Published in final edited form as:

Nat Genet. 2009 February ; 41(2): 211–215. doi:10.1038/ng.313.

Deletion of the late cornified envelope (LCE) 3B and 3C genes as a susceptibility factor for psoriasis

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Abstract

Psoriasis is a common inflammatory skin disease with a prevalence of 2% to 3% in Caucasians[1]. In a genome-wide search for copy number variants (CNV) using a sample pooling approach we have identified a deletion comprising *LCE3B* and *LCE3C*, members of the late cornified envelope (LCE) gene cluster[2]. The absence of *LCE3B* and *LCE3C (LCE3C-LCE3B-del)* is significantly associated (p=1.38E-08) with risk of psoriasis in 2,831 samples from Spain, The Netherlands, Italy and the USA, and in a family-based study (p=5.4E-04). *LCE3C-LCE3B-del* is tagged by rs4112788 (r^2=0.93), which is also strongly associated with psoriasis (p<6.6E-09). *LCE3C-LCE3B-del* shows epistatic effects with the HLA-Cw6 allele on the development of psoriasis in

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AUTHOR CONTRIBUTIONS R.deC., E.R.-M., P.L.J.M.Z., and J.R. contributed equally to this work. R.deC., G.M., R.P. and C.L. recruited the subjects from Spain. P.L.J.M.Z., M.K, M. den H. and J.S. recruited the subjects from The Netherlands. E.G. and G.N. recruited the subjects from Italy. P.K., A.B., R.N., W.L. and J.T.E. recruited the subjects from the USA. R.deC., E.R.-M., P.L.J.M.Z., J.R., W.L., E.D., E.G., I.J., E.B., P.S., R.N. and performed the genotyping and experimental work. R.deC., L.A., G.E., G.A., P.E.S., J.S. and X.E. analyzed the data. J.S. was responsible for the design and execution of the expression studies in keratinocytes. X.E., G.N., J.T.E., J.A., P.K., A.B., and J.S. supervised the work. X.E. designed the study and coordinated the work. All authors contributed to the final version of the paper.

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Competing interests statement The authors declare no competing financial interests.

Note: Full Methods and associated references are available on Nature Genetics website.

Dutch samples, and multiplicative effects in the other samples. *LCE* expression can be induced in normal epidermis by skin barrier disruption and is strongly expressed in psoriatic lesions, suggesting that compromised skin barrier function plays a role in psoriasis susceptibility.

Psoriasis is a chronic hyperproliferative inflammatory disease of the skin, scalp, nails, and joints that present in several clinical forms[1]. Psoriasis is generally regarded as an immunologically mediated disorder characterized by abnormal keratinocyte proliferation and differentiation, local vascular changes, and a mixed inflammatory infiltrate in the epidermis and dermis[3]. Psoriasis has a multifactorial aetiology, involving environmental (infections, drugs, stress, smoking and climate) and genetic factors[4].

Genetic analyses of multiply affected families have found several susceptibility loci for psoriasis[5]. The most strongly associated is on chromosome 6p21 within the MHC region (*PSORS1*)[6]. Variants associated with the human leukocyte antigen (HLA)-Cw6 contribute between 33% and 50% of the familial clustering of the disease[7]. In addition to *PSORS1*, genome-wide linkage analyses and association studies have highlighted psoriasis loci on several other chromosomes[5,8], and advances in the identification of the relevant genes have mainly revealed molecules involved in the immune response and expressed in T-cells and keratinocytes, such as HLA-C, IL12B, IL23R, and β-defensins[9–11].

Copy number variation is a rich source of genetic variability[12]. Several CNVs contribute to susceptibility to autoimmune and inflammatory disorders[13]. In a candidate gene approach, a higher copy number of the chromosome 8 β-defensin cluster has been demonstrated as a susceptibility factor for psoriasis[11]. In order to identify genomic regions that vary in copy number in patients with psoriasis, we have performed a genome-wide CNV analysis by array comparative genomic hybridization (aCGH) using the human Agilent 244A array, which contains approximately 244,000 probes and covers the entire genome with a 10-kb resolution. Here, we report the characterization and replication study of one such region on human chromosome 1q21, which was specifically characterized because it falls within a previously known psoriasis susceptibility locus (*PSORS4*)[14].

To reduce detection of inter-individual CNV variability unrelated to psoriasis we used a pooling approach. We assembled equimolar amounts of DNA in three pools, each containing 20 psoriasis samples. Each of these three pools was analyzed against a pool of 50 samples from unrelated subjects of the general population in the aCGH experiments. Four regions fulfilled criteria for a CNV potentially associated with psoriasis (Supplementary Material) and all corresponded to previously identified CNVs (Database of Genome Variants) (Supplementary Table 1). One such region on chromosome 1q21 involved, at least in one pool, four contiguous probes with $\log_2$ ratios >0.3 and two additional probes >0.25, the six probes spanning the *LCE3C* and *LCE3B* genes, members of the LCE cluster[2] (Figure 1).

To evaluate if the individual samples of patients with psoriasis had a reduction in copy number of *LCE3C* and/or *LCE3B* genes with respect to controls, as predicted by the aCGH study, we carried out quantitative PCR (qPCR) on 557 Spanish samples, including those used in the aCGH experiments (Supplementary Table 2). We targeted qPCR to exonic regions of *LCE3C*, and two flanking genes, *LCE2C* and *LCE3E*. We found that this CNV was biallelic and that 33% of the DNA samples from psoriasis patients had a reduction in the *LCE3C* copy number, compared with 24% of control samples (OR=1.62; 95%CI=1.04–2.51, p=0.02).

The LCE region has previously been defined in several studies as being a CNV[12] (Figure 1), but only recently it has been characterized as a 32.2 kb deletion (from nucleotides

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150,822,166 to 150,854,365 in hg18)[15,16]. We took advantage of these CNV coordinates to define the deletion breakpoints and develop a direct assay of the *LCE3C* and *LCE3B* deletion *(LCE3C_LCE3B-del)* by PCR amplification. We found a significantly higher frequency of the *LCE3C_LCE3B-del* allele in psoriasis patients (64%) compared with controls (55%) (p=0.0028) (Table 1). Concordance of results between *LCE3C* qPCR and direct PCR typing of *LCE3C_LCE3B-del* was excellent (weighted kappa=0.93; 95%CI=0.88–0.95).

To replicate the association of *LCE3C_LCE3B-del* with psoriasis initially found in the Spanish samples, the *LCE3C_LCE3B-del* frequency was assessed by PCR typing in four case-control samples from Italy (n=900), USA (n=890) and The Netherlands (n=484) (Table 1), and in a family-based study from the USA (1,395 affected in 562 families) (Supplementary Table 2). In all studies, we observed an increased risk for psoriasis in carriers of the *LCE3C_LCE3B-del* allele (OR=1.30–1.50). Overall, *LCE3C_LCE3B-del* was significantly higher in psoriasis patients (68%) than in control subjects (59%) (p=1.38E-08), according to a logistic model in which population was introduced as a confounding variable after non-significant heterogeneity was detected by population (Table 1). A total of 334 University of Michigan samples were informative for *LCE3C_LCE3B-del* using a family based association test (FBAT) leading to an association with psoriasis (p=5.4E-04) (Supplementary Table 4). The genotype analysis that estimated the OR for heterozygous and homozygous carriers suggests a potential dosage effect (Supplementary Table 3). Thus the presence of two copies of the *LCE3C* and *LCE3B* genes is protective against the development of psoriasis (p<0.0001). The percentage of psoriasis attributed to carrying at least one deleted allele (estimated population attributable risk) was 21% in the combined dataset.

We evaluated linkage disequilibrium (LD) between *LCE3C_LCE3B-del* and tagSNPs covering the *LCE3* and *LCE2* region (Figure 1, Supplementary Table 5 and Supplementary Figure 1). We found 14 SNPs strongly associated with *LCE3C_LCE3B-del* (Supplementary Table 6). The region of association with *LCE3C_LCE3B-del* spans over 130 kb, with allele C at rs4112788 (p=2.40E-126) being in strongest LD (r^2=0.93 and D'=0.99). rs4112788 maps 584 nucleotides downstream of *LCE3D* and 4.5 kb centromeric to *LCE3C_LCE3B-del*, and the strong LD suggests a single origin in the Caucasian population. The analysis of rs4112788 in all populations showed that this SNP is strongly associated with psoriasis (overall adjusted p-value p<6.6E-09) (Table 2). rs4112788 is also associated with psoriasis in the USA family sample by FBAT (p=0.0019) (Supplementary Table 4).

The region of association with psoriasis detected and investigated in our study is in the region of the *PSORS4* locus, originally identified in Italian families[14]. The *PSORS4* locus contains the epidermal differentiation complex (EDC), a cluster of at least 20 genes expressed during epithelial differentiation[2,17]. Genes in the *PSORS4* region have been investigated in several studies but none has been clearly shown to be involved in psoriasis[8,18]. However, the genes reported in those studies are in completely distinct LD blocks from *LCE3B/3C*, showing a low LD with rs4112788 (r^2<0.5). A comprehensive dissection of this region of chromosome 1 could provide further clues about the involvement of other genes besides *LCE3B/3C* that could explain previous linkage and association findings in psoriasis.

We evaluated the relationship between the *LCE3C_LCE3B-del* locus and the HLACw6 allele (as part of *PSORS1)*[7,9]. To test for an interaction between *PSORS1* and the *LCE3C_LCE3B-del* in the Spanish sample, we analyzed six SNPs in the region (Supplementary Table 7). These SNPs are in strong LD with HLA-Cw6[19] and as expected, each of them was highly associated with psoriasis and defines a strongly associated haplotype in the region (OR=6.62, 95%CI [4.12–10.64], p<0.00001, 10,000 permutations) (Supplementary Table 8). No evidence was found for interaction neither in the Spanish and Italian case-control samples nor in the USA family samples but we did observe this for the Dutch sample, where the presence of the *LCE3C_LCE3B-del* allele (as well as rs4112788) has a significant risk for psoriasis only in presence of HLA-Cw6 (Table 3).

The identification of an epistatic effect between the *HLA-C* and *LCE3C* loci in the Dutch population is notable because attempts to identify interaction between *HLA-C* and other loci have failed[20]. Nevertheless, an epistatic effect between the *PSORS1* and *PSORS4* loci was reported in Italian families[21]. Further work will be needed to understand whether significant epistasis detected only in Dutch samples is observed because of sampling error, population-specific effects or other aspects of methodology.

Finally, to further investigate the potential role of this CNV in psoriasis, we evaluated the patterns of expression of *LCE3C* in normal skin and in lesional and uninvolved psoriatic epidermis. qRT-PCR assays were designed for *LCE3C*, which is contained in the deletion, and for *LCE3E*, which is outside the deletion. qRT-PCR was performed on purified epidermal cells from seven normal skin biopsies and from lesional epidermis of nine psoriasis patients (Figure 2A). *LCE3C* and *LCE3E* expression was low to undetectable in all of the normal skin samples, irrespective of their *LCE3C_LCE3B-del* genotype, in agreement with what has been described previously[2]. Among psoriasis patients, only those harbouring at least one copy of the *LCE3C* gene showed *LCE3C* expression. All samples from lesional skin showed expression of *LCE3E*. For psoriasis samples 1 to 4 mRNA from purified epidermal cells of uninvolved skin was also available. Figure 2B shows that, similar to skin of healthy controls, no *LCE3C* or *LCE3E* expression is detected in uninvolved psoriatic skin, irrespective of the *LCE3C_LCE3B-del* genotype. We hypothesized that skin barrier disruption might be a physiological stimulus for LCE3 gene induction. We used tape stripping of normal skin as a model to investigate this in healthy volunteers. This procedure involves successive application of adhesive tape, which removes the stratum corneum, the top layer of the epidermis. The subsequent epidermal response involves keratinocyte hyperproliferation, accelerated differentiation and increased expression of genes involved in skin barrier formation. While *LCE3C* and *LCE3E* mRNA was absent in normal skin, we found that their expression was markedly induced by tape stripping (Figure 2C) except for one control individual (C5) with two *LCE3C_LCE3B-del* alleles who did not show *LCE3C* mRNA induction, as expected. Expression of the non-deleted *LCE3E* gene was induced in all individuals following tape stripping.

In healthy individuals, the expression level of induced *LCE3C* may vary according to the individual response to tape stripping. If we assume, however, that *LCE3C* and *LCE3E* are subject to similar regulation mechanisms, this offers a way of correcting these non-genomic effects on gene expression. To this end we plotted the ratio of *LCE3C*:*LCE3E* expression for 17 individuals against the number of non-deleted allele copies of the *LCE3C* gene. A significant correlation was found (Pearson's r=0.88, p=2.0E-06) between the normalized *LCE3C* expression and copy number (Supplementary Figure 3).

This genome-wide analysis has led to the identification of a region of chromosome 1q21 that harbours two genes (*LCE3C* and *LCE3B*) that are deleted in a significant fraction of psoriasis patients of Caucasian ancestry. Several SNPs in the region are associated with the deletion, one of them (rs4112788) being a close proxy of *LCE3C_LCE3B-del*. This strong LD of SNPs with a given CNV might be a common feature of biallelic CNVs, particularly useful in association studies for complex disorders, as has recently been detected for Crohn's disease and the deletion polymorphism upstream of the IRGM gene[22]. This might not be the case for complex CNVs, such as the β-defensin cluster on chromosome 8p23, which shows a significant association between increased β-defensin gene copy number and psoriasis susceptibility[11]. The complex nature of the β-defensin CNV likely precluded its identification in the aCGH performed here. Due to the strong LD between the CNV and rs4112788, it is not possible to define which variant better captures the association signal with psoriasis. However, lack of evolutionary conservation suggests that rs4112788 is a non-functional variant, not included in any promoter, enhancer or distant regulatory element (NCBI DCODE), making the deletion of the two *LCE* genes a more suitable candidate for the association detected here. However, both *LCE3C_LCE3B-del* and rs4112788 could be merely markers for another, unknown and untested variant. This will be resolved only after resequencing and fine mapping of the region and by the analysis of the potential joint contribution of other genes. We have also shown that *LCE3C* expression is induced upon epidermal activation as found in psoriatic and induced skin lesions. As 30% of the general population is not able to express these genes due to the deletion, there is probably some redundancy in the function of LCE genes in the cluster. It is possible that these other genes assume the functions of *LCE3C* and *LCE3B* imperfectly, contributing to the abnormal differentiation and epidermal hyperproliferation characteristic of psoriatic lesions. We would speculate that absence of intact *LCE3C* and *LCE3B* genes could lead to an inappropriate repair response following barrier disruption, which is insufficiently backed up by other LCE genes. A more leaky epidermal barrier following skin injury would allow easier penetration of exogenous agents (allergens and/or microorganisms)[23], which against a genetic background of HLA-Cw6 positivity could evoke a response of the adaptive immune system leading to overt inflammation.

METHODS

Subjects

Ethical approval by the relevant research ethics committees of each centre was obtained for all DNA samples collected, and written informed consent was obtained from all participants (Spain, The Netherlands, Italy and the USA). All subjects were of European descent. For details on diagnostic criteria and other characteristics of the patients see Supplementary Material.

Identification of CNV regions

To investigate the presence of CNVs associated with psoriasis we performed a DNA-pooling approach for aCGH using the Human Genome CGH Microarray Kit 244A, which contains over 244,000 probes and covers the entire genome with a 10-kb resolution between probes. Regions composed of at least three altered probes (including the entry probe) were retained for further study. Results observed in the 1q21 region for aCGH analysis was confirmed by a second technique using a qPCR analysis. For details on CNV analysis and results, and characterisation in each population sample see Supplementary Material.

SNP Genotyping

SNPs were genotyped using different platforms. We tested each polymorphism in the whole group to ensure consistency with Hardy-Weinberg Equilibrium (HWE). Because of multiple testing, we used a threshold of p=0.001. The final SNP dataset consisted of 15 SNPs (Supplementary Table 3) with an overall genotype call rate of 99%. See Supplementary Material for details on SNP genotyping methods in each population sample.

LCE3C_LCE3B -del and SNP association analysis

Logistic regression models were used to assess the genetic effect of the *LCE3C_LCE3B -del* and SNPs on psoriasis risk. Inter-group comparisons of genotype frequency differences were performed by regression analysis for co-dominant and genotype–specific models. Unadjusted crude odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Analysis was carried out using the SNPassoc R library, from The Comprehensive R Archive Network. For SNP association analysis the problem of multiple testing was solved using Bonferroni corrected value (accounting for multiple testing of 15 polymorphic SNPs and the genotype-specific models tested[24]) to a threshold p-value of 0.0015.

Interaction Analysis

For the interaction analysis in the Spanish population we used the genotype-specific model of heritability for each SNP based on the Akaike criteria (AIC) derived from the association analysis. We derived the p values for the interaction (epistasis) using the log-likelihood ratio test comparing the full interaction model to the additive SNP model, and the multiplicative effect using the likelihood ratio test of the additive model with the likelihood of the best model using single SNPs. A p-value of 0.00054 for significance after Bonferroni correction to account for multiple comparisons was used. For the Italian and Dutch samples, interaction analysis *of LCE3C_LCE3B-del* or rs4112788 and HLA-Cw6 was performed. Assessment for significant epistasis and multiplicative effects was carried out as described for the Spanish population. For analysis of interaction in the Michigan family sample, the method of Cordell *et al*[25] was followed.

Biopsies, RNA isolation and quantitative real-time PCR

All psoriasis patients had plaque-type psoriasis diagnosed by a dermatologist. Biopsies of normal, psoriatic and tape-stripped skin were taken under local anaesthesia. Tape stripping of human skin is the repeated application and removal of adhesive tape, which produces a standardized injury of the epidermis by removal of the stratum corneum[26]. All controls and patients were of native European Dutch origin. Permission for these studies was obtained from the local medical ethics committee ("Commissie Mensgebonden Onderzoek Arnhem-Nijmegen"), and volunteers gave written informed consent. The study was conducted according to the Declaration of Helsinki Ethical Principles. Detailed procedures for preparation of purified epidermis, RNA isolation, and real-time quantitative PCR are given as Supplementary Material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the participants in the genetic studies whose contributions made this work possible and personnel at the CeGen genotyping core facility (Barcelona node). We thank Drs. Tilo Henseler, Stefan Jenisch, Michael Weichenthal and Enno Christophers from the University of Kiel for making samples from Kiel, Germany available for analysis. We thank Annie Poon for technical assistance and the UCSF Psoriasis Center Staff for help with patient recruitment; and Joanne Gartlon for proof-reading the manuscript. This work was supported in part by funds from the "Generalitat de Catalunya", the Spanish Ministry of Science and Innovation and the European Commission (X.E., R.deC., L.A. E.R., G.E., and E.B.); ADIPSO (G.N.); and National Institutes for Arthritis, Musculoskeletal and Skin Diseases (AB., J.T.E., R.N., and P.E.S.). J.T.E. is supported by the Ann Arbor Veterans Affairs Hospital. W.L. is supported by a grant from the Dermatology Foundation.

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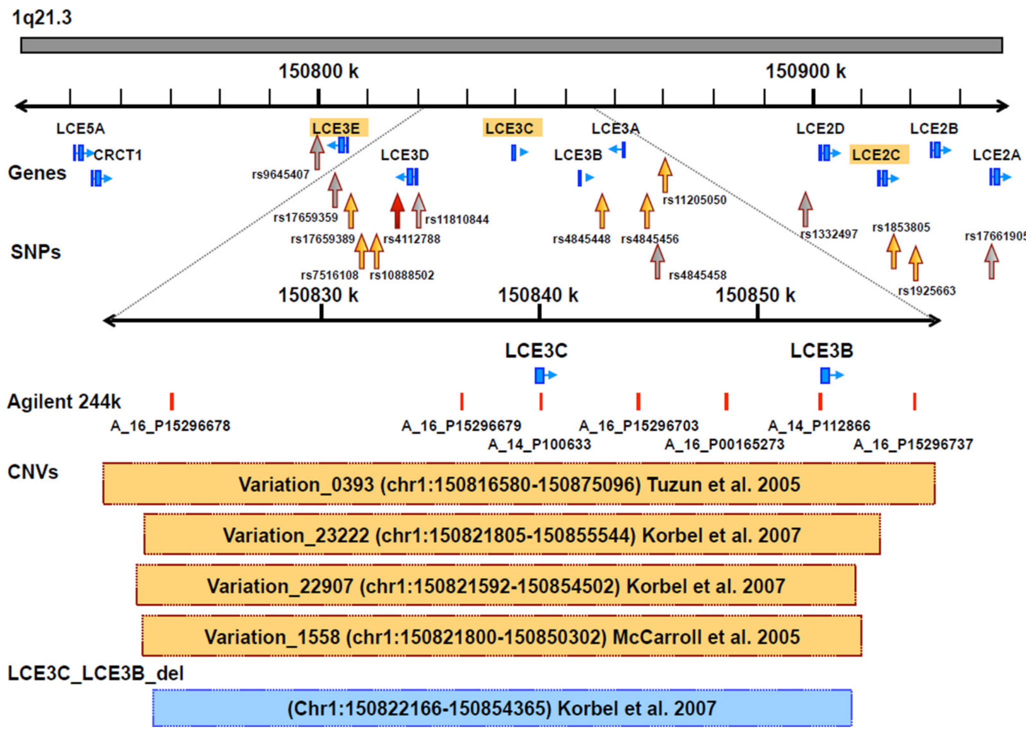

Figure 1. Region of the LCE cluster containing the *LCE3C_LCE3B-del* associated with psoriasis

The region shows 200 kb of the genomic region between *LCE5A* and *LCE2A* on human chromosome 1. The 11 genes of these regions are shown with their transcription orientation. Vertical yellow arrows indicate the position of the SNPs that showed association with psoriasis and with *LCE3C_LCE3B-del*. Vertical grey arrows indicate the position of those SNPs that did not show association with psoriasis. The location of the rs4112788 SNP is shown with a red arrow. The location of the Agilent probes that showed variability in aCGH experiments are shown as vertical bars. The CNV regions described in other studies are indicated. The *LCE3C_LCE3B-del* deletion, which spans 32,199 bp is highlighted. The genes for which TaqMan assays were developed are shown on a yellow background.

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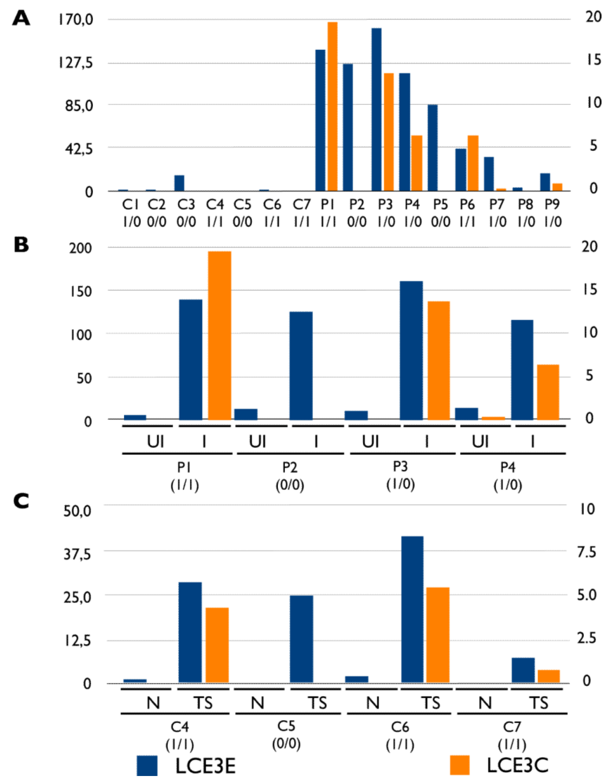

Figure 2. Patterns of mRNA expression of *LCE3C* in the epidermis of psoriatic and control subjects

(a) Evaluation of the expression profiles of *LCE3C* and *LCE3E* in the skin of control subjects (C1 to C7) and patients with psoriasis (P1 to P9). (b) Evaluation of the expression of *LCE3C* and *LCE3E* in uninvolved (UI) skin of psoriatic patients vs. involved lesional (I) skin. Expression levels (relative to the endogenous gene *RPLP0)* of *LCE3E* and *LCE3C* are represented by left and right Y-axis values respectively. The genotypes 0/0, 0/1 and 1/1 correspond to the *LCE3C_LCE3B-del* homozygotes, heterozygotes, and homozygotes for the presence of *LCE3C* and *LCE3B*. (c) Induction of expression of *LCE3C* and *LCE3E* in normal skin (N) by the tape-stripping (TS) model, which removes the stratum corneum of the epidermis.

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Table 1

Association of *LCE3C_LCE3B-del* with Psoriasis in 2,832 Caucasian Subjects from Different Populations

Population (samples)	Phenotype	Alleles	*LCE3C_LCE3B-del* (%)	*LCE3C_LCE3B* (%)	OR 95%CI	P-value
Spanish (557)	Psoriasis	350	225 (64)	125 (36)	1.47 (1.28–1.72)	0.0028
	Control	764	420 (55)	344 (45)		
Italian replicate (900)	Psoriasis	900	573 (64)	327 (36)	1.30 (1.12–1.51)	0.006
	Control	900	516 (57)	384 (43)		
Dutch replicate (484)	Psoriasis	408	281 (69)	127 (31)	1.50 (1.29–1.74)	0.0033
	Control	560	334 (60)	226 (40)		
USA replicate (890)	Psoriasis	1,192	847 (71)	345 (29)	1.36 (1.18–1.58)	0.0038
	Control	588	378 (64)	210 (36)		
Total (2,831)	Psoriasis	2,852	1,926 (68)	924 (32)	1.38 (1.19–1.61)	1.38E-08
	Control	2,812	1,648(59)	1,164(41)		

Odds ratio (OR) and 95% confidence interval 95% (CI) for *LCE3C_LCE3B* deleted allele *(LCE3C_LCE3B-del)* and psoriasis were obtained by logistic regression, overall and separately for each of the four populations; Overall OR and p-values are standardized by population according to a logistic model in which population was introduced as a confounding variable after (non-significant) heterogeneity was detected by population.

Table 2

Association of rs4112788 Genotypes in the LCE Cluster with Psoriasis in Spanish, Italian, Dutch and USA Samples

			Recessive model C/C versus T/T and C/T		Dominant model C/C and C/T versus T/T		Log-additive model			
Population	**Psoriasis***	**Controls***	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**P-value**	**r^2**
By study										
Spanish	175	382	1.58	1.09–2.30	2.67	1.46–4.88	1.62	1.23–2.13	4.93E-04	0.92
Italian	449	446	1.35	1.03–1.77	1.54	1.06–2.24	1.30	1.08–1.58	0.0065	0.88
Dutch	202	278	1.50	1.04–2.17	2.08	1.17–3.70	1.47	1.12–1.93	0.0046	0.99
USA	587	293	1.46	1.10–1.94	1.54	0.93–2.55	1.38	1.10–1.72	0.0051	0.95
Overall	1,413	1,399	1.54	1.32–1.79	1.98	1.57–2.49	1.48	1.33–1.66	3.38E-12	
Overall adjusted	1,413	1,399	1.45	1.24–1.70	1.79	1.41–2.28	1.41	1.25–1.58	6.56E-09	

Odds ratio (OR) and 95% confidence interval (CI) for psoriasis comparing homozygous (C/C), heterozygous (C/T) and homozygous genotype (T/T) of rs411178 overall and separately for each of the four populations; Overall OR are standardized by population according to a logistic model in which population was introduced as a confounding variable after (non-significant) heterogeneity was detected by population; P-values are derived from the log-additive model, with homozygotes for the C allele at higher risk for psoriasis than homozygotes for TT as a basal genotype; Predictive performance of LCE3C_LCE3B deleted allele is presented for each population using the coefficient of determination measure (r^2);

*Subjects with valid call for rs4112788.

Table 3

Genetic Interaction Analysis between *LCE3C_LCE3B-del* and *LCE3C_LCE3B-del* tag SNP and *PSORS1* loci.

			rs4112788 (log-additive)		*LCE3C_LCE3B-del* (log-additive)		HLA-Cw6 positive vs. negative			Epistasis[&]					
										rs4112788 – HLACw6*			*LCE3C_LCE3B-del* –HLACw6*		
	Psoriasis	**Controls**	**OR**	**95%C.I.**	**OR**	**95%C.I.**	**OR**	**95%C.I.**	**Cw6**	**OR**	**95%C.I.**	**p**	**OR**	**95%C.I.**	**p**
Spanish	176	382	1.61	1.23–2.13	1.63	1.23–2.15	2.56	1.68–3.92	+	1.86	1.34–2.57	0.213	1.87	1.34–2.60	0.247
									−	1.23	0.70–2.15		1.27	0.72–2.22	
Italian	450	450	1.30	1.08–1.59	1.28	1.06–1.54	2.50	1.86–3.36	+	1.25	0.87–1.81	0.875	1.14	0.80–1.62	0.544
									−	1.30	1.02–1.66		1.30	1.03–1.64	
Dutch	202	278	1.47	1.11–1.93	1.49	1.14–1.96	3.45	2.27–5.25	+	2.58	1.46–4.57	0.014	2.60	1.47–4.59	0.016
									−	1.15	0.83–1.59		1.17	0.84–1.63	

PSORS1 locus definition; in the Italian and Dutch samples direct HLA-Cw6 typing was available, and was analyzed using the carrier status definition for Cw6 allele. In the Spanish sample rs1062470 is used as a proxy for HLA-Cw6 by a dominant model of heritability for allele T (which is referred here as the positive group).

[&]for the epistasis analysis; logistic regression models were carried out which included an interaction term, (rs4112788 – HLA-Cw6* or *LCE3C_LCE3B-del* – HLA-Cw6*); p-values were derived from the log-likelihood ratio test between the model including both additive effects plus the interaction term (rs4112788/*LCE3C_LCE3B-del* –HLA-Cw6* + rs4112788 – HLA-Cw6*) against the model that only includes additive effects. OR indicate association of rs4112788/*LCE3C LCE3B-del* with psoriasis stratified by positive and negative HLA-Cw6 alleles. +, HLACw6 positive; and −, HLACw6 negative.