INVESTIGATIVE REPORT

Intra-familial Variation in Clinical Phenotype of CARD14-related Psoriasis

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Psoriasis is a multifactorial chronic inflammatory disease. Monogenic psoriasis has been described recently, including dominantly inherited plaque and generalized pustular types, related to activating mutations in the CARD14 gene. We describe here a family with CARD14-related psoriasis, exhibiting an extreme variability of clinical presentation (from mild plaque-type to generalized pustular psoriasis) and early disease onset. The affected family members harboured the c.349G>A [p.Gly117Ser] mutation in CARD14, which has not previously been linked to pustular psoriatic phenotype. Furthermore, most severely affected individuals carried 3 additional CARD14 coding region polymorphisms (rs2066964, rs34367357 and rs11652075), suggesting their possible effect on disease expression. Early-onset psoriasis co-segregated with the HLA-C*0602, indicating that HLA-C*0602 could potentially modulate the time of disease onset. In summary, this paper describes a family with CARD14-related psoriasis and discusses the possible influence of the specific haplotypes on intra-familial variation in the clinical phenotype of the disease. Key words: familial; psoriasis; CARD14 gene.

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Recently, monogenic forms of psoriasis have been described, including dominantly inherited plaque-type and generalized pustular psoriasis, related to activating mutations in the CARD14 gene (5). Furthermore, psoriasis-related phenotypes of recessive inheritance have been linked to mutations in IL36RN and IL1RN genes (6, 7).

We describe here a family with multiple cases of presumably dominantly inherited psoriasis, exhibiting an extreme variability of clinical presentation (from mild plaque-type to generalized pustular psoriasis) and early disease onset. The aim of the study was to analyse relevant candidate genes (CARD14, IL36RN and IL1RN), previously reported to be associated with psoriasis/generalized pustular eruption of Mendelian transmission, in the affected family members and to propose possible mechanisms for the intra-familial phenotype variability.

METHODS

We ascertained a non-consanguineous Jewish family of Yeminite-Ashkenazi origin, including parents and their 4 children. Candidate gene sequencing of the exons, exon intron junctions, 5’ untranslated regions (UTRs) and 3’ UTRs of the CARD14, IL36RN and IL1RN genes was initially performed on genomic DNA of the most severely affected individual (IV-1). Mutation was found only in CARD14 and, therefore, subsequently, other family members were screened for the CARD14 c.349G>A [p.Gly117Ser] mutation and the 3 coding region polymorphisms found in IV-1, including (c.1641G>C [p.Arg547Ser], c.1753G>A [Val585Ile] and c.2458C>T [p.Arg820Trp]). HLA-C allele analysis was performed to all 6 individuals examined. (For details see Appendix S1 and Table S1).

RESULTS

Clinical features

The investigated kindred included 2 parents (1 with psoriasis), and 4 siblings (3 with psoriasis) (Fig. 1). The father, patient III-2, had mild and stable plaque-type psoriasis involving the knees and elbows.  

1http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2405
The most severely affected patients were siblings IV-1 and IV-3. Patient IV-1 presented at the age of 5 months with extensive plaque-type psoriasis (up to erythroderma). His sister, patient IV-3 presented at the age of 8 years with mild plaque-type disease that followed upper respiratory tract infection, but 1 month later she developed generalized pustular psoriasis with protracted clinical course. (For details see Table SII). The youngest sibling, patient IV-4, was diagnosed with mild plaque-type psoriasis on his knees for the first time during this study, at the age of 5 years.

**Candidate gene analysis**

Family tree analysis suggested autosomal dominant inheritance with incomplete penetrance and variable expressivity. Sequencing of the CARD14 gene revealed patients III-2, IV-2, IV-3 and IV-4, and IV-1 to harbour the c.349G>A [p.Gly117Ser] mutation as well as 3 additional coding region polymorphisms (Fig. S1). The coding regions of IL36RN and IL1RN genes were also screened for mutations, and were found negative.

**HLA-C analysis**

Since early-onset and severe psoriasis have been reported to be associated with HLA C*0602 (Cw6) (8–10), HLA-C typing was performed (Fig. S1). Patients III-2, IV-1, IV-3, IV-4 were positive for a single HLA-C*0602 allele.

**DISCUSSION**

The protein product of the CARD14 gene has been shown to activate nuclear factor kappa B (NF-kB) signalling pathway in the epidermis (11, 12).

Activating mutations in CARD14 have been associated with plaque-type and pustular psoriasis (5); however, the particular c.349G>A [p.Gly117Ser] mutation has not previously been linked to pustular psoriatic phenotype. The aforementioned mutation has been studied extensively in a large family of European ancestry, and has been associated with plaque-type psoriasis accompanied by psoriatic arthritis in 30% of cases. Great variability in disease severity and age of onset was observed among the family members (5).

In the family described here no cases with psoriatic arthritis were identified, possibly reflecting the small number of patients examined.

Remarkably, in our family, pustular phenotype was observed for the first time in a patient harbouring the c.349G>A [p.Gly117Ser] mutation (patient VI-3). Thus, plaque-type and pustular psoriasis could represent the clinical spectrum of the CARD14-related disease, probably reflecting the combined effect of an individual mutation, genetic background and/or environmental factors. Case IV-2, the 14-year-old girl carrying the aforementioned mutation, was healthy, suggesting incomplete penetrance of the disease or its possible delayed onset. Both have been previously reported in patients with CARD14 mutations (5, 13). The absence of disease in this girl might be related to: (i) the fact that she does not carry maternally inherited CARD14 haplotype shared by all the other affected individuals on the second allele of this gene, or (ii) the fact that she does not have HLA-C*0602 or (iii) both.

In our case, beside the c.349G>A [p.Gly117Ser] mutation, 3 additional coding region polymorphisms (rs2066964 [c.1641G>C; p.Arg547Ser], rs34367357 [c.1753G>A; p.Val585Ile] and rs11652075 [c.2458C>T; p.Arg820Trp]) were identified in the most severely affected individuals IV-3 and IV-1, suggesting their possible role in disease severity. The same haplotype was also identified in individual IV-4, a 5-year-old boy with minimal plaque-type disease. At present it is unclear whether his phenotype is not fully developed because of his young age or whether additional unidentified factors are required to develop severe disease.

Three aforementioned polymorphisms represent previously reported common missense variants, conferring the risk of psoriasis in a number of cohorts examined (5, 14). Functional studies revealed rs2066964 [c.1641G>C; p.Arg547Ser] to have no significant effect on NF-kB pathway in vitro, possibly because of its location outside...
of the CARD and coiled-coil domains directly required for NF-kB activation (12). The function of the other 2 polymorphisms was not examined (5). Furthermore, since none of the polymorphisms was examined for its ability to activate NF-kB in the presence of c.349G>A [p.Gly117Ser] mutation, it is unknown whether they could modulate CARD14 activity in this setup. HLA-C*0602 (HLA-Cw6), the allelic variant of HLA-C, has been previously reported to be associated with severe and early-onset psoriasis (8–10). Recently the existence of this association has been questioned, since HLA*06 was found to be equally associated with mild and severe psoriasis in a large cohort of patients with psoriasis. The combination of a particular set of risk conferring alleles in genes related to the interleukin (IL)-23 and the NF-kB pathways with HLA-C*06 positivity was restricted to severe psoriasis, suggesting possible interaction of these loci (15). Furthermore, the risk conferring single-nucleotide polymorphisms (SNP), unique to chromosomes bearing HLA-C*0602, has been found to reside within the NF-kB binding site of the HLA-C enhancer, suggesting possible impact on HLA-C expression (16). Possible interaction between HLA-C*0602 and CARD14 has also been proposed, in which CARD14 would affect signalling downstream of antigen stimulation (5).

In the family studied here, the HLA-C*0602, the c.349G>A [p.Gly117Ser] mutation and, possibly, the disease-predisposing haplotype on the second allele of the CARD14 gene, were present in all affected individuals and accompanied early-onset psoriasis (mean age <10 years). Interestingly, the same c.349G>A [p.Gly117Ser] mutation in CARD14, described in the multiplex family of European origin, was not accompanied by HLA-C*0602, and was associated with later appearance of psoriasis (mean age 18 years) (17), suggesting that the presence of the HLA-C*0602 could modify the age of disease onset.

The current study is limited by the small number of patients and the lack of study of functional expression addressing the impact of CARD14 polymorphisms, when present together with the c.349G>A [p.Gly117Ser] mutation, on CARD14 protein activity and turnover. It is also possible that additional, presently unidentified, factors play a role in the final expression of the CARD14-related psoriatic phenotype.

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REFERENCES