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REVIEW

Association of the Late Cornified Envelope-3 Genes with Psoriasis and Psoriatic Arthritis: A Systematic Review

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ABSTRACT

Psoriasis (Ps) and psoriatic arthritis (PsA) are genetically complex diseases with strong genetic evidence. Recently, susceptibility genes for Ps and PsA have been identified within the late cornified envelop (*LCE*) gene cluster, especially the cluster 3 (*LCE3*) genes. It is noteworthy that the deletion of *LCE3B* and *LCE3C* (*LCE3C_LCE3B-del*) is significantly associated with these two diseases. Gene-gene interactions between *LCE3* genes and other genes are associated with Ps and PsA. *LCE3* genes also have pleiotropic effect on some autoimmune diseases, such as rheumatoid arthritis, atopic dermatitis and systemic lupus erythematosus. Further studies need to focus on the potential function of *LCE3* genes in the pathogenesis of Ps and PsA in the future.

KEYWORDS: *LCE3* genes; Psoriasis; Psoriatic arthritis; Systematic review

INTRODUCTION

Psoriasis (Ps) is a chronic inflammatory skin disease characterized by epidermal hyperproliferation, altered keratinocyte differentiation, and inflammation (Lowes et al., 2007). The prevalence of Ps in children and adult ranges from 0% to 2.1% and 0.91% to 8.5%, respectively (Parisi et al., 2013). About 30% of patients with Ps develop psoriatic arthritis (PsA), which is a chronic inflammatory arthropathy disease accompanied with psoriatic skin and nail lesions (Helliwell and Taylor, 2005). Ps and PsA are common skin diseases with strong genetic evidence (Chandran, 2013). Since 2008, our understanding of the genetic basis of Ps and PsA has been rapidly advanced mostly through genome-wide association studies (GWASs), which have identified numerous susceptibility genes or loci for these two diseases (Duffin et al., 2008; Chandran, 2013). The psoriasis susceptibility 4 (PSORS4) lies within the region of the epidermal differentiation complex (EDC), and this particular area is of special interest for Ps because it comprises a group of genes expressed in the upper strata of the epidermis (Capon et al., 2001). EDC includes gene clusters such as the late cornified envelop (*LCE*) genes which encode the stratum corneum proteins of the cornified envelope and have potential functions in epidermal terminal differentiation (Liu et al., 2008). The *LCE* cluster 3 (*LCE3*) genes have been reported to play important roles in the development of Ps and PsA. Many studies mainly focuse on the association of *LCE3* genes with these two diseases.

STRUCTURE, EXPRESSION, AND FUNCTION OF THE *LCE3* GENES

LCE gene cluster spans over 320 kb within EDC on chromosome 1q21.3. The *LCE* cluster contains multiple conserved

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genes that encode stratum corneum proteins, and these genes are expressed relatively late during fetal assembly of the skin cornified envelope (Marshall et al., 2001). The cluster is divided into six groups (*LCE1*, *LCE2*, *LCE3*, *LCE4*, *LCE5*, and *LCE6*) based on the chromosomal position and protein homology. *LCE1*, *LCE2*, and *LCE3* subclusters are scattered with three individual *LCE* genes (*LCE4A, LCE5A* and *LCE6A*), four *LCE* pseudogenes and several non-*LCE* genes (Jackson et al., 2005) (Fig. 1). *LCE3* cluster encompasses five genes (*LCE3A*, *LCE3B*, *LCE3C*, *LCE3D*, and *LCE3E*) with special structure (Fig. 1) and different functions (Table 1).

ASSOCIATION BETWEEN *LCE3* GENES AND PS/PSA

The allele frequencies of different SNPs within *LCE3* genes are significantly different between Ps/PsA patients and controls. In addition, gene expression studies indicated that *LCE3* genes showed highly differential expression between Ps lesions and healthy skin samples (Jackson et al., 2005; Bergboer et al., 2011; de Koning et al., 2012).

LCE3A

For *LCE3A*, a GWAS in Chinese Han population identified SNPs rs4845454 and rs1886734 associated with Ps at genome-wide significance level, indicating that *LCE3A* may be one of the susceptibility genes to Ps (Zhang et al., 2009). The effect of experimental skin barrier disruption on the expression of the cornified envelope structural proteins and keratinocyte differentiation-regulating proteins were investigated and the results showed that *LCE5A*, *LCE2B*, filaggrin (*FLG*), filaggrin family member 2 (*FLG2*), and loricrin (*LOR*) were significantly downregulated. Conversely, involucrin (*IVL*), *SPRR1*, *SPRR2*, hornerin (*HRNR*) and *LCE3A* were upregulated. Interestingly, there is no significant difference between normal epidermis and non-lesional skin of patients with Ps (de Koning

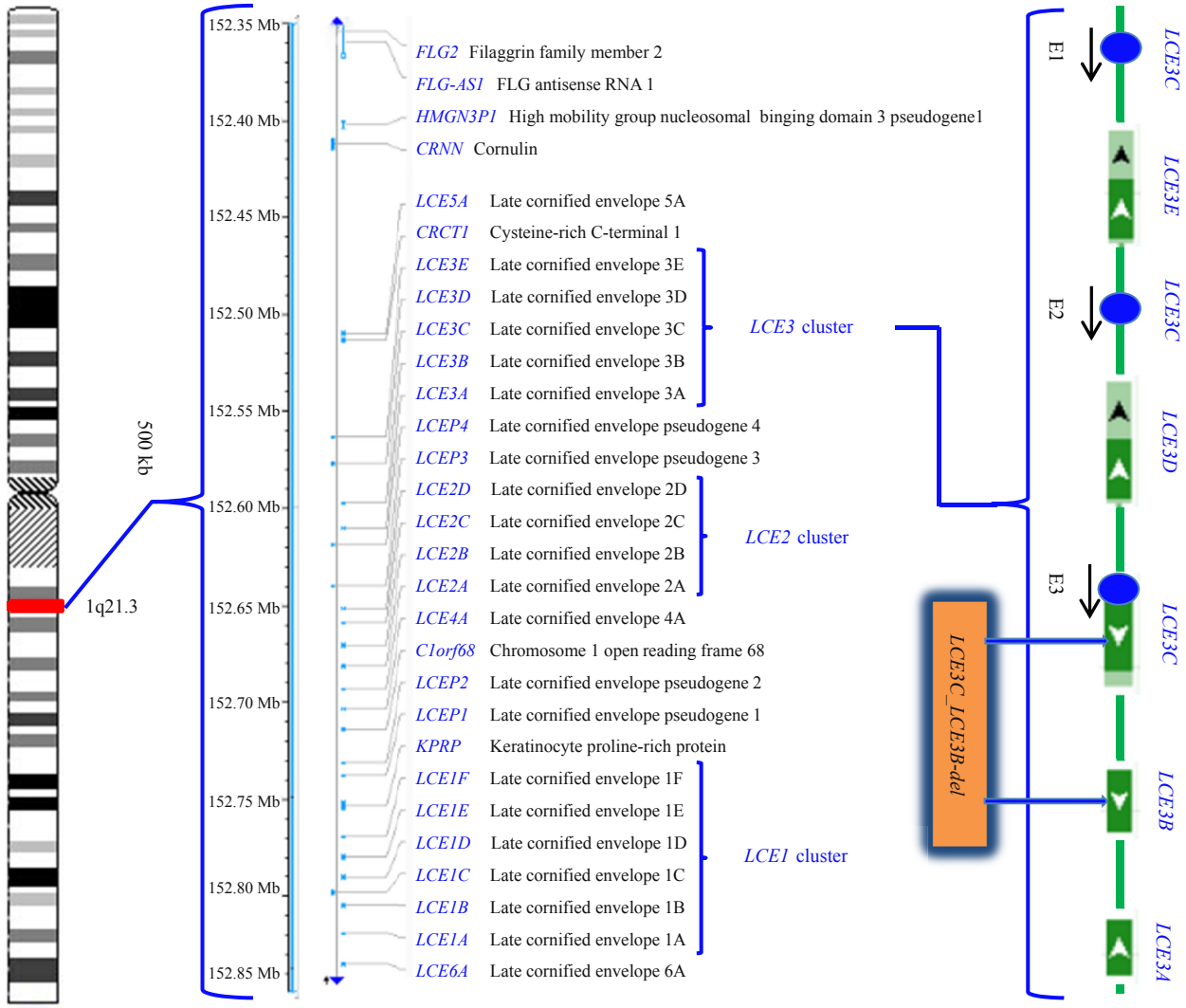

Fig. 1. The structure of late cornified envelope (*LCE*) gene cluster and *LCE3* genes.
The *LCE* gene cluster is located in a region called the epidermal differentiation complex (EDC) on chromosome 1q21.3. The *LCE* gene family is divided into six groups (*LCE1−6*). For the *LCE3* genes, boxes show exon−intron structures and arrows indicate the direction of transcription. E1, E2, and E3 correspond to the three exons of *LCE3C* (Jackson et al., 2005). The *LCE3C_LCE3B-del* removes the *LCE3B* and *LCE3C* genes from the *LCE3* cluster (Austin et al., 2014).