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Letter to the Editor

Hereditary mucoepithelial dysplasia/autosomal-dominant IFAP syndrome is a clinical spectrum due to *SREBF1* variants

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Short title: HMD/AD IFAP due to *SREBF1* variants

Abbreviations: HMD: hereditary mucoepithelial dysplasia; SREBP1: sterol regulatory element-binding protein 1; IFAP: ichthyosis follicularis with atrichia and photophobia; S1P: site-1-protease.

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To the Editor: We read with great interest the recent report by Morice-Picard et al. (2020) on how mutations in *SREBF1* (OMIM: 184756) are associated with hereditary mucoepithelial dysplasia (HMD) (OMIM: 158310). *SREBF1* encodes sterol regulatory element-binding protein 1 (SREBP1), which is involved in promoting the transcription of lipogenes that are associated with cholesterol and fatty acid biosynthesis (Zhang et al., 2017).

Morice-Picard et al. (2020) performed causative mutation search in seven patients from four independent families with HMD, and they concluded that the alteration of amino acid residue Arg557 by theheterozygous missense mutation c.1669C>T (p.Arg557Cys) or c.1670G>A (p.Arg557His) in *SREBF1* (NM_001005291.2) causes HMD, based on the results of seven patients from four independent families (Morice-Picard et al., 2020).

Here we report a Japanese woman (the proband) and her daughter who had clinical features of autosomal-dominant ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome.

Ethics committee approval was obtained by Nagoya University Graduate School of Medicine and all research was performed in accordance with the Declaration of Helsinki principles. Written informed consent was obtained from the participants. Sanger sequencing of genomic DNA from each patient found no mutations in *MBTPS2* (MIM: 300294), suggesting a genetic etiology distinct from that in typical X-linked IFAP syndrome (OMIM: 308205) in this pedigree. Next, we performed the whole-exome sequencing of genomic DNA from each patient. This sequencing found the heterozygous missense mutation c.1669C>T (p.Arg557Cys) in *SREBF1* (NM_001005291.2) in both patients. Neither parent of the proband was affected, and the mutation p.Arg557Cys in *SREBF1* in the present family is considered to be a *de novo*mutation. Interestingly, the *SREBF1* mutation in the present family is identical to that reported in HMD patients by Morice-Picard et al. (2020).

Mutations in *MBTPS2* underlie X-linked IFAP syndrome (Oeffner et al., 2009). Skewed X-inactivation contributes to the variable phenotypes in female cases of X-linked IFAP syndrome (Murase et al., 2020). In contrast, female patients with *SREBF1* mutations show the severe phenotypes seen in the present patients.

The triad of IFAP syndrome includes follicular ichthyosis, atrichia, and photophobia of varying severities (Oeffner et al., 2009). The two female patients in the present Japanese pedigree showed the full triad ofIFAP syndrome and presented with severe phenotypes of that syndrome (Sato-Matsumura et al., 2000). Briefly, the proband and her daughter had almost all the classical and some of the minor symptoms, including severe photophobia, extensive non-inflammatory follicular hyperkeratosis, non-scarring total alopecia, psoriasiform hyperkeratosis of the extremities, recurrent cheilitis, and nail deformity (Sato-Matsumura et al., 2000). From these clinical features, the present patients were diagnosed with IFAP.

Recently, Wang et al. (2020) described 11 pedigrees with autosomal-dominant IFAP syndrome that carried three mutations in *SREBF1*: c.1579C>T, p.Arg527Cys (nine pedigrees),c.1582_1584del, p.Asn528del (one pedigree), and c.1589T>C, p.Leu530Pro (one pedigree). The three detected *SREBF1* mutations caused the substitution or deletion of residues 527, 528, or 530, which are crucial for S1P cleavage in SREBP1 (Wang et al., 2020). Wang et al. (2020) concluded that

c.1579C>T in *SREBF1* is a recurrent hotspot mutation underlying autosomal-dominant IFAP syndrome. The different reference sequences of *SREBF1*—NM_001005291.2 and NM_004176.3—were adopted for the mutation search by Morice-Picard et al. (2020) and Wang et al. (2020), respectively, and in fact, c.1579C>T in the report by Wang et al.(2020) is identical to c.1669C>T in the report by Morice-Picard et al. (2020). The mutation identified in the present patients is also identical to the recurrent hotspot mutation in *SREBF1* detected in the HMD patients and the autosomal-dominant IFAP syndrome cases (Wang et al., 2020).

The present patients did not show erythema on the oral, nasal or vaginal mucosae, which are substantial in HMD (Scheman et al., 1989). However, the proband had vulvitis and a dark red, hyperkeratotic, papillomatous plaque on her vulva (Sato-Matsumura et al., 2000). The perineal lesions of the mother seemed to be consistently provoked by pregnancy, and the vulvitis subsided spontaneously within four weeks after her deliveries. Her vulvar lesions resembled the perineal lesion that is characteristic of HMD.

HMD and IFAP syndrome share many clinical symptoms: photophobia, keratosis pilaris, non-scarring alopecia, psoriasiform plaques, and angular cheilitis (Hernández-Martín et al., 2012). Table 1 summarizes acomparison of characteristic clinical features from previous reports on HMD and autosomal-dominant IFAP syndrome patients. Notably, there are many differences between patients with HMD and those with autosomal-dominant IFAP syndrome, although there are some similarities between these two phenotypes. Notably, the present patients had psoriasiform perineal intertrigo, which was seen in six of the seven HMD patients due to the alteration of the amino acid residue Arg557 in SREBP1 (Morice-Picard et al., 2020). The heterozygous missense mutation c.1669C>T (p.Arg557Cys) in *SREBF1* (NM_001005291.2)might have led to the overlapping symptoms and the HMD, and autosomal-dominant IFAP might be on a spectrum of clinical phenotypes.

It was revealed that SREBP1 variants cause impairments to site-1-protease (S1P) cleavage that inhibit nuclear translocation of the transcriptionally activated form of SREBP1 *in vitro* (Wang et al., 2020). Moreover, RNA sequencing of scalp skin from autosomal-dominant IFAP syndrome patients shows significant reductions in transcript levels of keratin genes and low-density lipoprotein receptor, which are known to be expressed in the outer root sheath of hair follicles (Wang et al., 2020). These findings

indicate that SREBP1 signaling is necessary for hair growth, skin barrier function, epidermal differentiation, and ocular function.

In conclusion, we identified a family with autosomal-dominant IFAP syndrome caused by the recurrent hotspot mutation c.1669C>T (p.Arg557Cys) in *SREBF1* (NM_001005291.2). This hotspot mutation hasbeen reported in HMD families and autosomal-dominant IFAP families, independently (Morice-Picard et al., 2020, Wang et al., 2020). The present patients showed perineal lesions characteristic of HMD in addition to the typical clinical features of autosomal-dominant IFAP syndrome. The present family suggests that the mutation c.1669C>T (p.Arg557Cys) in *SREBF1* (NM_001005291.2) might be a recurrent hotspot mutation for HMD and autosomal-dominant IFAP syndrome and that HMD and autosomal-dominant IFAP syndrome due to the *SREBF1* mutations are diseases on the same clinical spectrum.

Data availability statement: No datasets were generated or analyzed during the current study.

Conflicts of interest: None declared

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Author contributions
Conceptualization: CM, MA; Data curation: CM, TT, TN; Formal analysis: TO; Funding acquisition: TT, MA; Investigation: CM, TT ; Project Administration:

CM, TT; Resources: TN; Supervision: MA; Validation: TT, MA; Visualization: CM; Writing: CM, TT, MA

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Table 1. Comparison of clinical features seen in HMD and autosomal-dominant IFAP syndrome caused by *SREBF1* variants

Affected Organs	Clinical features	Hereditary mucoepithelialdysplasia	Autosomal-dominant IFAP syndrome	The present patients
Eyes	**Photophobia**	Frequent	Yes	Yes
	Keratitis	Frequent	Yes	Yes
	Cataracts	Often	Usual	No
Hair and Nails	**Hypotrichosis**	Yes	Yes	Yes
	Onycho-dystrophy	ND	Seldom	Yes
Skin	**Follicular keratosis**	Yes	Yes	Yes
	Psoriasiform perineal intertrigo	Usual	No	Yes
	Angular cheilitis	ND	Seldom	Yes
Mouth	**Red oral mucosa**	Yes	No	No
	Deeply fissured tongue	Yes	No	No
Internal organs	**Lung disease**	No	No	No

Modified from Hernández-Martín et al. ND, not described