commonly associated genes in the PsC and PsA cohorts, *HLA-C* showed a markedly stronger level of association with PsC compared with PsA ($P_{nominal} = 7.22 \times 10^{-48}$ and $P_{nominal} = 8.31 \times 10^{-20}$, respectively). Conversely, *TRAFIP3* ($P_{nominal} = 3.26 \times 10^{-9}$ and $P_{nominal} = 1.37 \times 10^{-5}$, respectively) showed a stronger association with the PsA cohort than with the PsC cohort. Directly testing the differences in allelic distribution between both PsV subgroups, only the risk allele distribution at the *HLA-C* locus was significantly different between PsC and PsA ($P_{nominal} = 1.69 \times 10^{-6}$).

Association with age at onset of cutaneous and joint disease

We found a significant association of *HLA-C* with an earlier age at onset of cutaneous disease in the PsV cohort ($P_{nominal} = 4.88 \times 10^{-14}$). In our PsV cohort, we found that women tend to develop the disease ~3.5 years earlier than men (mean female = 28.68 ± 17.6 years, mean male = 32.2 ± 16.5), and this difference is significant ($P_{nominal} = 3.9 \times 10^{-5}$). Using gender as a covariate did not modify the significance of this locus ($P_{nominal} = 4.88 \times 10^{-14}$ to $P_{nominal} = 2.75 \times 10^{-13}$).

Analyzing the age at onset of cutaneous disease within PsC and PsA subgroups, we found a similar level of association with variation at *HLA-C*. Both in PsC and PsA, we found that individuals carrying one copy of the *HLA-C* risk allele had an average age at onset almost 7 years earlier than individuals carrying zero copies (33.5 ± 17.9–26.2 ± 17.9 years in PsC, $P_{nominal} = 2.3 \times 10^{-8}$, 35.2 ± 16–28.9 ± 14.9 years in PsA, $P_{nominal} = 4.01 \times 10^{-6}$). Analyzing the association of the 32 loci with the age at onset of arthritis in the PsA subphenotype, we found no statistically significant association.

Association with severity of cutaneous disease

Using all PsV cases, we identified a strong association of the *LCE3D* locus ($P_{corr} = 0.0005$; Table 3) with severity of cutaneous disease. For this locus, individuals carrying two copies of the risk allele were ~25% more frequent in the moderate-to-severe skin disease group than in the mild disease group (45.8 versus 37%). In this association, the odds ratio (OR) is >1, supporting the role of the PsV risk allele in the development of more severe forms of skin disease. We also found a significant association of *HLA-C* locus with severity ($P_{corr} = 0.03$).

Association with skin disease subtypes

Analyzing all 32 risk alleles with skin disease subtypes in the PsV group, we did not find any significant association after multiple test correction (Supplementary Material, Tables S1 and S2). The strongest nominal association was found with *RNF114* and guttate subtype ($P_{nominal} = 0.0097$).

Association with nail disease

In the PsV analysis of this clinical variable, we found a trend for association between variation at *IL1RN* and nail involvement ($P_{corr} = 0.073$; Supplementary Material, Table S3). This association was found to be significant in the PsC group ($P_{corr} = 0.00691$).

Association with presence of familial PsV

HLA-C was the only locus showing a trend for association with familial aggregation in the PsV cohort ($P_{corr} = 0.06$). This significance was notably increased by comparing only extreme cases (0 versus ≥3 affected relatives, $P_{corr} = 0.0016$) (Supplementary Material, Table S4). In the subgroup analysis, *HLA-C* was only significantly associated comparing extreme cases in the PsA subgroup ($P_{corr} = 0.047$).

Table 2. Association study of 32 loci previously reported to be associated with PsV in our 3502 individual case–control cohort and with PsC ($n = 1050$) and PsA ($n = 955$) disease groups

Locus	Chr	SNP	Basepairs	Risk Al.	Ref. OR[a]	Frq. Ctrl	OR (95% CI)	*P*-value	OR PsC (95% CI)	*P* PsC	P_c PsC	OR PsA (95% CI)	*P* PsA	P_c PsA
IL28RA	1	rs4649203	24392507	A	1.17	0.76	1.07 (0.96–1.2)	0.12	1.12 (0.98–1.28)	0.057	0.97	1.03 (0.9–1.17)	0.36	1
IL23R	1	rs11209026	67478546	G	1.49	0.93	1.43 (1.17–1.74)	0.00032	1.41 (1.11–1.8)	0.003	0.16	1.44 (1.12–1.85)	0.0021	0.11
LCE3D	1	rs4112788	150817900	G	1.29	0.62	1.1 (0.99–1.21)	0.035	1.16 (1.03–1.31)	0.0078	0.38	1.04 (0.92–1.17)	0.29	1
RYR2	1	rs2485558	235345148	G	1.16	0.2	1.11 (0.99–1.25)	0.044	1.1 (0.95–1.27)	0.1	0.99	1.12 (0.97–1.3)	0.059	0.97
REL	2	rs702873	60935046	C	1.17	0.52	1.14 (1.03–1.25)	0.0048	1.18 (1.05–1.33)	0.0022	0.12	1.09 (0.97–1.22)	0.076	0.99
IL1RN	2	rs397211	113608612	T	1.09	0.67	1.06 (0.95–1.17)	0.16	1.1 (0.97–1.25)	0.064	0.98	1.01 (0.89–1.14)	0.44	1
IFIH1	2	rs17716942	162968937	T	1.33	0.84	1.23 (1.07–1.41)	0.0017	1.13 (0.96–1.32)	0.08	0.99	1.36 (1.14–1.61)	0.00023	0.013
LOC131185	3	rs6809854	18759427	G	1.19	0.2	1.03 (0.91–1.16)	0.34	0.98 (0.85–1.14)	0.61	1	1.07 (0.93–1.24)	0.18	1
ERAP1	5	rs27524	96127700	A	1.2	0.43	1.06 (0.96–1.17)	0.11	1.05 (0.94–1.18)	0.2	1	1.07 (0.96–1.21)	0.12	0.99
IL13	5	rs20541	132023863	G	1.12	0.84	1.26 (1.1–1.44)	0.00051	1.33 (1.13–1.57)	0.00034	0.02	1.19 (1.01–1.4)	0.021	0.72
TNIP1	5	rs17728338	150458511	A	1.27	0.07	1.46 (1.22–1.74)	1.89E-5	1.43 (1.16–1.76)	0.00044	0.02	1.48 (1.2–1.82)	0.00016	0.0074
IL12B	5	rs3213094	158683347	C	1.39	0.78	1.3 (1.15–1.46)	1.09E-5	1.32 (1.14–1.53)	7.58E-05	0.0049	1.27 (1.1–1.47)	6.00E-04	0.035
PTTG1	5	rs2431697	159812556	C	1.2	0.45	1.07 (0.97–1.17)	0.098	1.09 (0.97–1.22)	0.078	0.99	1.04 (0.93–1.17)	0.24	1
HLA-C	6	rs10484554	31382534	T	4.66	0.15	2.35 (2.08–2.66)	6.26E-45	2.77 (2.41–3.19)	7.22E-48	<1E-5	1.96 (1.7–2.27)	8.41E-20	<1E-5
TRAF3IP2	6	rs458017	111802784	C	1.46	0.05	1.8 (1.47–2.19)	1.59E-9	1.65 (1.31–2.07)	1.37E-5	0.00062	1.95 (1.56–2.45)	3.26E-9	<1E-5
TNFAIP3	6	rs610604	138241110	G	1.22	0.32	1.2 (1.09–1.33)	2.00E-4	1.2 (1.07–1.36)	0.0014	0.076	1.2 (1.06–1.35)	0.0019	0.10
DPP6	7	rs916514	154099909	A	1.22	0.88	1.18 (1.01–1.38)	0.018	1.08 (0.9–1.29)	0.23	1	1.32 (1.09–1.6)	0.0027	0.15
CSMD1	8	rs10088247	3671607	C	1.17	0.27	0.95 (0.86–1.06)	0.81	1.02 (0.9–1.16)	0.4	1	0.89 (0.78–1.01)	0.96	0.93
TSC1	9	rs1076160	134765855	T	1.12	0.44	0.99 (0.9–1.09)	0.56	0.99 (0.88–1.11)	0.57	1	1 (0.89–1.12)	0.54	1
MMP27	11	rs1939015	102081585	A	1.17	0.83	0.97 (0.85–1.1)	0.72	1.02 (0.88–1.19)	0.39	1	0.91 (0.78–1.06)	0.9	0.99
RPS26	12	rs12580100	54725476	A	1.26	0.89	1.14 (0.98–1.34)	0.052	1.08 (0.9–1.3)	0.22	1	1.22 (1–1.48)	0.027	0.80
IL23A	12	rs2066808	55024240	A	1.49	0.96	1.01 (0.8–1.27)	0.48	0.94 (0.72–1.23)	0.69	1	1.09 (0.82–1.46)	0.29	1
GJB2	13	rs3751385	19660956	A	1.15	0.23	0.92 (0.82–1.03)	0.92	0.91 (0.8–1.05)	0.91	0.99	0.93 (0.81–1.07)	0.85	1
COG6	13	rs7993214	39248912	C	1.41	0.68	1.18 (1.07–1.31)	0.00079	1.2 (1.06–1.35)	0.0026	0.15	1.17 (1.03–1.33)	0.0072	0.35
NFKBIA	14	rs8016947	34902417	G	1.19	0.56	1.13 (1.03–1.25)	0.0056	1.13 (1.01–1.27)	0.018	0.66	1.14 (1.01–1.28)	0.017	0.64
FBXL19	16	rs12924903	30836471	A	1.19	0.32	1.13 (1.02–1.25)	0.0092	1.14 (1.01–1.29)	0.017	0.64	1.12 (0.99–1.27)	0.036	0.89
NOS2	17	rs4795067	23130802	G	1.19	0.32	1.17 (1.06–1.29)	0.0013	1.11 (0.99–1.26)	0.04	0.92	1.23 (1.09–1.38)	0.00052	0.029
SERPINB8	18	rs514315	59807765	T	1.15	0.59	1.09 (0.99–1.2)	0.048	1.08 (0.97–1.22)	0.091	0.99	1.09 (0.97–1.23)	0.076	0.99
TYK2	19	rs12720356	10330975	A	1.37	0.93	1.04 (0.86–1.26)	0.36	1.25 (0.99–1.59)	0.034	0.87	0.88 (0.71–1.1)	0.89	0.99
SMARCA4	19	rs12983316	10975352	G	1.15	0.11	1.03 (0.88–1.2)	0.38	1 (0.83–1.2)	0.51	1	1.06 (0.88–1.27)	0.3	1
SDC4	20	rs1008953	43414140	C	1.19	0.75	1.16 (1.04–1.3)	0.0049	1.21 (1.06–1.39)	0.0025	0.14	1.11 (0.97–1.27)	0.072	0.99
RNF114	20	rs2235617	47988384	C	1.2	0.64	1.14 (1.03–1.26)	0.0059	1.18 (1.04–1.33)	0.0042	0.22	1.1 (0.98–1.24)	0.063	0.98

OR estimates are expressed relative to the published risk allele. P_c, significance values after correcting for multiple testing.

[a]Ref. OR: effect size estimate calculated from the reference GWAS data combining discovery and replication estimates using fixed-effects models.

Table 3. Loci showing nominal *P*-values <0.05 with cutaneous disease severity in PsV, PsC and PsA cohorts

Locus	Chr	SNP	OR PsV	*P* PsV	P_c PsV	OR PsC	*P* PsC	P_c PsC	OR PsA	*P* PsA	P_c PsA
IL23R	1	rs11209026	1.57 (1.14–2.15)	0.0068	0.155	1.63 (1.07–2.48)	0.028	0.5	1.6 (0.92–2.79)	0.12	0.95
LCE3D	1	rs4112788	1.38 (1.19–1.59)	1.80E-05	0.0005	1.27 (1.04–1.55)	0.023	0.47	1.52 (1.19–1.93)	0.00085	0.02
IL13	5	rs20541	0.97 (0.79–1.19)	0.8	1	0.72 (0.53–0.97)	0.038	0.64	1.23 (0.88–1.71)	0.27	0.99
HLA-C	6	rs10484554	1.29 (1.11–1.51)	0.0012	0.033	1.06 (0.86–1.3)	0.65	1	1.43 (1.12–1.85)	0.0059	0.13
GJB2	13	rs3751385	0.92 (0.77–1.08)	0.32	1	0.76 (0.6–0.95)	0.021	0.43	1.2 (0.92–1.57)	0.2	0.99
RNF114	20	rs2235617	1.26 (1.08–1.46)	0.0027	0.074	1.14 (0.93–1.4)	0.22	0.99	1.43 (1.12–1.83)	0.0047	0.11

Association with HLA subtypes and analysis of epistasis

We found a significant association of *HLA-C* with *HLA-B27* positivity in the PsA cohort ($P_{corr} = 0.0085$, Supplementary Material, Table S5), where *HLA-B27* positivity was associated with a lower frequency of the *HLA-C* risk allele (i.e. 1.9% of *TT* homozygous for *HLA-C* in *HLA-B27*-positive patients, compared with 7.8% of *TT* homozygous in *HLA-B27*-negative PsA patients).

Confirming previous observations, we found that the genotypic distribution for *HLA-C* locus in our cohort of PsV patients is closer to a dominant model rather than a multiplicative model [OR dominant = 2.7 (95% CI 2.33–3.12), OR multiplicative = 2.01 (95% CI 1.78–2.28)]. Based on this model, however, no statistically significant association was found in the PsV (Supplementary Material, Table S6). Compared with PsV or PsA analyses, however, we found a notably larger number of loci nominally associated with *HLA-C* positivity in the PsC group ($n = 2$ and $n = 1$ versus $n = 5$ loci with $P_{nominal} < 0.05$). Within the set of five loci nominally associated in the PsC group, there is *ERAP1*, a locus recently shown to interact epistatically with *HLA-C* in PsV. Thus, we sought to test for the presence of interaction between *HLA-C* and *ERAP1* as well as between *HLA-C* and the other four nominally associated loci in the PsC group. We confirmed the epistatic association between *ERAP1* and *HLA-C* ($P_{nominal} = 0.042$; Supplementary Material, Fig. S1A) and identified a new nominally significant interaction between *HLA-C* and *SERPINB8* ($P_{nominal} = 0.014$; Supplementary Material, Fig. S1B). Correcting for multiple testing, however, none of the two interactions is significant. In order to provide additional evidence for *HLA-C-SERPINB8* new epistatic association, we analyzed the gene expression interaction pattern of both loci comparing paired samples of normal and inflamed skin of psoriasis patients using publicly available gene expression data. We found a suggestive evidence of interaction ($P_{interaction} = 0.015$) between the gene expression of both genes and skin inflammation status.

DISCUSSION

PsV is a heterogeneous disease that has a complex genetic background. Very recently, GWAS in large population cohorts have identified a large number of loci that are confidently associated with the risk to develop this chronic disease (5–9,15). Using a large case–control cohort of >3500 individuals, we have replicated the association of several of these loci with the susceptibility to PsV and, most importantly, we have found new associations with clinically relevant subphenotypes.

Our results replicate the association of 19 alleles with the risk to develop PsV. Within these loci, we provide the first independent replication of association with PsV risk for *COG6* and *SERPINB8* loci. *COG6* was a potential novel locus identified in the first GWAS scan performed in PsV (13). The same *COG6* locus single-nucleotide polymorphism (SNP; rs7993214) has been only directly tested in the discovery sample of Nair *et al*. (924 cases and 1156 controls), also a Caucasian population of European ancestry, but no significant association was identified ($P = 0.24$). Given that in our sample the estimated effect size is lower than that originally identified (OR = 1.18 and OR = 1.4, respectively), it is possible that the true effect size in Caucasian European populations is relatively low, requiring large sample sizes for its replication. The association of *SERPINB8* locus with PsV was originally identified and replicated in large cohorts of Han Chinese individuals (9). Interestingly, replication using Caucasian populations of European ancestry (Germany and USA) did not yield significant replication (9). In our population, the risk estimate, although significant, was low (OR = 1.09, $P = 0.048$), which could explain the difficulties in Caucasian European populations to replicate this result. Two other loci replicated in this study, *DPP6* and *RYR2*, were considered suggestive candidates for PsV risk (7). Our study is the first to provide the independent replication of this association and therefore to confirm their implication in PsV susceptibility.

Using a large cohort of patients, we have identified, for the first time, the association of *IFIH1* locus with PsA. *IFHI1* encodes helicase C domain 1 protein, which mediates the induction of the interferon response to viral RNA, and polymorphisms in this gene have been associated with several autoimmune disorders like type I diabetes mellitus (16). Thus, these findings suggest that the interferon signaling pathway has a fundamental role in PsA development.

In a recent study of a UK Caucasian cohort (17), *IL13* gene has been advocated to be specifically associated with PsA but not to PsV. This result is in disagreement with the original finding by Nair *et al*. (5), where the association of *IL13* with PsC is notably high. In our cohort, *IL13* is significantly associated with *PsC* and not with *PsA*. In line with the original findings in the US cohort, our data do not support that *IL13* represents a pathway specific for PsA pathology.

In our study, we analyzed a large cohort of PsA patients of similar size to that of the PsC patients. Although useful for the objectives of this study, the combined PsV sample has a larger proportion of PsA cases than would have been obtained by

random ascertainment from dermatology departments. In our PsV cohort collected by dermatologists, only 12% of cases were PsA patients (diagnosed by a rheumatologist), a prevalence similar to that estimated in UK (18) and US (19) populations (13.8 and 11%, respectively). Not excluding this group of patients from the PsC group (total $n = 1193$), however, had a minimal effect on the significance values on the 32 tested alleles compared with the PsC group (data not shown). Also, excluding PsC patients with <10 years since diagnosis, reduced the association with *HLA-C* in 5 orders of magnitude (Supplemental Material, Table S7), reflecting that the small number of individuals who could still develop PsA in this group is unlikely to affect the strength of the results. Together, these results highlight the fact that genetic association studies with randomly collected PsV cohorts are strongly biased toward the PsC subphenotype.

Our finding that *HLA-C* is strongly associated with an earlier age at onset of PsV is consistent with previous findings (20). Here, we refine this initial observation by confirming that the genetic association with the age at onset of cutaneous disease is high in both PsC and PsA disease groups. It has also been proposed that PsV patients can be stratified into two types of PsV (type I and type II) according to the age at onset of the disease (<40 and >40 years, respectively), where type II has a lack of association with *HLA-C* (14). Our data are in agreement with the observation that there is a major allelic difference in the *HLA-C* locus between these two types of patients (χ^2 test comparing frequencies $P_{\text{nominal}} = 3.7 \times 10^{-11}$), but the type II group of patients still display a strong significance ($P_{\text{nominal}} = 4.39 \times 10^{-7}$). Other studies in Caucasian European populations (20) also support the reduction in the penetrance of this locus with age rather than a total lack of association.

In our study, we identified for the first time a strong association of variation at *LCE3D* locus with severity of cutaneous disease. *LCE3D* genes contribute to the formation of the skin barrier, and the SNP genotyped in our study (rs4112788) has been demonstrated to be a perfect proxy of the deletion status of two genes in this region. Recent histopathological studies (21) suggest that the deleted genes are expressed specifically in PsV skin lesions and not in the normal skin, perhaps serving as protective elements in this tissue. According to our results, it is likely that the incomplete skin barrier repair response associated with *LCE3D* deletion leads to more chronic and destructive proinflammatory effects. We also observed a significant association of the PsV risk allele of the *HLA-C* locus with disease severity. This finding is in accordance with a previous study in Icelandic population (20).

Of note, while being the most used measure of severity in clinical practice, other clinical measures have been proposed to define disease severity besides body surface area (BSA). For example, the psoriasis area and severity index score is generally used in clinical trials to measure treatment efficacy (22). However, the large correlation between the different measures of disease severity (23) increases the likelihood that the present highly significant association of *LCE3D* with disease severity will be replicated irrespective of the method used, provided that sufficiently large samples are used. Supporting this is the fact that we replicated the association of *HLA-C* with severity previously identified in the Icelandic population even though a different severity scale was used for this purpose. Future studies oriented at refining this original association with *LCE3D*, and disease severity and the potential use in the personalization of therapy are warranted.

A large fraction of PsV patients develop nail disease (24) but no precise genetic mechanism has yet been associated with this variation. Our results indicate that variation at *IL1RN* is a major genetic factor influencing this trait in PsC patients. IL1RN is a major regulator of interleukin 1 A proinflammatory activity, antagonizing its binding to the IL-1R1 cell receptor (25). Importantly, mutations in *IL1RN* gene have shown to cause an autoinflammatory disease in which affected children develop nail changes similar to those seen in PsV patients (26). This strong functional evidence supports the implication of the *IL1RN* pathway in the nail inflammatory pathophysiology. In the PsA subgroup, however, the association of *IL1RN* locus was not statistically significant. Of note, nail disease prevalence in our PsA cohort was lower than reported previously (27). Compared with previous studies, however, the present PsA cohort has been diagnosed under recent diagnostic criteria (28) and most of it has been directly referred from rheumatological centers, thus representing a highly homogeneous PsA cohort. Future studies using sufficiently powered and homogeneous patient cohorts will help to clarify the particular role of *IL1RN* in the genetic etiology of nail disease in PsA.

In our study, we confirmed the epistatic model of interaction between *HLA-C* and *ERAP1* identified in the UK population in the PsC cohort (6). In this cohort, we also found a suggestive interaction of *HLA-C* with the *SERPINB8* gene. Functional data support the existence of an interaction between these two loci. Confirmation of this complex genetic association in independent case–control cohorts will be necessary.

In conclusion, in this study, we have validated several PsV risk loci in an independent Caucasian population and we have evaluated, for the first time, the relevance of PsV risk loci with several clinical traits of interest. We have found new genetic associations with PsA, cutaneous disease severity and nail affection. In a highly heterogeneous disease like PsV, additional studies like the present one will be fundamental to identify those biological mechanisms of most relevance for each clinical subphenotype.

MATERIALS AND METHODS

Clinical samples

A case–control cohort of 3502 individuals was used to test all 32 alleles for association with PsV and its main clinical subphenotypes. Both patients and controls belong to the Immune-Mediated Inflammatory Disease Consortium (IMIDC) and were collected between June 2007 and December 2010. A total of 1189 PsV patients were recruited from the outpatients' clinics of the participating dermatology departments from 11 Spanish University Hospitals. All eligible patients had to have chronic plaque type of PsV (the commonest form of PsV) affecting torso and/or extremities with at least 1 year of duration at the time of recruitment. All PsV patients were

>18 years old, although the disease could have been diagnosed at an earlier age. During recruitment, the presence of arthropathy was recorded in all PsV patients, and those cases where PsA had been diagnosed by a rheumatologist ($n = 139$, 11.7%) were included in the PsA study sample. Thus, excluding patients with arthritis, 1050 PsC patients were analyzed in the present study. Importantly, 71% of PsC patients had >10 years of disease duration which should reduce the probability of inclusion of patients who will develop PsA. PsA is, however, a substantially less prevalent disease than is PsC, and therefore, the participation of more clinical departments was needed to reach a similar sample size than PsC. A total of 816 PsA patients were finally recruited from 15 rheumatology departments of Spanish University Hospitals. In this group, PsA cases were defined as individuals that fulfill the CASPAR criteria (i.e. ClASsification criteria for Psoriatic Arthritis) (28). PsA patients had to have been diagnosed at least 1 year before the inclusion in the study and had to be more than 18 years old at the time of recruitment (although disease diagnosis could have taken place earlier). Including patients collected from dermatology (14.6%) and rheumatology departments (85.4%), a total of 955 PsA patients were analyzed in the present study.

A detailed questionnaire concerning multiple clinical and epidemiological variables was collected for both PsC and PsA cohorts. Table 1 summarizes the principal clinical characteristics that were used in this study. In standard clinical practice, the severity of cutaneous affection is categorized into mild or moderate to severe psoriasis. Mild psoriasis is defined as those patients that have never reached >10% of BSA affection at the time of sample collection nor in their clinical record (35–37). These patients are being usually well controlled with topical therapy. To reduce the probability of misclassification and taken into account that moderate-to-severe psoriasis usually needs systemic agents for its control, we additionally took into account the information on systemic treatments (included non-localized phototherapy) as a criteria of moderate-to-severe psoriasis, for those very few patients without information of BSA in their medical records.

Control individuals were recruited from blood bank donors attending at >10 University Hospitals from different regions in Spain in collaboration with the Spanish National DNA Bank. All the controls included in this study were screened for the presence of PsV or any autoimmune disorder, as well as for the presence of family history of autoimmune disorders in first-degree relatives. Individuals with an autoimmune disease or autoimmune disease family history were excluded. To further increase the hypernormality in this cohort, only control individuals above 30 years old fulfilling the previous criteria were finally included. In total, 1497 controls, 40% of which were females, were finally genotyped. Of note, 95.6% of control individuals were >40 years old at the time of recruitment (mean age $\pm$ SD 50.1 $\pm$ 7.1 year). All case and control individuals were Caucasian European and born in Spain and in the Spanish peninsula. To further prevent the potential influence of stratification in the association analyses, the recruitment of cases and controls was performed at clinical centers similarly distributed in Spain's peninsular geography. Finally, to reduce the impact of recent demographic events that could introduce stratification, the grandparents of all cases and controls had to be born in Spain, as well. Informed consent was obtained from all participants and protocols were reviewed and approved by local institutional review boards. The present study was conducted according to the Declaration of Helsinki principles.

Selection of SNPs previously associated with PsV disease risk

A total of 32 SNPs representing 32 different PsV susceptibility loci were included in this study. These loci can be divided in four different groups. The first group consists of the three PsV risk loci already established before the first PsV GWAS in 2008 (13). These loci correspond to *HLA-C* (3), *IL12B* and *IL23R* (4). The second group of studied loci consists on those loci that have been associated with PsV in several GWAS studies and include *LCE3D* (4,6,7,15), *ERAP1* (6,9), *IL13* (5,6), *IL23A* (5,6), *TNIP1* (5,6,9), *TRAF3IP2* (6,7), *TNFAIP3* (5,6,9), *NFKBIA* (6,7) and *RNF114* (5,6). The third group consists of loci identified in one GWAS but failed to replicate in an independent GWAS and includes *COG6* (5,13), *IL1RN* (5,9), *TSC1* (5,9) and *SMARCA4* (5,9). Finally, the last group of loci are those loci that had been discovered and replicated in only one GWAS but whose association with disease risk has not been evaluated in other genome-wide scans and includes *IL28RA* (6), *RYR2* (6), *REL* (6), *IFIH1* (6), LOC131185 (3p24 region) (6) , *PTTG1* (7), *DPP6* (7), *MMP27* (7), *GJB2* (9), *FBLX19* (8), *NOS2* (8), *SERPINB8* (9), *TYK2* (6), *RPS26* (8), *CSMD1* (9) and *SDC4* (8). For each studied locus, the SNP showing the strongest statistical association across GWASs was selected for analysis. In those loci where secondary but independent associations had been characterized, a unique SNP was selected for genotyping in our study.

Three of the published GWASs performed discovery and replication analysis of candidate loci on PsV patients, without directly evaluating the association of each locus with the presence of PsA. Therefore, the contribution of these loci to the risk of PsA and the comparison with PsC has still not been determined. This group of loci includes *IL28RA*, *RYR2*, *REL*, *IFIH1*, *LOC131185*, *ERAP1*, *PTTG1*, *DPP6*, *MMP27*, *GJB2*, *COG6*, *SERPINB8* and *TYK2*.

DNA extraction and genotyping

Blood samples were obtained from cases and controls during the sample recruitment period (years 2007–2010). Genomic DNA was isolated from all samples using the Chemagic Magnetic Separation Module I (Chemagen, Germany). DNA was normalized to 100 ng/μl based on spectrophotometric absorbance values and ~20% of samples were randomly tested for integrity (PicoGreen, Invitrogen).

Genotyping of all cases and controls was performed at the HudsonAlpha Institute for Biotechnology (Alabama, USA) using the Taqman Real-Time PCR platform (Applied Biosystems). The average completeness of genotypes was 98.4%. Using genotypes performed in replicate ($n = 1360$), we estimate a consensus error rate of 0.5% in our data. All SNPs were in Hardy–Weinberg equilibrium (exact test, $P > 0.001$).

Control for population stratification

In order to evaluate the potential impact of population stratification in our cohort, we genotyped 90 previously described AIMs (29) (Supplementary Material, Table S8) in the full sample using Taqman RT–PCR technology (Applied Biosystems). Structure software 2.0 (30) was used to attempt to identify population substructure by grouping individuals into K subpopulations ($K = 1–5$, 100 000 replications in the burn-in period of the chain for parameter estimation).

Statistical analysis

To provide an estimate of the power of the present study design to detect the associated loci with PsV, we performed statistical power calculations by using the Genetic Power Calculator web application assuming an $\alpha = 0.05$ type I error (31). Given that for most SNPs, the null for no association with global PsV has been clearly rejected, we did not apply adjustment for multiple testing. For each locus, the risk allele frequency and the genetic risk effects were used from those studies with the largest case–control cohorts and showing high statistical evidence. We calculated a summary estimate of the effect size for each risk locus by combining the OR estimates from the discovery and replication cohorts using the fixed-effects model.

We used allelic association tests to replicate the original findings and to test for the association with PsA and PsC. To test for the association with PsV, one-tailed P-values were calculated using 2×2 contingency tables of allele frequencies and a Fisher's exact test. Significant replication was considered if the P-value was <0.05 and the association had the same direction of effect as the originally reported. To test for the association with PsA, PsC and binary clinical variables, two-tailed P-values were calculated from the allele frequency table and the χ^2 test. When required, the influence of potential confounder effects on SNP association was evaluated using logistic regression and including the confounder as covariate in the logistic regression model. Similarly, the association of genotypes with quantitative variables (i.e. age at onset of skin disease and age at onset of joint disease) and the evaluation of confounders group were analyzed by using linear regression. The presence of interactions between loci was evaluated using logistic regression modeling as described in PLINK (32), with the estimation of one parameter to measure the independent contribution of each SNP and a third parameter to estimate the interaction between the two SNPs at the allelic level. *HLA-C* and *SERPINB8 g*ene expression interaction was evaluated using microarray data of normal and inflamed skin from psoriatic patients published by Nair *et al*. (5) and deposited in NCBI's Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/, accession GSE13355). Log2 normalized gene expression values for *HLA-C* and *SERPINB8* probes were analyzed using logistic regression with an interaction term.

To facilitate the comparison of the results from the different analyses, all effect size estimates (OR) are reported relative to the published PsV risk allele. All statistical association analyses were performed using the R statistical programming environment (version 2.9.1) (33). In order to account for the burden of multiple testing and the possibility of false positives, we also performed a max(T) permutation-based significance P-value that controls for the family wise error rate (34).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at *HMG* online.

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Conflict of Interest statement. None declared.

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