Deletion of the Late Cornified Envelope Genes *LCE3C* and *LCE3B* Is Associated with Psoriasis in a Chinese Population

Miaozhu Li[1,5], Yumei Wu[2], Guoliang Chen[3], Yifeng Yang[1,5], Daizhan Zhou[1,5], Zhou Zhang[1,5], Di Zhang[1,5], Yinwei Chen[2], Zhiyong Lu[2], Lin He[1,4,5], Jie Zheng[2] and Yun Liu[4]

A common deletion comprising *LCE3B* and *LCE3C*, members of the late cornified envelope (*LCE*) gene cluster, has been shown to be significantly associated with psoriasis in several Caucasian populations. The expression of *LCE* can be induced by skin barrier disruption, leading to psoriatic lesions. To identify whether deletion of genes in the *LCE* region is a genetic risk factor in the pathogenesis of psoriasis, we genotyped the *LCE3C* and *LCE3B* deletion and single-nucleotide polymorphism rs4112788, which is in strong linkage disequilibrium with the *LCE* gene cluster, via direct sequencing in 468 psoriasis patients and 768 controls in a Chinese population. We found that deletion of the two *LCE* genes was associated with psoriasis (odds ratio = 1.917; 95% confidence interval = 1.291–2.847, $P = 0.001$), a conclusion that was similar to that of another independent Chinese cohort study. The deletion was not significantly associated with the age of disease onset, and there was no significant epistatic interaction between deletion and *PSORS1* risk allele on 6p21.3. Our study confirms an association between the deletion of *LCE3C* and *LCE3B* and psoriasis in a Chinese population.

Journal of Investigative Dermatology (2011) **131,** 1639–1643; doi:10.1038/jid.2011.86; published online 21 April 2011

INTRODUCTION

Psoriasis vulgaris is a chronic inflammatory and hyperproliferative skin disease that affects ~2% of the world's population (Christophers, 2001). Generally regarded as an immunologically mediated disorder, it is characterized by vascular changes, abnormal keratinocyte proliferation and differentiation, and mixed infiltration of immunocompetent cells in the epidermis and dermis (Krueger and Bowcock, 2005). It is widely accepted that psoriasis is caused by a combination of environmental and genetic factors (Bowcock and Cookson, 2004). Genetic analyses have identified several psoriasis-susceptibility loci; the most strongly associated one (*PSORS1*) is within the major histocompatibility complex region, on chromosome 6p21 (Nair *et al.*, 2006).

Copy number variation is a major source of human genetic diversity (Redon *et al.*, 2006; Kidd *et al.*, 2008), and it has been associated with susceptibility or resistance to several diseases, particularly autoimmune and inflammatory disorders (Estivill and Armengol, 2007). Recent studies have focused on the deletion of two genes of the late cornified envelope (*LCE*) gene family, *LCE3B* and *LCE3C*, which are located in the epidermal differentiation complex. The *LCE* cluster encoding stratum corneum proteins has a wide range of expression in various epithelia, responds to different environmental conditions (Jackson *et al.*, 2005), and may perform a crucial role when the skin barrier functions as a physiological stimulus, leading to psoriatic lesions (de Cid *et al.*, 2009). The deletion of *LCE* genes was first identified as being significantly associated with psoriasis in individuals of western European descent (de Cid *et al.*, 2009). Expression data in the same study suggested that either carriers of the deletion had a compromised repair response or the absence of *LCE3C* and *LCE3B* genes induced an inappropriate repair response following barrier disruption, triggering compensation by the other *LCE* genes (de Cid *et al.*, 2009). This finding was replicated in a study of psoriasis patients in Germany (Huffmeier *et al.*, 2009a), although another study by one of the same authors found that the deletion did not contribute to psoriatic arthritis (Huffmeier *et al.*, 2009b). A study of Spanish subjects found no association of allele and genotype

[1]*Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, People's Republic of China;* [2]*Department of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, People's Republic of China;* [3]*Division of Dermatology, Huashan Hospital, Fudan University, Shanghai, People's Republic of China;* [4]*Institutes of Biomedical Sciences, Fudan University, Shanghai, People's Republic of China and* [5]*Bio-X Center, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Ministry of Education, Shanghai Jiao Tong University, Shanghai, People's Republic of China*

Correspondence: Jie Zheng, Department of Dermatology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200025, People's Republic of China.
E-mail: jie-zheng2001@126.com or
Yun Liu, Institutes of Biomedical Sciences, Fudan University, Shanghai, 303 Mingdao Building, 138 Yixueyuan Road, Shanghai 200032, People's Republic of China.
E-mail: superliuyun@gmail.com

Abbreviations: CI, confidence interval; CNV, copy number variant; LCE, *late cornified envelope;* LCE3C_3B-del, *deletion of* LCE3C *and* LCE3B *genes; LD, linkage disequilibrium; OR, odds ratio; SNP, single-nucleotide polymorphism*

Received 26 September 2010; revised 15 February 2011; accepted 22 February 2011; published online 21 April 2011

© 2011 The Society for Investigative Dermatology

frequencies with patients versus controls, but did confirm that homozygous *LCE3C_3B-del* (deletion of *LCE3C* and *LCE3B* genes) is a risk factor for developing psoriasis without psoriatic arthritis (Coto *et al*., 2010). Very recently, a meta-analysis confirmed an association between *LCE3C_LCE3B* deletion and psoriasis in several ethnic groups and detected its interaction with *HLA-Cw6* (Riveira-Munoz *et al*., 2011). Finally, a pleiotropic effect of *LCE3C_3B-del* was verified by ELISA as a susceptible genetic risk factor for rheumatoid arthritis in a Spanish population (Docampo *et al*., 2010), but the deletion was found not to be associated with atopic dermatitis in a cohort study of other Europeans (Bergboer *et al*., 2010). In addition, single-nucleotide polymorphisms (SNPs) in the vicinity of the deletion were shown to be associated with psoriasis in an independent Chinese population (Zhang *et al*., 2009).

Although psoriasis is found worldwide, the incidence in Western populations, at 2–5% (Cargill *et al*., 2007), is much higher than that in East Asian populations, in which the incidence is only 0.1–0.3% (Yip, 1984). Most of the reported studies have been in European populations; little has been published about the relationship between *LCE3C_3B-del* and psoriasis in Asian populations. We therefore aimed to use a case–control cohort to investigate whether *LCE* deletion contributes to susceptibility to psoriasis and assessed its potential epistatic interaction with *PSORS1* in the Chinese population. We also investigated the distribution of rs4112788, a SNP that is in strong linkage disequilibrium (LD) with the deletion.

RESULTS

We identified the *LCE* region using PCR amplification and direct sequencing to define the deletion break points and confirmed that in the Chinese study population there was also a deletion encompassing 32.2 kb (chr1: 150,822,167–150,854,364; hg18, build NCBI36), similar to the deletion region reported for psoriasis patients in European populations (de Cid *et al*., 2009).

Both *LCE3C_3B-del* and rs4112788 were in Hardy–Weinberg equilibrium in the control groups (the *P*-value of Hardy–Weinberg equilibrium is 0.46 and 0.65). Genotyping rates were 99.5% for the *LCE* copy number variant (CNV) and 98.4% for rs4112788.

We assessed the genetic effect of *LCE3C_3B-del* on psoriasis risk using regression analysis and found *LCE3C_3B-del* to be significantly associated with psoriasis, in both the dominant model (odds ratio (OR) = 1.917; 95% confidence interval (CI) = 1.291–2.847, $P = 0.001$) and the additive model (OR = 1.268; 95% CI = 1.045–1.538, $P = 0.016$) after adjusting for gender and age (Table 1).

When we examined the data for only patients with type I psoriasis with onset before 40 years of age, no significant differences in age at disease onset were observed among the three *LCE* genotypes. We compared the controls and patients who did not develop arthritis ($n = 457$). No significant change of OR was detected given that most (84.6%) of the patients in our study had psoriasis vulgaris.

There was a significant association of the SNP rs4112788 with psoriasis in both the dominant model (OR = 1.688; 95% CI = 1.150–2.478, $P = 0.007$) and the additive model (OR = 1.213; 95% CI = 1.004–1.466, $P = 0.045$), adjusting for gender and age (Table 1). The association for rs4112788 did not remain significant after correction for multiple testing. The LD between *LCE* CNV and rs4112788 was relatively high ($D' = 0.893$, $r^2 = 0.782$), yet lower than in a previous study in a Chinese population ($r^2 = 0.91$) (Riveira-Munoz *et al*., 2011).

We also tested the interaction between deletion of *LCE* genes and *PRORS1* in our sample. We chose rs1576 and rs1265078 as proxy markers for the *PSORS1* locus; both were in strong LD with *HLA-Cw6* as well (Asumalahti, 2002). These SNPs were closely related to psoriasis as expected (Supplementary Table S2 online); however, the *P*-value derived from the log-likelihood ratio test was 0.0856, showing no evidence of interaction between the *PSORS1* and *LCE3C-LCE3B-del* loci in our samples.

DISCUSSION

LCE3C_3B-del has previously been reported in case–control studies in several populations (de Cid *et al*., 2009; Coto *et al*., 2010; Riveira-Munoz *et al*., 2011), but most such studies have been based on European samples. The prevalence of psoriasis varies from 0.5 to 4.6% between countries and races

Table 1. Association of *LCE3C* CNV and rs4112788 with psoriasis in cases and controls

				Genotype distribution, *n* (%)			Additive model		Dominant model		Recessive model	
	Alleles	Subjects	Risk allele frequency (%)	NR/NR	NR/R	R/R	OR (95% CI)	P^1	OR (95% CI)	P^1	OR (95%CI)	P^1
LCE3C_3B-del	$D^2 > N$	Case	62.9	49 (10.6)	246 (53.0)	169 (36.4)	1.268	0.016	1.917	0.001	1.159	0.274
		Control	59.0	122 (16.0)	380 (49.9)	259 (34.0)	1.045–1.538		1.291–2.847		0.889–1.511	
rs4112788	$C^2 > T$	Case	63.7	52 (11.4)	228 (49.9)	177 (38.7)	1.213	0.045	1.688	0.007	1.085	0.543
		Control	59.9	124 (16.5)	355 (47.3)	272 (36.2)	1.004–1.466		1.150–2.478		0.834–1.413	

Abbreviations: CI, confidence interval; CNV, copy number variation; D, deletion; *LCE3C_3B-del*, deletion of *LCE3C* and *LCE3B* genes; N, nondeletion; NR, non-risk allele; OR, odds ratio; R, risk allele.
[1]Calculated *P*-values were adjusted for age and gender.
[2]Risk allele.

(Lebwohl, 2003). We defined the deletion break points of *LCE3C_3B-del* in a Chinese population and observed strong evidence for association between the deletion and psoriasis, in line with the studies in European populations (de Cid *et al.*, 2009; Huffmeier *et al.*, 2009a). The absence of *LCE3C* and *LCE3B* may trigger skin barrier function in epithelia and then induce expression of the other *LCE* genes in the cluster, thus affecting global transcription of the epidermal differentiation complex via *cis*-regulatory elements such as conserved noncoding elements (de Guzman Strong *et al.*, 2010). This then results in abnormal differentiation and hyperproliferation of epidermis, as previously reported (de Cid *et al.*, 2009). A previous study reported a negative association of LCE3C_3B-del between psoriatic arthritis and controls in individuals of German origin (Huffmeier *et al.*, 2009b), but because of the limited number of psoriatic arthritis patients in our study ($n=11$, 2.4%), we were unable to investigate a deletion-frequency difference between patients with psoriasis vulgaris and those with psoriatic arthritis.

The SNP rs4112788, which is in strong LD with *LCE3C_3B-del*, was also genotyped and its association was found to be in the same direction as that of the deletion, with a slightly lower significance. In contrast to the study in a German population (Huffmeier *et al.*, 2009b), a recent study found that rs4112788 was strongly associated with both psoriasis and psoriatic arthritis (Bowes *et al.*, 2010), but it did not genotype *LCE* CNV for technical reasons.

Because of the relatively strong LD between *LCE* CNV and rs4112788, we cannot rule out that rs4112788 might have a marginal possibility of capturing the association signal with psoriasis. However, considering that rs4112788 is a nonfunctional variant according to NCBI DCODE evolutionary conservation data, the deletion of *LCE3B* and *LCE3C* might be a more plausible candidate for the association detected here. Fine mapping of the region is needed to identify causal variation(s), and further functional studies would be required to confirm the mechanism underlying psoriasis predisposition.

One limitation of this investigation was the discrepancy of age and gender between our psoriasis patients and controls. Because of the difficulty of recruiting age- and gender-matched controls, we calculated the logistic regression analysis with gender and age as covariates to exclude their influence on the risk assessment. The association of *LCE3C_3B-del* and rs4112788 with psoriasis was significant in dominant and additive models with or without any adjustment; therefore, we could still conclude that deletion of the two *LCE* genes and rs4112788 are risk factors for psoriasis. The analysis results between cases and controls without any adjustment is shown in the Supplementary Material online (Supplementary Table S3).

The existence of potential epistasis of LCE3C_3B-del with HLA-Cw6 for psoriasis was found in Dutch and US (Michigan) samples (de Cid *et al.*, 2009), but not in the study's other subgroups. We also evaluated the relationship between *LCE3C_3B-del* and *PSORS1*; however, no significant epistatic effect was observed. Similarly, no interaction between *LCE3C_LCE3B* and *HLA_Cw06* was reported in a previous study in some Asian populations including Chinese (Riveira-Munoz *et al.*, 2011). It seems that there is no significant epistasis of the two loci in the Chinese population, and further work is needed to investigate whether the positive interaction is a population-specific effect or the product of methodological analysis.

In conclusion, this study confirms an association between the *LCE* region and psoriasis and, in an independent investigation of deletion of *LCE_LCE3B* and rs4112788 in a Chinese population, evidences their contributions to susceptibility to psoriasis. No significant differences in the epistatic interaction of deletion with *PSORS1* were detected. Similar studies, using large sample sizes, need to be extended to other ethnic populations.

MATERIALS AND METHODS

Study population

A total of 468 psoriasis patients (mean age 40.27 ± 15.70 years; 58.8% male) were recruited by dermatologists from Ruijing Hospital and Huashan Hospital in Shanghai. Additional clinical information, such as age and family history, was collected by questionnaire. The psoriasis was considered "early onset" if the condition appeared at $\leqslant 40$ years of age; the other patients were categorized as "late onset". Patient characteristics are shown in more detail in Table 2. As controls, 768 healthy individuals (mean age 52.00 ± 15.91 years; 41.3% male) without psoriasis were recruited from the same communities, thus representing the same geographic area and ethnic population. The study protocols were approved by the institutional review board of the ethics committee of the Shanghai Institute for Biological Sciences and conducted according to the Declaration of Helsinki Principles. Written informed consent was obtained from all subjects before enrollment. High-molecular-weight genomic DNA was prepared from venous blood using the QuickGene 610L Automatic DNA/RNA Extraction System (Fujifilm, Tokyo, Japan).

Table 2. Main characteristics of the 468 patients with psoriasis

Gender (male/female)	275 (58.8%)/193 (41.2%)
Mean age (years ± SD)	40.27 ± 15.70 (9–84)
Type of psoriasis	
Vulgaris	396 (84.6%)
Guttate	29 (6.2%)
Arthritis	11 (2.4%)
Erythroderma	9 (1.9%)
Other	23 (4.9%)
Affected relatives (familial psoriasis)	28 (17%)
Early-onset psoriasis[1]	315 (67.3%)
Mean age (years ± SD)	33.67 ± 12.81
Late-onset psoriasis[1]	153 (32.7%)
Mean age (years ± SD)	58.30 ± 9.03

[1]Early-onset psoriasis, age $\leqslant 40$ years; late-onset psoriasis, age > 40 years.

Genotyping

CNV genotyping. We genotyped the *LCE3C_3B-del* region using direct sequencing encompassing 32,198 bp (chr1: 150,822,167–150,854,364). To amplify the break-point-spanning PCR product of 419 bp, we used LCE3C_LCE3B-del primers in the presence of the deletion (Supplementary Table S1 online). The cycling conditions were 95 °C for 10 minutes, 40 cycles of three steps (95 °C for 30 seconds, 61 °C for 30 seconds, and 72 °C for 40 seconds), followed by 72 °C for 10 minutes, and 4 °C thereafter. The region of *LCE3B* and *LCE3C* was detected with LCE3C_LCE3B primers (Supplementary Table S1 online) to specifically amplify 207-bp product within the deletion region. The cycling conditions were 95 °C for 10 minutes, 35 cycles of three steps (95 °C for 30 seconds, 58 °C for 30 seconds, and 72 °C for 30 seconds), followed by 72 °C for 10 minutes, and 4 °C thereafter. Purified PCR products were then sequenced using a BigDye Terminator Cycle Sequencing Kit and ABI PRISM 3730XL DNA capillary sequencers (Applied Biosystems, Foster City, CA). The genotyping success rate did not differ significantly between cases and controls (98.9 and 99.7%, respectively). To estimate the error rate of genotyping, 150 control and patient samples were replicated and genotyped with 100% concordance.

SNP genotyping. The SNP rs4112788 (T/C) was genotyped using direct sequencing with SNP rs4112788 primers (Supplementary Table 1 online). The cycling conditions were 95 °C for 10 minutes, 35 cycles of three steps (95 °C for 30 seconds, 58 °C for 30 seconds, and 72 °C for 45 seconds), followed by 72 °C for 10 minutes, and 4 °C thereafter. Purified PCR products were analyzed on an ABI 3730xl DNA Analyzer (Applied Biosystems). Genotype data were obtained in 98.4% of the DNA samples. Forty randomly selected replicated samples were included and genotyped with 100% concordance.

The SNPs rs1576 (G/C) and rs1265078 (G/C) were genotyped using the TaqMan SNP genotyping assay on an ABI7900 system (Applied Biosystems). The standard 5-μl PCRs were carried out using TaqMan Universal PCR Master Mix reagent kits according to the manufacturer's guidelines. Genotype data were obtained in 99.8 and 99.6% of the samples for each SNP, respectively. Forty replicated quality control samples were included and genotyped with 100% concordance.

Statistical analysis

We used SHEsis (Shi and He, 2005) to perform the Hardy–Weinberg equilibrium tests and to compare the differences in allele and genotype frequencies between cases and controls, as well as to calculate LD coefficients (D' and r^2) in control individuals. We used the homozygote of the *LCE3C_3B* allele as a reference and 0, 1, and 2 copies of the *LCE3C_3B* allele. Logistic regression analysis was used to calculate ORs, 95% CI values, and corresponding *P*-values, with gender and age as covariates, assuming additive, dominant, and recessive models based on previous reports (de Cid *et al.*, 2009). In the additive model, homozygotes for the deleted allele (−/−), heterozygotes (−/+), and homozygotes for the nondeleted allele (+/+) were coded as an ordered categorical variable for the genotype (2, 1, and 0). The dominant model was defined as 1/1 + 1/0 versus 0/0 and the recessive model as 1/1 versus 1/0 + 0/0. The best genetic model was selected using the Akaike information criterion (AIC) value, and the lowest AIC value was considered the best-fitting model for the fitted variant. We used Bonferroni corrections for the multiple-testing corrections. All data management and statistical analysis were carried out using SPSS software (release 17.0; SPSS, Chicago, IL).

To test for interaction, we followed the methods described by Rafael de Cid *et al.* (2009), and we used the genotype-specific model to assess the epistasis effect. Potential interaction between *LCE3C_LCE3B-del* or rs4112788 and rs1576 or rs1265078 was evaluated with a log-likelihood ratio test between models, including only the additive effect against both additive effect and the full interaction terminology, and all models were adjusted by gender and age.

CONFICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank all the participants in this study. The work was supported by the 973 Program (2010CB529600 and 2007CB947300), the 863 Program (2006AA02A407 and 2009AA022701), the Shanghai Municipal Commission of Science and Technology Program (09DJ1400601), the National Key Project for Investigational New Drug 2008ZX09312-003, and the National Natural Science Foundation of China (nos. 909190492, 30972529, 30872278, and 30471562).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

REFERENCES

Asumalahti K (2002) Coding haplotype analysis supports *HCR* as the putative susceptibility gene for psoriasis at the MHC PSORS1 locus. *Hum Mol Genet* 11:589–97

Bergboer JG, Zeeuwen PL, Irvine AD *et al.* (2010) Deletion of late cornified envelope *3B* and *3C* genes is not associated with atopic dermatitis. *J Invest Dermatol* 130:2057–61

Bowcock AM, Cookson WO (2004) The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum Mol Genet* 13(Spec No 1):R43–55

Bowes J, Flynn E, Ho P *et al.* (2010) Variants in linkage disequilibrium with the late cornified envelope gene cluster deletion are associated with susceptibility to psoriatic arthritis. *Ann Rheum Dis* 69:2199–203

Cargill M, Schrodi SJ, Chang M *et al.* (2007) A large-scale genetic association study confirms *IL12B* and leads to the identification of *IL23R* as psoriasis-risk genes. *Am J Hum Genet* 80:273–90

Christophers E (2001) Psoriasis – epidemiology and clinical spectrum. *Clin Exp Dermatol* 26:314–20

Coto E, Santos Juanes J, Coto Segura P *et al.* (2010) Mutation analysis of the *LCE3B/LCE3C* genes in psoriasis. *BMC Med Genet* 11:45

de Cid R, Riveira-Munoz E, Zeeuwen PL *et al.* (2009) Deletion of the late cornified envelope *LCE3B* and *LCE3C* genes as a susceptibility factor for psoriasis. *Nat Genet* 41:211–5

de Guzman Strong C, Conlan S, Deming CB *et al.* (2010) A milieu of regulatory elements in the epidermal differentiation complex syntenic block: implications for atopic dermatitis and psoriasis. *Hum Mol Genet* 19:1453–60

Docampo E, Rabionet R, Riveira-Munoz E *et al.* (2010) Deletion of the late cornified envelope genes, *LCE3C* and *LCE3B*, is associated with rheumatoid arthritis. *Arthritis Rheum* 62:1246–51

Estivill X, Armengol L (2007) Copy number variants and common disorders: filling the gaps and exploring complexity in genome-wide association studies. *PLoS Genet* 3:1787–99

Huffmeier U, Bergboer JG, Becker T *et al.* (2009a) Replication of LCE3C-LCE3B CNV as a risk factor for psoriasis and analysis of interaction with other genetic risk factors. *J Invest Dermato* 130:979–84

Huffmeier U, Estivill X, Riveira-Munoz E *et al.* (2009b) Deletion of *LCE3C* and *LCE3B* genes at PSORS4 does not contribute to susceptibility to psoriatic arthritis in German patients. *Ann Rheum Dis* 69:876–8

Jackson B, Tilli CM, Hardman MJ *et al.* (2005) Late cornified envelope family in differentiating epithelia—response to calcium and ultraviolet irradiation. *J Invest Dermatol* 124:1062–70

Kidd JM, Cooper GM, Donahue WF *et al.* (2008) Mapping and sequencing of structural variation from eight human genomes. *Nature* 453:56–64

Krueger JG, Bowcock A (2005) Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis* 64(Suppl 2):ii30–6

Lebwohl M (2003) Psoriasis. *Lancet* 361:1197–204

Nair RP, Stuart PE, Nistor I *et al.* (2006) Sequence and haplotype analysis supports *HLA-C* as the psoriasis susceptibility 1 gene. *Am J Hum Genet* 78:827–51

Redon R, Ishikawa S, Fitch KR *et al.* (2006) Global variation in copy number in the human genome. *Nature* 444:444–54

Riveira-Munoz E, He SM, Escaramis G *et al.* (2011) Meta-analysis confirms the LCE3C_LCE3B deletion as a risk factor for psoriasis in several ethnic groups and finds interaction with HLA-Cw6. *J Invest Dermatol* 131:1105–9

Shi YY, He L (2005) SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res* 15:97–8

Yip SY (1984) The prevalence of psoriasis in the Mongoloid race. *J Am Acad Dermatol* 10:965–8

Zhang XJ, Huang W, Yang S; *et al.* (2009) Psoriasis genome-wide association study identifies susceptibility variants within *LCE* gene cluster at 1q21. *Nat Genet* 41:205–10