RESEARCH LETTER

Novel *ABCA12* Missense Variant in a Patient with Congenital Ichthyosis and Palmoplantar Keratoderma

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To the Editor,

Inherited epidermal differentiation disorders (EDD) include ichthyoses and palmoplantar keratodermas (PPK) for which a new classification is in progress (1). The group of autosomal recessive congenital ichthyosis (ARCI) refers to EED characterized by diffuse scaling, inconstant erythema, and pruritus. So far, 13 ARCI-related genes were identified. Variants in *ABCA12* are associated with Harlequin ichthyosis (OMIM#242500), the most severe ARCI phenotype, as well as congenital ichthyosiform erythroderma and lamellar ichthyosis (OMIM#601277). ABCA12, a member of the ATP-binding cassette transporter proteins, plays a crucial role in keratinocyte lipid transport through lamellar bodies to form the extracellular lipid layers of the *stratum corneum* (2). PPK is characterized by a skin thickening of palms and soles (3, 4). Among the various involved genes, *DSG1* is transmitted in an autosomal dominant manner and associated with striate, focal, or diffuse not painful PPK (OMIM#148700). *PERP* is transmitted in an autosomal dominant or recessive manner and patients present with woolly often yellowish hair, periorificial plaques, cheilitis, dystrophic nails, and PPK (OMIM#619208).

We report the case of a female patient born to healthy Caucasian non-consanguineous parents without any family history of EDD. At birth, she presented with erythroderma and diffuse fine white scaling that improved rapidly to become very mild (except on the scalp where there were scales of moderate severity) but disabling because of severe pruritus. In the first months of life, she developed mild diffuse PPK. She had no other skin, hair, or nail anomalies (**Fig. 1**).

Histological examination of a skin biopsy from the patient's arm showed hypergranulosis and marked orthohyperkeratosis (**Fig. 2**A). Using an NGS panel of 108 genes involved in EDD, we identified 2 heterozygous compound variants in *ABCA12* (NM_173076.2). The variant c.4139A>G (p.(Asn1380Ser)), inherited from the father, was known and previously reported as pathogenic in several unrelated patients with congenital ichthyosiform erythroderma or lamellar ichthyosis (5). The inframe deletion c.7304_7306del (p.(Glu2435del)), inherited from the mother, has never been reported previously and was absent from databases (*dbSNP*, *GnomAD*). It affects the ABC transporter 2 domain of ABCA12. Intriguingly, 2 other previously unreported heterozygous missense variants associated with PPK were identified in the patient: c.215C>T (p.(Ala72Val)) in *PERP* (NM_022121.4) and c.3080T>C (p.(Ile1027Thr)) in *DSG1* (NM_001942). The former was inherited from

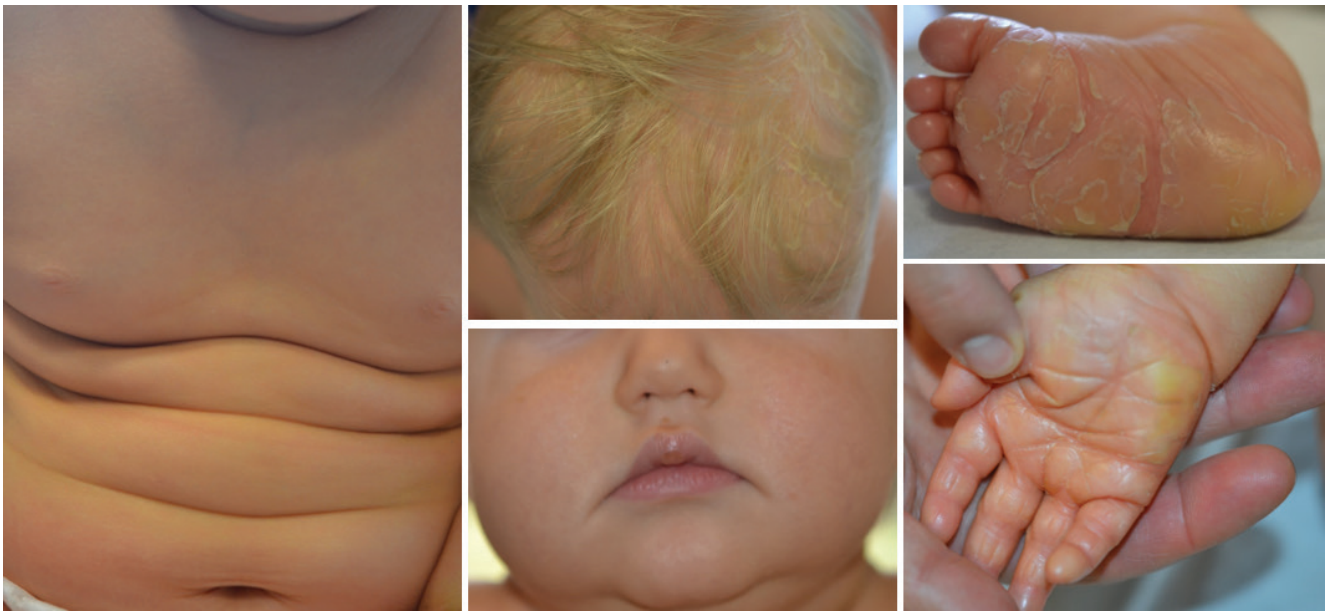

Fig. 1. Clinical features of the patient's skin at age 1 year.

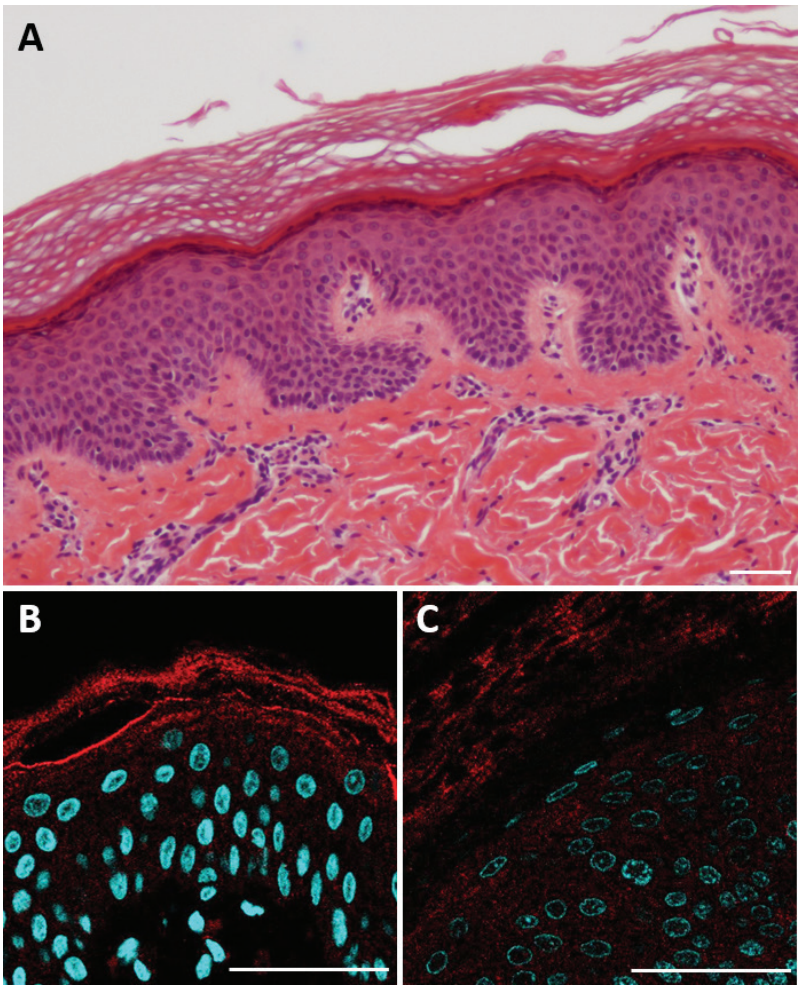

Fig. 2. Histological and immunohistological features of the patient's skin. (A) Haematoxylin and eosin stained section from the skin of the patient. Scale bar = 50 µm. (B, C) Immunofluorescence of (B) normal human skin section and (C) patient's skin section realized with an antibody-recognizing glucosylceramide (red). Nuclei are visualized with DAPI (blue). Scale bar = 50 µm.

the mother and the latter from the father. According to the ACMG-AMP guidelines (6), the inframe deletions in *ABCA12*, *PERP*, and *DSG1* variants were assigned variants of uncertain significance. The respective involvement of each of these variants in the patient's complex phenotype (mild congenital ichthyosiform erythroderma, moderate scalp scaling, intense pruritus, mild PPK) is unknown.

To assess a potential loss of function of ABCA12, we analysed the distribution pattern of glucosylceramide (GlcCer), the lipid transported by ABCA12 in lamellar granules (7). The patient's skin exhibited punctiform and weak staining of GlcCer in the *stratum granulosum* and the *stratum corneum* (**Fig. 2**B), whereas control skin showed GlcCer staining primarily in the granular layer, forming a continuous and more intense band beneath the *stratum corneum* (**Fig. 2**C). This is consistent with an affected function of ABCA12 in the patient's skin and suggests that *ABCA12* variants are responsible for the scaling and erythroderma. Regarding the PPK, the *DSG1* and *PERP* variants could not solely cause PPK, as both asymptomatic parents each carried 1 variant. *ABCA12* variants could also be responsible for the PPK. Indeed, 2 siblings heterozygous compound for 2 novel missense *ABCA12* variants, showing erythematous and scaly migratory patches and very mild diffuse PPK, were recently reported (8). The interaction between the *ABCA12*, *DSG1* and *PERP* variants could also have influenced our patient's phenotype.

This case underscores the necessity to develop functional *in vitro* tests to determine the role of variants of uncertain significance in a complex phenotype.

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IRB approval status: Skin biopsies and blood samples were collected for diagnosis and gathered in a biological collection (DC-2011-1388, French National Ethics Committees). Written informed consent was obtained from the legal representative of the patient, allowing the authors to use the biological specimens collected for research purposes. The patient's legal guardian in this manuscript has given written informed consent to publication of their case details.

The authors have no conflicts of interest to declare.

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