Variant Analysis of CARD14 in a Chinese Han Population with Psoriasis Vulgaris and Generalized Pustular Psoriasis

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TO THE EDITOR

Psoriasis is a common, chronic, inflammatory, organ-specific autoimmune skin disease with a complex genetic background (Nestle et al., 2009; Zhang et al., 2013). Psoriasis vulgaris (PsV) is the most common type, accounting for approximately 85–90% of all psoriasis patients, and characterized by raised, well-demarcated, erythematosus oval plaques with adherent silvery scales (Nestle et al., 2009). Generalized pustular psoriasis (GPP) is the least prevalent form of psoriasis and is considered to be a potentially life-threatening, multi-systemic disease (Körber et al., 2013), characterized by the sudden eruption of generalized sterile pustules in a wave-like manner (Mengesha and Bennett, 2002).

Genetic factors have been shown to have a critical role in the pathogenesis of psoriasis, and several genes and genomic regions have been reported associated with some clinical forms of this disease (http://omim.org/), including the gene for caspase recruitment domain family member 14 (CARD14), which has been identified by fine-mapping of psoriasis susceptibility locus 2 (PSORS2) in European and Taiwanese patients (Hwu et al., 2005; Jordan et al., 2012a). To date, 23 variants have been reported in the CARD14 gene (Supplementary Table S3 online), mainly in patients with PsV (Jordan et al., 2012a; 2012b; Körber et al., 2013). However, most studies of CARD14 have been carried out in European populations, and studies in Chinese patients are rare.

We performed direct DNA sequencing in 236 psoriasis patients (174 PsV and 62 GPP patients) and 365 controls to investigate the prevalence of CARD14 variants in the Chinese Han population. We also compared CARD14 variants between patients with GPP and PsV and between pediatric- and late-onset PsV.

A total of four new, rare heterozygous missense variants (allele frequency <1%) were found in the CARD14 exon, all with frequencies of 0.2% in psoriasis patients: p.Met19Val (c.355A>G) and p.Arg166His (c.497G>A) were only seen in GPP with PsV patients, and p.Ala216Thr (c.646G>A) and p.Thr591Met (c.1772C>T) (rs200102454) were only seen in PsV patients. We predicted the effects of the four variants on protein function using the Sorting Intolerant From Tolerant (SIFT) tool (http://sift.bii.a-star.edu.sg). Only p.Thr591Met was predicted to have damaging effects (score = 0.03), whereas the other three were predicted to be tolerated (Supplementary Table S4 and Supplementary Figure S1 online).

An additional known rare heterozygous variant p.Asp176His (c.526G>C) (rs144475004), was detected with frequencies of 1.9% in psoriasis patients and 1.8% in controls. Three common single-nucleotide polymorphisms (SNPs), rs2066964, rs34367357, and rs11652075, were also detected in our samples, with frequencies of 44.1 vs. 7.4 vs. 44.3% in psoriasis patients and 46.0 vs. 5.6 vs. 48.2% in controls, respectively. There were no differences between the groups in terms of the four variants (Supplementary Table S5 and Supplementary Figure S1 online).

CARD14 is located within PSORS2 and encodes a nuclear factor (NF)-κB activator. Variants in CARD14 have recently been detected in association with psoriasis, mostly in patients with PsV (Jordan et al., 2012b). Particular rare variants within CARD14 could lead to psoriasis by upregulating psoriasis-associated genes in keratinocytes (Jordan et al., 2012a).

The present study identified five rare variants that, in combination, were more common in psoriasis patients...
compared with controls. Regarding the predicted effects of these rare variants on protein function, p.Thr591Met and p.Arg682Trp were predicted to be damaging, possibly by regulating the activation of NF-κB, leading to inflammation and epidermal hyperplasia. The other variants were not predicted to be damaging, and their functions remain unknown.

GPP is considered to differ from PsV in terms of its etiology, especially regarding variants in the IL36RN gene (Körber et al., 2013; Li et al., 2013; Sugiura et al., 2013). In our study, variants within CARD14 significantly associated with GPP, compared with controls. However, we failed to find any difference between GPP and PsV, which might be attributed to the insufficient sample size. To elucidate whether the gene CARD14 is a specific susceptibility gene for PsV or GPP, further study with a large sample size is needed.

Different genes have been reported to be responsible for diseases with different onset ages (Swanbeck et al., 1995; Cheng et al., 2014). In conclusion, we performed an association analysis in patients with early-onset psoriasis (onset age <40 years) and identified significant associations with the SNP rs4649203, rs2303138 in IL28A, and rs303138 in IL12B. The rs4649203 and rs2303138 in IL28A and IL12B genes were significantly associated with early-onset psoriasis in patients with a childhood-onset age of <15 years. Different variants have been reported to be associated with early-onset and late-onset psoriasis. However, our study failed to distinguish between pediatric-onset psoriasis and late-onset psoriasis, and further study with a large sample size is needed.

In conclusion, we performed an association analysis between CARD14 variants and psoriasis in a Chinese Han population. The results suggest that rare CARD14 variants may have an important role in the pathogenesis of GPP.

Table 1. Analysis of five rare CARD14 variants using Fisher’s exact test

| Allele | p.Met119Val | p.Arg166His | p.Ala216Thr | p.Thr591Met | p.Arg682Trp |
|--------|-------------|-------------|-------------|-------------|-------------|
| AA     | 94          | 80          | 174         | 61          | 235         |
| Aa     | 0           | 0           | 0           | 1           | 1           |
| aa     | 0           | 0           | 0           | 0           | 0           |
| Allele frequency (a) | 0.393 (0.561) | 0.263 (0.438) | 0.145 (0.29) | 0.145 (0.29) | 0.145 (0.29) |
| P (Psoriasis versus control) | 0.393 (0.561) | 0.263 (0.438) | 0.145 (0.29) | 0.145 (0.29) | 0.145 (0.29) |
| P (PsV versus GPP) | 0.263 (0.438) | 0.322 (0.998) | 1 (1) | 1 (1) | 0.263 (0.438) |
| P (GPP versus control) | 0.322 (0.998) | 1 (1) | 0.322 (0.998) | 1 (1) | 0.322 (0.998) |
| P (P-PsV versus L-PsV) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) |
| Abbreviations: GPP, generalized pustular psoriasis; L-PsV, late-onset psoriasis vulgaris; P-PsV, pediatric-onset psoriasis vulgaris; PsV, psoriasis vulgaris (including P-PsV and L-PsV); Ps, psoriasis (including PsV and GPP). In the table, there are two types of P-values—nominal and corrected, of which the latter are in parentheses, calculated by false-discovery rate.
TO THE EDITOR

Effective therapies for melanoma are limited despite the fact that the incidence is increasing at a greater rate than that of any other cancers (Chen et al., 1996). Identification of key molecules regulating growth, progression, and metastasis in melanoma is essential to provide novel therapeutic strategies. We previously developed RET-transgenic mice of line 304/B6 carrying oncogenic RET (RFP/RET) under regulation of the metallothionein-I promoter (RET-mice), in which skin melanoma develops spontaneously (Kato et al., 1998). As melanoma in RET-mice histopathologically resembles human melanoma, RET-mice have been used worldwide as a standard model for melanoma (Kato et al., 1998; Kumasaka et al., 2010).

The Espin gene encodes an actin filament–binding protein (Bartles et al., 1996; Sekerková et al., 2006). Espin affects the actin cytoskeleton, resulting in a special association with microvillar specializations of sensory cells (Sekerková et al., 2004). Our recent study showed that Espin expressed in melanoma cells in mice and humans affects metastasis through the regulation of invasion via lamellipodia formation (Yanagishita et al., 2014). That was the first report showing a correlation between Espin and cancer cells. However, there has been no study showing whether Espin regulates the proliferation of cancer cells. In this study, we examined the effect of Espin on anchorage-dependent and -independent growth of melanoma cells.

Anti-Espin rabbit polyclonal antibody (Yanagishita et al., 2014), murine