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Letter

Hereditary mucoepithelial dysplasia results from heterozygous variants at p.Arg557 mutational hotspot in *SREBF1*, encoding a transcription factor involved in cholesterol homeostasis

Fanny Morice-Picard^{1,4} (0000-0002-4316-916X), Vincent Michaud² (0000-0002-5788-392X), Eulalie Lasseaux² (0000-0002-4475-5099), Hamid Reza Rezvani⁴ (0000-0001-8067-1338), Claudio Plaisant² (0000-0002-0928-8608), Didier Bessis³ (0000-0002-3815-5417), Christine Leauté-Labrèze^{1,4} (0000-0002-4110-2607), Benoit Arveiler^{2,5} (0000-0002-2987-2932), Alain Taieb^{1,4} (0000-0002-0928-8608), Aurélien Trimouille^{2,5} (0000-0002-3457-5684), Franck Boralevi^{1,4} (0000-0002-0477-5909)

¹Service de Dermatologie Pédiatrique, Université de Bordeaux, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France, ²Service de Génétique Médicale, Université de Bordeaux, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

³Service de Dermatologie Pédiatrique, Université de Montpellier, Centre Hospitalier Universitaire de Montpellier, Montpellier, France

⁴Université de Bordeaux, INSERM, U1211, Bordeaux, France.

⁵Université de Bordeaux, INSERM, U1035, Bordeaux, France.

Corresponding author:

Fanny Morice-Picard, MD PhD
Department of Dermatology and Pediatric Dermatology,
National Reference Centre for Rare Disorders
Centre Hospitalier Universitaire du Bordeaux
Place Amélie Raba-Léon,
F-33076 Bordeaux cedex, France.
Phone : 003357820199
Fax : 0033556794976
E-mail : fanny.morice-picard@chu-bordeaux.fr

To the editor

Hereditary mucoepithelial dysplasia (HMD [MIM158310]) is an autosomal dominant disorder characterized by chronic mucoepithelial lesions including hair, skin and mucosae (Witkop et al. 1982; Witkop et al. 1979). Clinically patients are almost constantly presenting with the triad of non-scarring alopecia, well-demarcated fiery red mucosa and psoriasiform perineal involvement, helpful for the diagnosis of HMD (Boralevi et al. 2005). The pathogenesis of the disorder remained so far unknown. As HMD involves epithelia and mucosa and is associated with a paucity of desmosomes and cytoplasmic filamentous fibers, it has been considered to be a disorder of desmosome or gap junction formation. Differential diagnosis includes *ichthyosis follicularis*, *atrachia*, and *photophobia syndrome* (IFAP[MIM308205]), a severe and rare X-linked disorder caused by mutations in the gene encoding the Membrane-Bound Transcription Factor Peptidase (*MBTPS2*) (Oeffner et al. 2009; Rothe and Lucky 1995). *MBTPS2* mutations are absent in patients with HMD.

In this report, we described that HMD is associated with a hot-spot variant in sterol regulatory element binding transcription factor 1 (*SREBF1* [MIM 184756]), a transcription factor that controls cholesterol and fatty acid synthesis (Oishi et al. 2017; Sato et al. 1994). This study included 7 patients from four different families, all of European descent (Figure 1). Clinical examination of all patients was performed under research protocols approved by the local ethics committee. All patients presented with clinical and histological features suggestive of HMD including chronic keratitis, fiery red coloration of the vestibular oral mucosa, keratosis pilaris and non-scarring diffuse alopecia (Figure 1A and 1B-F). Perineal psoriasiform plaques were present in patients P1 and P2 (Figure 1G). None had lung disease. Clinical findings of the patients are summarized in Table S1.

Written informed consent was obtained from patients and their parents. To identify the causative mutations underlying HMD, we used DNA samples from patients for whole-exome sequencing (WES). We analyzed one trio (affected patient P1 and her parents), two patients (P2, P3) from two unrelated families presenting with a sporadic form of the disease and one patient (F1) from a family in which the disorder was transmitted as an autosomal dominant pattern (Figure 1a)(Table S1). WES found a *de novo* heterozygous variant in exon 9 of the *SREBF1* gene (NM_001005291.2: c.1669C>T p.(Arg557Cys)) in patient P1, the same heterozygous missense variant in patient P2, and a missense variant c.1670G>A p.(Arg557His) in *SREBF1* gene at the same Arg557 codon in patients P3 and F1. The segregation of the variant with disease, was confirmed by Sanger sequencing in 3 additional patients (F2, F3 and F4)(Figure 2A). It was absent in healthy son (S1) of patient F1 (SA). Both variants were absent from dbSNP, the Human Gene Mutation database, the UCSC Genome Browser, 1000 Genomes, Ensembl, or the gnomAD and predicted deleterious by multiple softwares (SIFT, Mutation Taster, Polyphen-2 HumVar)(Table S3). Together the identification of (1) a *de novo* occurrence of a rare heterozygous variant affecting a highly conserved aminoacid in patients, (2) the finding of mutations affecting the same aminoacid in three additional unrelated families with HMD and (3) the segregation of the mutation with disease in the family, provide sufficient evidence that mutations in *SREBF1* cause HMD (Figure 2B).

SREBF1 codes in 20 exons for SREBP1 (Sterol regulatory element-binding protein 1), a transcription factor for cholesterol and fatty acid synthesis. SREBP1 is synthesized as a membrane-bound precursor, attached to the endoplasmic reticulum (ER) and nuclear envelope and is cleaved within Golgi apparatus. SREBP cleavage-activating protein (SCAP) is a sensor of sterols required to shift SREBP1 from the ER to the Golgi apparatus (Nohturfft et al. 1999). To enhance transcription, the active NH(2)-terminal domain of SREBP1 is released

from endoplasmic reticulum membranes to the cytosol by two sequential cleavages. The first is catalyzed by Site-1 protease (S1P), that cleaves the hydrophilic luminal loop of SREBP (Nohturfft et al. 1999) and the second at Site-2, requires the action of MBTPS2 (Sato et al. 1994). The liberated NH₂-segment enters the nucleus and activates genes controlling cholesterol synthesis and uptake (Sakai et al. 1996). The Arginine 557 in the luminal loop was found to be essential for cleavage (Hua et al. 1996). The variants found in our patients affect this highly conserved Arg557 and may disturb cleavage and maturation of SREBP1 (Figure 2c).

To our knowledge, HMD is the first disorder to be associated with *SREBF1* mutations. Smith-Magenis syndrome (SMS), a contiguous gene syndrome due to an interstitial deletion of chromosome 17p11.2 including *SREBF1*, was shown to be associated with hypercholesterolemia and with haploinsufficiency of *SREBF1* (Smith et al. 2002).

Hypercholesterolemia is not reported in patients with HMD and was not found in our patients.

IFAP syndrome is the condition that shares most similarities with HMD suggesting a common pathway (Boralevi et al. 2008). *MBTPS2* mutations in IFAP syndrome are associated with a reduced function of the cellular regulatory system affecting cholesterol homeostasis, through cleaving SREBP1 (Oeffner et al. 2009). Given these results, it could be suggested that the effects of *MBTPS2* variants upon SREBP1 function could be the predominant mechanisms responsible for manifestations in IFAP patients (Oeffner et al. 2009). Deficiency in lipid metabolism is found in different genodermatoses generally associated with a disturbed differentiation of epidermal structures as observed in the ichthyoses or in the hereditary hypotrichoses (Elias et al. 2012; Palmer et al. 2019).

SREBF1 has recently been involved in the production of anti-inflammatory fatty acids in macrophages thus providing evidence that SREBP1 contributes to the resolution phase of

TLR4-induced gene activation by reprogramming macrophage lipid metabolism (Oishi et al. 2017). Additional studies are required to see if uncleaved mutated SREBP1 could alter ER homeostasis, lead to an unfolded protein response and to the dyskeratotic features and cytoplasmic vacuoles associated with psoriasiform skin lesions in patients (Boralevi et al. 2005).

Together our results suggest that HMD is associated with hotspot *SREBF1* variants and provide evidence of a pathophysiological link between HMD and IFAP syndrome. Further mechanistic studies are required to understand the precise consequences of the Arg557 mutation on the function of SREBP1 that lead to hereditary mucoepithelial dysplasia.

Data availability statement

No datasets were generated

Conflict of interest statement

The authors have no conflict of interest to declare.

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CRedit statement

Conceptualization: FB, FMP; Investigation: FB, AT, FMP, DB; Formal Analysis: CP, EL, VM, FMP;

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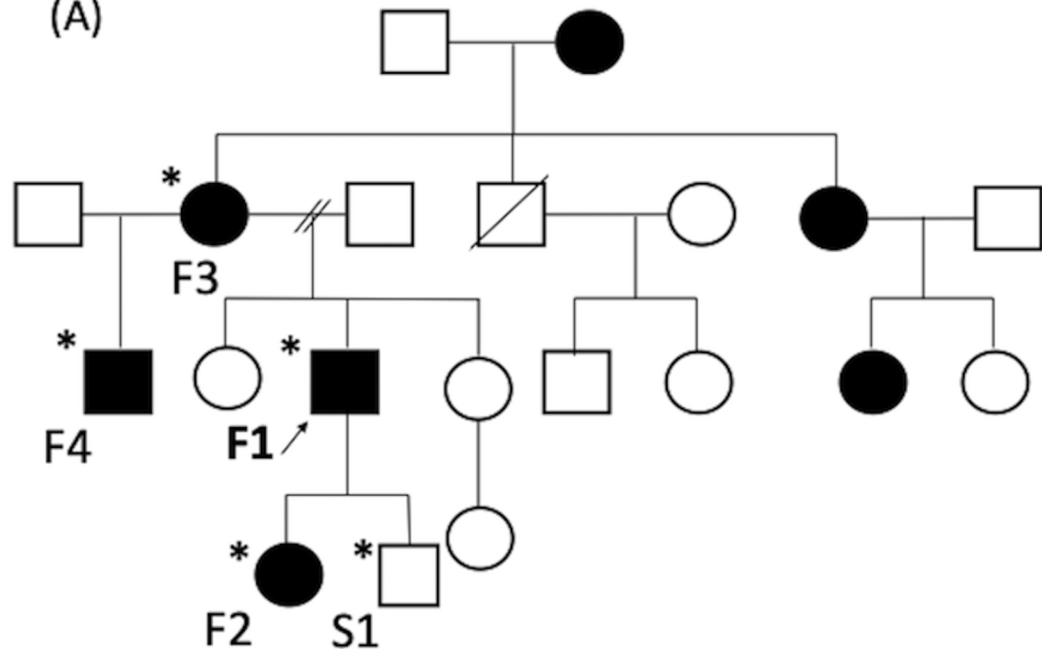
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Legends to figures

Figure 1. Clinical features. (A) The pedigrees of family A is presented here. Black symbols denote affected individuals; Individuals in bold correspond to Exome sequenced individuals; Available DNA is indicated by a *. (B) Characteristic fiery red colouration of the vestibular oral mucosa in patient F2 (black arrow), (C) alopecia in patient P1, (D) in patient F2, (E) patient P2 and (F) P3. (G) Psoriasiform eruption in patient P1. Patients or their parents consented to the publication of their image.

Figure 2. Mutation analysis. (A) Sequencing of *SREBF1* revealed two different heterozygous variants in exon 18 of the gene: c.1669G>A in patient P1 (de novo), c.1670C>T in **F1**, F2, F3 and F4 and absence of variant in healthy individual S1 (son of F1). (B) Schematic representation of the structure of SREBP1 indicating the localization of the mutated Arg557 within the lumen domain necessary for recognition and cleavage by Site-1 Protease and partial amino acid sequence alignment of SREBP1. High conservation of residues of Arg557 through different species is shown. (C) Schematic representation of the proteolytic maturation of SREBP1 requiring three proteins. The first, SREBP cleavage-activating protein (SCAP) escorts SREBP1 from the ER to the Golgi apparatus, where the Site-1 protease (S1P) and MBTPS2 act sequentially to release the NH2-terminal bHLH domain from the membrane to the nucleus. Localization of the mutated Arg557 within the lumen domain necessary for recognition and cleavage by Site-1 Protease is indicated. The mutations found in our patients affect this highly conserved Arg and could be responsible for a failure of cleavage and maturation of SREBP1.

(A)



(B)



(C)



(D)



(E)



(F)



(G)



