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Meta-analysis confirms the *LCE3C_LCE3B* deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with *HLA-Cw6*

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Conflict of Interest
The authors declare no conflict of interest.

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Abstract

A multicenter meta-analysis including data from 9389 psoriasis patients and 9477 control subjects was performed to investigate the contribution of the deletion of genes *LCE3C* and *LCE3B*, involved in skin barrier defense, to psoriasis susceptibility in different populations. The study confirms that the deletion of *LCE3C* and *LCE3B* is a common genetic factor for susceptibility to psoriasis in European populations [$OR_{Overall}$ = 1.21 (1.15–1.27)], and for the first time directly demonstrated the deletion's association with psoriasis in [Chinese OR = 1.27 (1.16–1.34); Mongolian OR = 2.08 (1.44–2.99)] populations. The analysis of the *HLA-Cw6* locus showed significant differences in the epistatic interaction with the *LCE3C* and *LCE3B* deletion in at least some European populations, indicating epistatic effects between these two major genetic contributors to psoriasis. The study highlights the value of examining genetic risk factors in multiple populations to identify genetic interactions, and indicates the need of further studies to understand the interaction of the skin barrier and the immune system in susceptibility to psoriasis.

Introduction

Psoriasis is a common chronic inflammatory disease of the skin with a variable worldwide prevalence, being common in European descent individuals and less frequent in Asian ancestry populations (Bowcock et al, 2005). To date, several loci have been underlined as psoriasis risk susceptibility factors, with *PSORS1*, a Major Histocompatibility Complex (MHC) class I region on chromosome 6p21, being the locus with the largest effect identified to date (Nestle et al, 2009). Within *PSORS1*, the *HLA-Cw06* allele has been pinpointed as the risk variant that confers the strongest susceptibility to psoriasis (Nair et al, 2006).

In a previous study we reported the association of the deletion of two late cornified envelope (*LCE*) genes, *LCE3C* and *LCE3B*, (*LCE3C_LCE3B-del*) with psoriasis in 1426 unrelated psoriatic patients and 1406 controls from four populations of European ancestry. The *LCE3C_LCE3B-del* involves a 32.2-kb deletion, removing genes *LCE3C* and *LCE3B* of the *LCE* cluster, which is part of the epidermal differentiation complex (EDC) on chromosome 1q21.3. Association with rs4112788, a tag single nucleotide polymorphism (SNP) for the biallelic *LCE3C_LCE3B-del* copy number variant (CNV), located 584 nucleotides downstream of *LCE3D*, was also found. Interaction analysis showed epistatic effects between the *LCE3C_LCE3B-del* and *HLA-Cw06* allele only in the Dutch population (de Cid et al, 2009). At the time of publication, an independent genome wide association scan (GWAS) in a Chinese cohort also identified association of rs4112788 with the disease, indicating a major role of the *LCE* locus in psoriasis susceptibility (Zhang et al, 2009). Furthermore this locus was replicated in a German case control study of psoriasis vulgaris (Hüffmeier et al, 2010) and in a Spanish case control study of chronic plaque type psoriasis vulgaris (Coto et al, 2010). Since these initial studies in psoriasis, the *LCE3C_LCE3B* locus has been evaluated in other and psoriasis-related phenotypes. Hüffmeier found no association of this locus with susceptibility to psoriatic arthritis in German samples (Hüffmeier et al, 2010), while association with this phenotype has been detected in British and Irish (Bowes et al, 2010) and in Spanish (Docampo et al, unpublished) patients. Finally, Bergboer et al has found negative association of the *LCE3C_LCE3B* locus with atopic dermatitis (Bergboer et al, 2010).

The aim of this meta-analysis with individual patient data was to further investigate the contribution of *LCE3C_LCE3B-del* to psoriasis susceptibility and its possible interaction with the *PSORS1* locus. Thirteen cohorts from twelve populations, nine of European ancestry [Finland, France, Germany, Ireland, Italy, Spain, The Netherlands, UK, and US (US-California: US-CA, and US-Michigan: USMI)], and three of Asiatic origin (China, Mongolia and Japan) were included in the study (See Supplementary Methods for sample description). Overall, 9389 psoriasis cases and 9477 control samples were analyzed for the association of *LCE3C_LCE3B-del* with psoriasis. Association of rs4112788 was also investigated in eleven of the 13 datasets included. A possible relationship between *PSORS1* and *LCE3C_LCE3B-del* and its tag SNP was assessed through interaction analysis using directly typed *HLA-Cw06* when available, or rs130076, a SNP in linkage disequilibrium (LD) with it (Asumalahti et al, 2002).

Results and Discussion

Association analyses of the genotyping data confirmed that the deletion of both *LCE3C* and *LCE3B* genes is a susceptibility determinant for psoriasis in European ancestry populations, with a significantly higher frequency of the *LCE3C_LCE3Bdel* allele in psoriatic patients compared with control individuals. [$OR_{Overall}$ = 1.21 (1.15–1.27), $P_{Overall} = 4.58\times10^{-13}$] (Table 1). As no significant evidence of heterogeneity between European ancestry populations was observed, a combined OR was calculated under a population fixed effects model. In addition, the estimation of an overall OR under a population random effects model –which better accommodates potential heterogeneity across populations of the genetic effects estimates due to genuine differences and/or different biases- was practically identical, which is a further indication of absence of significant heterogeneity (Lau et al, 1997; Ioannidis et al, 2007) (Table 1 and Figure 1). At the genotype level, analysis suggests a potential dosage effect with genotypes having two copies of genes *LCE3C* and *LCE3B* being a protective factor against the development of the disease in European ancestry populations ($OR_{Overall}$ = 1.20 (1.15–1.28), $P_{Overall} = 1.42\times10^{-13}$) (Supplementary Table 1).

Genotyping of Asian population samples for the *LCE3C_LCE3B-del* confirmed that the strong genetic association with SNPs at the *LCE3* genes detected in the Chinese population (Zhang et al, 2009) is due to the presence of the deletion of *LCE3C* and *LCE3B*. Genotyping for *LCE3C_LCE3B-del* in the other Asian populations further confirmed its presence in these populations. The deletion has the same sequence structure as that found in Caucasian populations. The detection of significant heterogeneity among the Asiatic population for *LCE3C_LCE3B-del* allelic frequencies impeded the estimation of the overall association of *LCE3C_LCE3B-del* with the psoriatic phenotype in Asian ancestry populations. The deletion is strongly associated with psoriasis in Chinese and Mongolian populations in regard of both the allelic (OR = 1.27 (1.16–1.34), $P = 1.70\times10^{-07}$; OR = 2.08 (1.44–2.99), $P = 8.16\times10^{-05}$, respectively) and the genotype level (OR = 1.28 (1.16–1.41), $P = 1.41\times10^{-07}$; OR = 2.04 (1.41–2.94), $P = 9.38\times10^{-05}$, respectively) (Supplementary Table 1). In Japanese population however, the higher frequency of the deleted allele among the psoriatic individuals compared with controls did not reach the level of significance (P = 0.063) (Table 1).

Analysis of rs4112788 showed association of allele C with the disease in the European ancestry populations [$OR_{Overall}$ = 1.21 (1.15–1.27), $P_{Overall} = 1.42\times10^{-12}$] (Table 1, Figure 1) as well as in the Chinese population [OR = 1.34 (1.21–1.46), $P = 6.42\times10^{-10}$] (Table 1). At the genotype level, a statistically significant higher risk for psoriasis was observed in individuals homozygous for the C allele in populations with European ancestry ($OR_{Overall}$ = 1.20 (1.15–1.27), $P_{Overall} = 1.81\times10^{-12}$) as well as in China ($OR_{Overall}$ = 1.35 (1.22–1.47), $P_{Overall} = 3.62\times10^{-12}$). (Supplementary Table 2). The high coefficient of determination

measure (r^2) (over 0.85 in all populations) indicates that rs4112788 is a close proxy of the *LCE3C_LCE3B-del* allele, also in the Chinese population (Table 1). This is the first direct indication that the strong association of psoriasis with rs4112788, detected in the initial analysis in Chinese samples (Zhang et al, 2009) is also associated with the *LCE3C_LCE3B-del* allele.

Interestingly, we observed a significant negative correlation between the frequency of *LCE3C_LCE3B-del* among controls and the corresponding OR for psoriasis for the eight populations from Europe examined –the more common the risk allele, the smaller its effect on psoriasis risk (Supplementary Figure 1). Allele frequency, and the correlated effect strength, appears to follow an approximate north-south gradient pattern. Even though this observation could be due to sampling error, and additional European populations would need to be studied, a genuine significance of this phenomenon on the genetic predisposition to psoriasis cannot be ruled out.

Direct typing of *HLA-Cw06* in the Netherlands, Italy, Japan, Mongolia and US samples allowed the estimation of a potential interaction between the *LCE3C_LCE3B* deletion, or its tag SNP rs4112788, with *PSORS1* locus. Apart from the already known interaction observed in the Dutch population alone, evidence for interaction was observed also in the US-MI dataset, but not in the Italian sample. The existence of heterogeneity among the cohorts with European ancestry prevented the analysis of the interaction in those cohorts as a whole. Evidence of interaction between either *LCE3C_LCE3B-del* or *rs4112788* with *HLACw06* was not observed in the Japan and Mongolia datasets (Table 2).

In the remaining populations, interaction with *PSORS1* was assessed through its proxy marker rs130076. No evidence for interaction was seen with *LCE3C_LCE3B-del* or its tag SNP in any of the populations interrogated (Supplementary Table 3). To investigate whether the association of rs130076 with psoriasis (Supplementary Table 4) is independent or secondary to *HLA-Cw06*, the effect of this SNP was analyzed in a stratified analysis that defined strata by carriage of *HLA-Cw06* in the Italian dataset (since the Italian was the only population in which both rs130076 and *HLA-Cw06* were genotyped). In the subset of samples that does not contain an *HLA-Cw06* allele, rs130076 was no longer significantly associated with psoriasis [OR = 4.64 (2.74–7.84), $P = 3.61\times10^{-09}$ in *HLA-Cw06* positive samples *versus* OR = 1.05 (0.73–1.50), P = 0.7938 in *HLA-Cw06* negative samples]. This suggests that the association of this locus is dependent on *HLA-Cw06*, at least in the Italian population, and therefore interaction analysis between the *LCE3C_LCE3B* deletion (or its tag SNP) with *PSORS1* might be interchangeably performed using either *HLA-Cw06* or rs130076, although it may not be coincidental that significant interaction was detected in 2 of the 5 datasets with *HLA-Cw06* typing, but in none of the eight datasets with rs130076 typing. The existence of a potential epistasis found only in the Dutch and US-MI datasets but in none of the remaining datasets in which *HLA-Cw06* was typed, might be due to population-specific effects, different genetic backgrounds or varying environmental exposures among datasets. The fact that no interaction was observed between *LCE3C_LCE3B-del* and *HLA-Cw06* in the Chinese dataset is probably due to the fact that despite *HLA-Cw6* is a major risk allele for psoriasis in the Chinese population, it does not explain by itself the full linkage evidence of the *PSORS1* locus in that population (Fan et al, 2008).

In summary, we have confirmed that the deletion of genes *LCE3C* and *LCE3B* is a common genetic factor for susceptibility to psoriasis in European populations, and for the first time directly demonstrated the deletion's association with psoriasis in some Asian groups. Interestingly, we detected significant differences in the epistatic interaction of the deletion with *HLA-Cw6*, with a positive interaction in the Dutch and US Michigan samples but no

interaction with other European cohorts. This study highlights the value of examining genetic risk factors in multiple populations, and suggests further studies in experimental models of disease are needed to understand the interaction of the skin barrier and the immune system in susceptibility to psoriasis.

Materials and Methods

Genotyping

Typing of the *LCE3C_LCE3B-del* CNV was performed by direct PCR using a four primers or three primers assay as previously described (deCid et al, 2009) allowing the simultaneous detection of intact and deleted alleles. Genotyping rates for *LCE3C_LCE3B-del* ranged from 92.5% to 100% in all European ancestry populations and from 97.3% to 100% in Asian populations. In regard to rs4112788, genotyping rates ranged from 93.7% to 99.6% in European ancestry populations, while it reached 99.2% in Chinese. SNP assays in Spain, Netherlands, Italy and US California were genotyped as previously described (deCid et al, 2009). In the Ireland dataset, SNPs genotyping was performed using competitive allele specific PCR at Kbiosciences, Hoddesdon, Herts, UK, and in Finnish data set using matrix-assisted laser desorption/ionisation time-of-light masspectrometry (Sequenom, San Diego CA, US). In the remaining populations, SNPs genotyping was conducted using TaqMan® assays (Applied Biosystems). HLA allele discrimination in sample collections from The Netherlands and Italy were performed as described (de Cid et al, 2009). In Japanese and Mongolian cohorts HLA typing was conducted with LABType® SSO typing test (ONE LAMBDA, INC.) and LABScan™ 100 flow analyzer. *HLA-Cw06* genotypes in the US Michigan sample were determined by genotyping 7 SNPs in exons 2 and 3 of the *HLA-C* gene, as previously described (Nair et al, 2006).

Statistical analysis

LCE3C_LCE3B–del and SNP association analysis. Logistic regression models assessed the genetic effect of the *LCE3C_LCE3B–del* and SNPs on psoriasis risk. Calculations for genotype frequency differences were performed by regression analysis for co-dominant, dominant, recessive and log-additive models. The best genetic model was selected using the Akaike information criteria (AIC). Heterogeneity among populations was assessed by the Woolf-test that evaluates the homogeneity of odds ratios. Overall values were calculated when the homogeneity assumption among populations was plausible, and were adjusted by population according to a logistic model that introduces population as a confounding variable. Potential interaction between *LCE3C_LCE3B–del* or rs4112788 and *HLA-Cw06* or rs130076 was evaluated from the log-likelihood ratio test between a model that includes both the additive effect and the interaction term against a model that only includes additive effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

MHC	Major Histocompatibility Complex
LCE	Late Cornified Envelope
LCE3C_LCE3B-del	deletion of *LCE3C* and *LCE3B* genes
EDC	Epidermal Differentiation Complex
GWAS	Genome Wide Association Scan
LD	Linkage Disequilibrium

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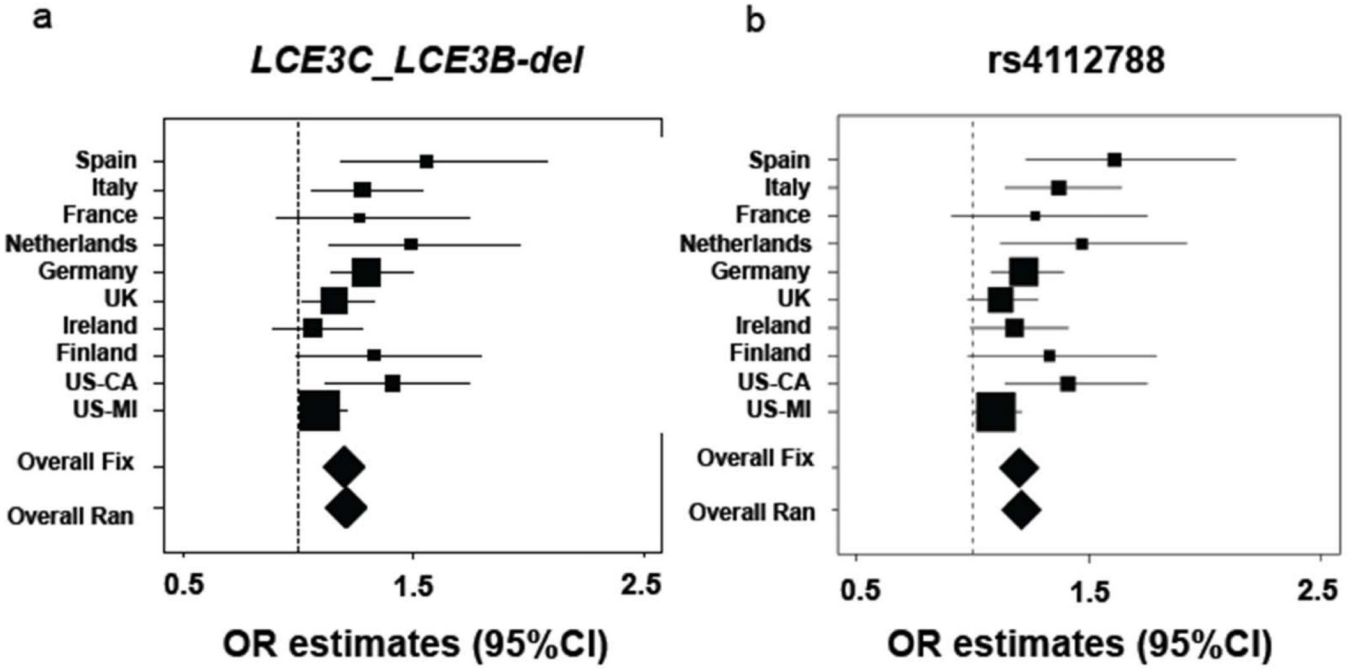

Figure 1. Meta-analysis of *LCE3C_LCE3B-del* and rs4112788 for association with psoriasis across populations of European ancestry

Panel **a** shows the data for *LCE3C_LCE3B-del* and panel **b** for rs4112788. Squares show the point estimate of the odds ratio (OR) and its 95% confidence intervals (95% CIs) with regard to genotype frequencies. Diamonds show the summary effect by fixed (Overall Fix and random (Overall Ran) effects model. Different square sizes represent different weights of each population.

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Table 1

Association of *LCE3C_LCE3B-del* and its tag SNP rs4112788 with psoriasis in individuals of European and Asian ancestry

		***LCE3C_LCE3B* CNV**					**rs4112788**					
Data set	**Status**	***LCE3C_ LCE3B*-del**	**Intact**	**HWE**	**OR (95% CI) (del vs. intact)**	***P*-value**	**Allele C**	**Allele T**	**HWE**	**OR (95% CI) (C vs. T)**	***P*-value**	r^2
Spain	Control	420 (55.0)	344 (45.0)	0.10	1.49 (1.15–1.93)	0.00284	427 (55.9)	337 (44.1)	0.67	1.57 (1.21–2.05)	0.00079	0.92
	Psor	227 (64.5)	125 (35.5)	0.02			233 (66.6)	117 (33.4)	0.09			
Italy	Control	516 (57.3)	384 (42.7)	0.03	1.30 (1.08–1.58)	0.00603	510 (57.2)	382 (42.8)	0.08	1.39 (1.15–1.68)	0.00079	0.93
	Psor	573 (63.7)	327 (36.3)	0.48			583 (64.9)	315 (35.1)	1.00			
France	Control	211 (64.3)	117 (35.7)	0.08	1.26 (0.90–1.77)	0.1767	216 (65.1)	116 (34.9)	0.06	1.29 (0.99–1.95)	0.1405	0.96
	Psor	196 (69.5)	86 (30.5)	1.00			202 (70.6)	84 (29.4)	1.00			
The Netherlands	Control	334 (59.6)	226 (40.4)	0.54	1.50 (1.14–1.96)	0.00329	333 (59.9)	223 (40.1)	0.62	1.54 (1.18–2.02)	0.00155	0.99
	Psor	281 (68.9)	127 (31.1)	0.63			278 (68.8)	126 (31.2)	0.74			
Germany	Control	1,215 (64.9)	657 (35.1)	0.67	1.31 (1.15–1.48)	3.03e-05	1,151 (64.7)	627 (35.3)	0.56	1.22 (1.07–1.38)	0.00229	0.94
	Psor	1,899 (70.8)	785 (29.2)	0.43			1,799 (69.1)	803 (30.9)	0.47			
UK	Control	1,370 (67.1)	672 (32.9)	0.94	1.16 (1.01–1.33)	0.0306	1,303 (66.4)	659 (33.4)	0.57	1.12 (0.98–1.28)	0.0872	0.86
	Psor	1,323 (70.3)	559 (29.7)	0.10			1,390 (68.9)	626 (31.1)	0.30			
Ireland	Control	1,311 (69.2)	583 (30.8)	0.17	1.07 (0.89–1.29)	0.459	1,335 (68.8)	605 (31.2)	0.33	1.18 (0.99–1.41)	0.0695	0.94
	Psor	554 (70.7)	230 (29.3)	0.90			624 (72.2)	240 (27.8)	0.47			
Finland	Control	436 (65.1)	234 (34.9)	0.05	1.37 (1.01–1.87)	0.046	433 (65.6)	227 (34.3)	0.09	1.37 (1.00–1.88)	0.0512	0.98
	Psor	194 (71.9)	76 (28.1)	0.39			188 (72.3)	72 (27.7)	0.19			
US-CA	Control	378 (64.3)	210 (37.7)	0.04	1.36 (1.11–1.68)	0.00378	379 (64.0)	213 (36.0)	0.13	1.37 (1.11–1.69)	0.00339	0.95
	Psor	847 (71.1)	345 (28.9)	0.09			835 (70.9)	343 (29.1)	0.06			
US-MI	Control	2,478 (64.8)	1,348 (35.2)	0.52	1.09 (1.00–1.20)	0.0584	2,472 (65.0)	1332 (35.0)	0.45	1.10 (1.00–1.20)	0.0515	0.98
	Psor	2,835 (66.8)	1,411 (33.2)	0.33			2,828 (67.0)	1,390 (33.0)	0.46			
Overall[1]	Control	6,028 (64.2)	3,364 (35.8)	—	1.21 (1.15–1.27)[2]	4.58e-13[2]	6,087 (64.2)	3,389 (35.8)	—	1.21 (1.15–1.27)[2]	1.42e-12[2]	—
	Psor	5,902 (69.6)	2,580 (30.4)	—	1.21 (1.15–1.28)[3]	1.47e-12[3]	6,132 (69.2)	2,726 (30.8)	—	1.21 (1.15–1.28)[3]	1.44e-12[3]	
China	Control	2,174 (57.3)	1,620 (42.7)	0.95	1.27 (1.16–1.34)	1.70e-07	2,173 (57.6)	1,601 (42.4)	1.0	1.34 (1.21–1.46)	6.42e-10	0.91
	Psor	2,518 (63.1)	1,472 (36.9)	0.21			2,543 (64.4)	1,403 (35.6)	0.01			
Japan	Control	631 (58.8)	443 (41.2)	0.79	1.17 (0.99–1.40)	0.0638	ND	ND	—	—	—	—

		LCE3C_LCE3B CNV					rs4112788					
Data set	**Status**	***LCE3C_ LCE3B*-del**	**Intact**	**HWE**	**OR (95% CI) (del vs. intact)**	***P*-value**	**Allele C**	**Allele T**	**HWE**	**OR (95% CI) (C vs. T)**	***P*-value**	r^2
	Psor	689 (62.6)	411 (37.4)	1.00								
Mongolia	Control	166 (49.4)	170 (50.6)	0.36	2.08 (1.44–2.99)	8.16e-05	ND	ND	—	—	—	—
	Psor	134 (67.0)	66 (33)	0.82								

Abbreviations: CI, confidence interval; CNV, copy number variant; HWE, Hardy–Weinberg equilibrium; ND, no data available; OR, odds ratio; SNP, singlenucleotide polymorphism; US-CA, US-California data set; US-MI: US-Michigan data set.

[1]Overall analyses for the European ancestry populations are computed according to a logistic model in which population was introduced as a confounding variable (based on a [2]fixed effects model and a [3]random effects model) after no significant evidence of heterogeneity was detected according to the Woolf test on homogeneity of odds ratios (*P*=0.0763 for *LCE3C_LCE3B* CNV; *P*=0.0553 for rs4112788). Overall values for the Asian ancestry populations are not presented as the Woolf test on homogeneity of odds ratios showed statistical significant heterogeneity among them (*P*=0.02091). Predictive performance of allele C with *LCE3C_LCE3B-del* is presented for each population using the coefficient of determination measure (r^2).

Table 2

Genetic interaction analysis between *HLACwo6* in *PSORS1* and *LCE3C_LCE3B-del* and its rs4112788 tag SNP

	***HLA-Cw06*[1]**				**Epistasis[2]**					
	Positive vs. negative				**rs4112788-*HLA-Cw06***			***LCE3C_LCE3B- HLA-Cw06***		
Data set	**OR**	**95% CI**	***P*-value**	**Group**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
The Netherlands	3.45	2.27–5.25	2.974e-09	+	2.58	1.46–4.57	0.0160	2.60	1.47–459	0.0180
				−	1.15	0.83–1.60		1.17	0.84–1.63	
Italy	2.5	1.86–3.36	4.994e-10	+	1.22	0.45–1.75	0.57897	1.14	0.80–1.62	0.5445
				−	1.38	1.09–1.76		1.30	1.03–1.64	
US-MI	3.69	3.19–4.27	1.063e-75	+	1.44	1.19–1.75	0.00028	1.44	1.19–1.75	0.00027
				−	0.95	0.85–1.06		0.95	0.85–1.06	
Japan	9.25	3.94–21.7	6.854e-11	+	ND			1.09	0.23–5.08	0.9266
				−	ND			1.17	0.98–1.39	
Mongolia	34.39	16.48–1.7	1.902e-31	+	ND			1.46	0.82–2.59	0.1286
				−	ND			3.67	1.30–10.37	

Abbreviations: CI, confidence interval; ND, no data; OR, odds ratio; SNP, single-nucleotide polymorphism; US-MI, US-Michigan data set.

[1] OR and 95% CI for psoriasis of directly typed *HLA-Cw06* was analyzed using the carrier status definition for *Cw06* allele.

[2] Epistasis analysis performed by logistic regression models that included an interaction term (rs4112788-*HLA-Cw06* or *LCE3C_LCE3B*-del-*HLA-Cw06*); *P*-values are derived from the log-likelihood ratio test between the model including both additive effects plus the interaction term against the model that only includes additive effects. Overall values for the European and Asian ancestry populations are not presented, as significant heterogeneity based on allelic frequencies was detected by population according to the Woolf test on homogeneity of ORs (P=0.0045 and P=0.0012, respectively).

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