Deletion of LCE3C and LCE3B genes at PSORS4 does not contribute to susceptibility to psoriatic arthritis in German patients

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ABSTRACT

Introduction Psoriasis susceptibility locus 4 (PSORS4) is a susceptibility locus for psoriasis vulgaris (PsV), a common inflammatory, hyperproliferative skin disorder. Recently, a deletion of 2 late cornified envelope (LCE) genes within epidermal differentiation complex on chromosome 1 was shown to be enriched in 1426 patients with PsV, suggesting compromised barrier function in deletion carriers. This genetic association was subsequently confirmed in a German cohort.

Methods In order to investigate whether this variant also predisposes to psoriatic arthritis (PsA), this deletion and 3 single nucleotide polymorphisms (SNPs) in strong linkage disequilibrium with it were genotyped in a case-control cohort of 650 patients and 937 control individuals of German origin.

Results LCE deletion frequency did not significantly differ between patients with PsA and controls (65.0% vs 65.5%). Similarly, no evidence for association to the three SNPs was observed.

Discussion This is the first non-human leucocyte antigen (HLA) risk factor predisposing only to skin type of psoriasis, supporting the concept of partially overlapping antigen risk factor predisposing only to skin type of psoriasis. While several genes at PSORS4 (for example, LOR, LCE1C, PGLYRP, SPRR genes, PRR9 genes and IVL) have been proposed to account for psoriasis susceptibility, very recently, a copy number variation (CNV) within the late cornified envelope (LCE) gene cluster was identified by a genome-wide scan using pooled DNAs. The deletion of 2 late cornified envelope genes (LCE3C and LCE3B) was shown to be enriched in 1426 patients with psoriasis and to be associated in a large family-based cohort. The results of the same study suggested that carriers of the deletion have a compromised repair response after barrier disruption in the skin.

In the present work, we were interested in investigating whether the LCE deletion also contributes to susceptibility to PsA.

METHODS

We analysed a large case-control study comprising 650 patients with PsA, a subset of the 748 patients previously described. For this subset high-quality DNA from Qiagen column purification was available (Qiagen, Hilden, Germany). All 650 patients fulfilled the recently defined CASPAR (for ‘Classification of Psoriatic Arthritis’) criteria and were recruited by board certified rheumatologists. In comparison to the previously described, larger cohort, clinical characteristics were very similar: the mean (SD) age of onset for PsV was 28.2±13.0 years; 61.9% of the patients were men. For 78% of the patients, the diagnosis of PsA was made ≥3 years before recruitment and 96% of patients had a skin involvement ≥3 years before recruitment. Peripheral joint involvement was detectable in the majority of cases (619 or 95.2%); this was oligoarticular in 141 patients and polyarticular in 474 (21.7% and 72.9% of the entire cohort, respectively). Diagnosis of spinal involvement was based on symptoms of inflammatory back pain, characteristic clinical signs of restricted vertebral movement and/or sacroiliac pain upon physical examination, and a subsequent confirmation by radiographic signs of either sacroiliitis and/or spondylitis. Spinal involvement was observed in 132 patients, accounting for 20.3% of the PsA cohort. In these patients, sacroiliitis or spondylitis or both were partly associated with concomitant peripheral joint disease. The 937 control individuals were the same as previously reported.

We genotyped the CNV with a modified protocol from that used by Cid et al, and this loci is of special interest for PsV since it comprises the epidermal differentiation complex (EDC), a group of genes expressed in the upper strata of the epidermis. While several genes at PSORS4 (for example, LOR, LCE1C, PGLYRP, SPRR genes, PRR9 genes and IVL) have been proposed to account for psoriasis susceptibility, very recently, a copy number variation (CNV) within the late cornified envelope (LCE) gene cluster was identified by a genome-wide scan using pooled DNAs. The deletion of 2 late cornified envelope genes (LCE3C and LCE3B) was shown to be enriched in 1426 patients with psoriasis and to be associated in a large family-based cohort. The results of the same study suggested that carriers of the deletion have a compromised repair response after barrier disruption in the skin.

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results and discussion

For all variants, Hardy–Weinberg equilibrium was fulfilled in both groups of patients and control individuals. Genotyping rates of LCE3C-LCE3B-del, rs10888502, rs4112788 and rs4845456 were between 94.1% and 96.4%. Almost all variants were in perfect LD with each other, except for LD between the CNV and rs10888502. We observed similar allele frequencies for all variants in patients and control individuals; differences were not significant as determined by χ² statistics (table 1). Similar results were obtained for haplotypes that were calculated using Haplovew20 (data not shown).

A power analysis revealed that we have 95% power to detect a risk factor with an allele frequency of 68% to 72% and an OR of 1.37 to 1.38 in our case-control cohort under the assumption of an identical allele frequency range. The lack of association is most probably not due to the geographical origin of the patients, as we identified highly significant association to the deletion in an independent study of patients with PsV without joint manifestation retrieved from the same population (Germany)22 similar in magnitude to that recently reported.19 Likewise, we did not observe evidence for association in the subset of 502 patients with PsA with manifestation ≤40 years of age (type I psoriasis) and average age of onset in the subset was comparable to the one of the above mentioned PsV cohort (24.0±9.5 and 23.2±11.9, respectively). Finally, no evidence for association was observed in subgroups of carriers or non-carriers of the PSORS1 risk allele.

Given the almost identical allele frequencies between both groups, it is highly unlikely, that the genotyping error determined can account for the lack of association. Our results suggest that the LCE3C-LCE3B-del, primarily identified in patients with skin type psoriasis, does not predispose to joint manifestation at least in German patients. Therefore this susceptibility factor is more specific to the skin manifestation than most of the risk factors for psoriasis identified, to date. Accordingly, our finding is also experimental support for the concept that besides common genetic factors, also clearly distinct ones contribute to the aetiology of distinguishable clinical manifestations such as psoriasis of skin and joints.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethical committees of the University of Erlangen-Nuremberg and of the University of Münster, Germany.

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