Koebner Phenomenon in Psoriasis Is Not Associated with Deletion of Late Cornified Envelope Genes *LCE3B* and *LCE3C*

Journal of Investigative Dermatology (2012) **132,** 475–476; doi:10.1038/jid.2011.336; published online 3 November 2011

TO THE EDITOR

The late cornified envelope (*LCE*) genes are a group of highly homologous genes located on chromosome 1 in the epidermal differentiation complex, which is a 1.6-Mb region on the human genome containing a large number of genes involved in epidermal differentiation. The epidermal differentiation complex contains a total of 18 *LCE* genes, divided over six groups (Jackson *et al.*, 2005). Two genes of the *LCE3* group, *LCE3B* and *LCE3C*, are subject to copy number variation caused by a commonly deleted segment of 32 kb (de Cid *et al.*, 2009). Individuals can have copy number 0 (homozygous for the deletion), 1 (heterozygous for the deletion), or 2 (homozygous for the wild-type ancestral haplotype). Deletion of *LCE3B* and *LCE3C* (*LCE3C_LCE3B*-del) is a strong and widely replicated risk factor for psoriasis (de Cid *et al.*, 2009; Zhang *et al.*, 2009; Huffmeier *et al.*, 2010; Riveira-Munoz *et al.*, 2011). Recent studies indicate that *LCE3C_LCE3B*-del may also be a risk factor for other (auto) immune diseases (Docampo *et al.*, 2010, 2011; Lu *et al.*, 2011), but it is not associated with atopic dermatitis (Bergboer *et al.*, 2010). LCE proteins are expressed in a limited number of epithelia (Marshall *et al.*, 2001; Jackson *et al.*, 2005) and we have recently shown that the genes of the *LCE3* group, including the psoriasis-associated *LCE3B* and *LCE3C* genes, show distinct expression patterns under inflammatory conditions or upon skin injury (de Cid *et al.*, 2009; Bergboer *et al.*, 2011). Out of all the identified psoriasis-associated risk factors, only *LCE3C_LCE3B*-del and copy number variation in the beta-defensin cluster (Hollox *et al.*, 2008) affect expression of putative skin barrier proteins. Although the observed odds ratios (ORs) in various cohorts are smaller than those published for *HLA-Cw6* (current notation *HLA-C*06*) (Liu *et al.*, 2008; Nair *et al.*, 2009), the strongest known psoriasis risk factor, *LCE3C_LCE3B*-del, has a large population-attributable risk (23%; de Cid *et al.*, 2009). Both the significant contribution to the genetic basis of psoriasis and its plausible biological function render *LCE3C_LCE3B*-del an important risk factor that is amenable to mechanistic studies.

In 1877, Heinrich Koebner described the appearance of psoriatic lesions in the uninvolved skin of psoriatic patients as a consequence of trauma. Now, it is known that patients with other dermatological conditions can koebnerize as well (Weiss *et al.*, 2002). Several causes for this phenomenon are known, such as trauma, allergic or drug reactions, and therapeutics, although the pathogenesis is not well understood (Weiss *et al.*, 2002). In previous studies it was shown that on an average 25% of psoriasis patients will koebnerize on external stimulation of the skin (Weiss *et al.*, 2002). We hypothesized that the deletion of the *LCE3B* and *LCE3C* genes could lead to an inferior barrier function or to an impaired repair function following barrier disruption. This would make the skin more susceptible to penetration by microbial or other environmental molecules, which could trigger innate or adaptive immune responses. On the basis of our hypothesis that the Koebner reaction may be caused by breaching the skin barrier and/or insufficient barrier repair, we investigated a possible association of the Koebner phenomenon with *LCE3C_LCE3B*-del. In a Dutch cohort of psoriasis patients who were previously typed for *LCE3C_LCE3B*-del (by PCR; de Cid *et al.*, 2009) and *HLA-C*06:02* status (by PCR; de Cid *et al.*, 2009), we assessed their propensity to koebnerize following skin injury. The ''Commissie mensgebonden onderzoek Arnhem-Nijmegen'' approved this study. Patients/parents of the patients gave their informed consent. The investigations were carried out according to the Declaration of Helsinki principles. Adult patients were approached via written questionnaires. In the case of juvenile psoriasis patients we approached the parents by telephone. Both the patients/parents and the interviewers were unaware of the *LCE3C_LCE3B*-del and *HLA-C*06* status of the patients. We assessed, on a 4-point scale, how often a psoriasis plaque appeared after skin damage of their non-involved skin: never, rarely, often, or very common. The individuals who responded with ''often'' or ''very common'' were considered as Koebner-positive patients and the others as Koebner-negative patients. We approached 259 patients, of whom 192 responded (response rate 74%). Of these, 46 patients (24%) were Koebner positive. This percentage is in line with the previously reported data (Weiss *et al.*, 2002). We found similar figures for adults (22%, $n=24$) and children (27%, $n=22$). Table 1 shows an equal distribution over the three *LCE3B/C* genotypes for the Koebner-positive and -negative groups. Logistic regression analysis demonstrates that there is no association between *LCE3C_LCE3B*-del and the Koebner phenomenon in psoriasis patients ($P=0.835$, OR 1.06, 95% confidence interval (CI): 0.64–1.74). In addition, for *HLA-C*06* we did not observe an association with the Koebner phenomenon ($P=0.310$, OR 1.43, 95% CI: 0.72–2.82). This is in contrast with a previously reported association between Koebner effect and *HLA-C*06* in Icelandic psoriasis patients (Gudjonsson

Abbreviations: CI, confidence interval; LCE, late cornified envelope; LCE3C_LCE3B-*del, deletion of the* LCE3B *and* LCE3C *genes; OR, odds ratio*

Table 1. No association between *LCE3B/C* copy number and koebnerization in psoriasis patients

LCE3B/C copy number	Genotype	Koebner positive	Koebner negative	*P*	OR (95% CI)
0	del/del	20 (43%)	66 (45%)	0.835	1.06 (0.64–1.74)
1	del/wt	21 (46%)	65 (45%)		
2	wt/wt	5 (11%)	15 (10%)		

Abbreviations: CI, confidence interval; del, deletion; OR, odds ratio; wt, wild type.

et al., 2002). This discrepancy may have several causes, such as the study design (family-based vs. population-based), ethnic background, inaccurate reporting because of self-reported data, or the lower statistical power of our study (66%, input values were derived from Gudjonsson *et al.* (2002); significance level 0.05, OR 2.3, allele frequency 0.28, dominant model).

Our results suggest that the Koebner phenomenon in psoriasis is unlikely to be dependent on the *LCE3B/C* genotype. Therefore, the biological role of *LCE3B* and *LCE3C* deletion in development and/or maintenance of psoriasis remains to be explained.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We would like to thank all the patients who participated in this study.

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Decrease of Ceramides with Very Long–Chain Fatty Acids and Downregulation of Elongases in a Murine Atopic Dermatitis Model

Journal of Investigative Dermatology (2012) **132,** 476–479; doi:10.1038/jid.2011.333; published online 8 December 2011

TO THE EDITOR

Ceramide is a family of lipid molecules composed of a sphingoid base and a fatty acid (FA) (Masukawa *et al.*, 2008). Ceramide constitutes a major lipid component of cutaneous permeability barrier, accounting for ~50% of the epidermal membrane structure (Mizutani *et al.*, 2009). Accordingly, the alteration of ceramide in the dermatoses with barrier dysfunction has been a subject of intensive research

Abbreviations: AD, atopic dermatitis; CBF, cutaneous barrier function; FA, fatty acid; OXZ, 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one; SC, stratum corneum; TEWL, trans-epidermal water loss