Acta Derm Venereol 2016; 96: 885–887

INVESTIGATIVE REPORT

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

Marina ESKIN-SCHWARTZ[1,6#], Lina BASEL-VANAGAITE[2,3,5,6,#], Michael DAVID[1,6], Irina LAGOVSKY[3,6], Dan BEN-AMITAI[4,6], Pola SMIRIN-YOSEF[3,7], Lihi ATZMONY[1,6] and Emmilia HODAK[1,6]

[1]Department of Dermatology and [2]Raphael Recanati Genetics Institute, Rabin Medical Center, Beilinson Hospital, [3]Felsenstein Medical Research Center, Rabin Medical Center, [4]Pediatric Dermatology Unit and [5]Pediatric Genetics, Schneider's Children's Medical Center of Israel, Petah Tikva, and [6]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, and [7]Genomic Bioinformatics Laboratory, Department of Molecular Biology, Ariel University, Ariel, Israel
[#]Both authors contributed equally to this manuscript.

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*.**

Accepted Mar 10, 2016; epub ahead of print Mar 17, 2016

Acta Derm Venereol 2016; 96: 885–887.

Marina Eskin-Schwartz, Department of Dermatology, Tel-Aviv Sourasky Medical Center, Weizman str. 6, Tel-Aviv, Israel. E-mail: shwartzmarina@gmail.com

Psoriasis is a chronic multifactorial inflammatory disease involving the skin, nails and joints (1). Along with the most common plaque-type psoriasis, other clinical forms of the disease are known, such as guttate, pustular and palmoplantar types (2).

PSORS 1 (psoriasis susceptibility locus 1), the most well-studied locus conferring susceptibility to psoriasis, resides within the major histocompatibility complex (MHC) locus (3). Detailed PSORS 1 analysis revealed that Cw6 (the allelic variant of HLA-C) confers the risk to develop psoriasis; however, no specific gene causing psoriasis was found in that region (4).

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, pustular 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 Yemenite-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[1] and Table SI[1]).

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.

[1]https://doi.org/10.2340/00015555-2405

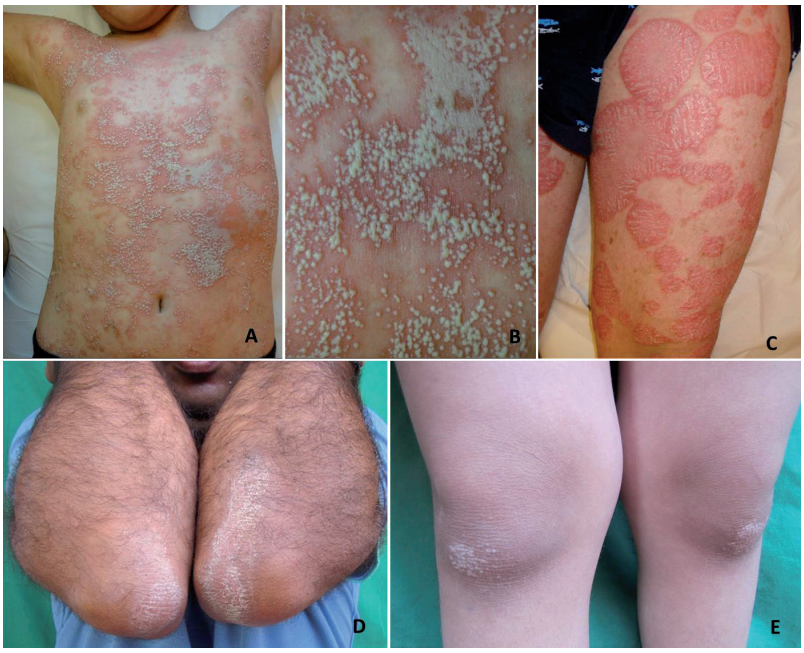

Fig. 1. The spectrum of clinical phenotypes of *CARD14*-related psoriasis: from Von Zumbush to minimal plaque-type disease. (A–B: patient IV-3; C: patient IV-1; D: patient III-2; E: patient IV-4).

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[1]).

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[1]). 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[1]). 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-κB 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.

ACKNOWLEDGEMENT

Professor Katzenebogen foundation Grant, Tel-Aviv University, 2012–2013.

The authors declare no conflicts of interest.

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