TO THE EDITOR

We read with great interest the recent report by Morice-Picard et al. (2020) on how mutations in SREBF1 (Online Mendelian Inheritance in Man: 184756) are associated with hereditary mucoepithelial dysplasia (HMD) (Online Mendelian Inheritance in Man: 158310). SREBF1 encodes 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 a causative mutation search in seven patients from four independent families with HMD, and they concluded that the alteration of amino acid residue Arg557 by 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 patients with HMD by Morice-Picard et al. (2020).

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

Ethics committee approval was obtained from Nagoya University Graduate School of Medicine (Nagoya, Japan), 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 (Online Mendelian Inheritance in Man: 300294) in these Japan), 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 (Online Mendelian Inheritance in Man: 300294), suggesting a genetic etiology distinct from that in typical X-linked IFAP syndrome (Online Mendelian Inheritance in Man: 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 patients with HMD by Morice-Picard et al. (2020).

Mutations in MBTPS2 underlie X-linked IFAP syndrome (Oeffner et al., 2009). Skewed X-inactivation could contribute 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 of IFAP 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 noninflammatory follicular hyperkeratosis, nonscarring 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 AD 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 site-1-protease cleavage in SREBP1 (Wang et al., 2020). Wang et al. (2020) concluded that c.1579C>T in SREBF1 is a recurrent hotspot mutation underlying AD 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 patients with HMD and the AD 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 4 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, nonscarring alopecia, psoriasiform plaques, and angular cheilitis (Hernández-Martí n et al., 2012). Table 1 summarizes a comparison of characteristic clinical features from previous reports on patients with HMD and AD IFAP...
syndrome. Notably, there are many differences between patients with HMD and those with AD 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 patients with HMD owing to the alteration of the amino acid residue Arg557 in SREBF1 (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 AD IFAP might be on a spectrum of clinical phenotypes.

It was revealed that SREBF1 variants cause impairments to site-1 protease cleavage that inhibit nuclear translocation of the transcriptionally activated form of SREBF1 in vitro (Wang et al., 2020). Moreover, RNA sequencing of scalp skin from patients with AD IFAP syndrome shows significant reductions in transcript levels of keratin genes and low-density lipoprotein receptors, which are known to be expressed in the outer root sheath of hair follicles (Wang et al., 2020). These findings indicate that SREBF1 signaling is necessary for hair growth, barrier function, epidermal differentiation, and ocular function.

In conclusion, we identified a family with AD IFAP syndrome caused by the recurrent hotspot mutation c.1669C>T (p.Arg557Cys) in SREBF1 (NM_001005291.2). This hotspot mutation has been reported in families with HMD and those with AD IFAP, independently (Morice-Picard et al., 2020; Wang et al., 2020). These patients showed perineal lesions characteristic of HMD in addition to the typical clinical features of AD 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 AD IFAP syndrome and that HMD and AD IFAP syndrome due to the SREBF1 mutations are diseases on the same clinical spectrum.

Data availability statement
No datasets were generated or analyzed during this study.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS
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REFERENCES


Table 1. Comparison of Clinical Features Seen in HMD and AD IFAP Syndrome Caused by SREBF1 Variants

<table>
<thead>
<tr>
<th>Affected Organs</th>
<th>Clinical Features</th>
<th>HMD</th>
<th>AD IFAP Syndrome</th>
<th>The Present Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Photophobia</td>
<td>Frequent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Keratitis</td>
<td>Frequent</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td>Often</td>
<td>Usual</td>
<td>No</td>
</tr>
<tr>
<td>Hair and nails</td>
<td>Hypotrichosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin</td>
<td>Onychodystrophy</td>
<td>ND</td>
<td>Seldom</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Follicular keratosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Psoriasiform perineal intertrigo</td>
<td>Usual</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Angular cheilitis</td>
<td>ND</td>
<td>Seldom</td>
<td>Yes</td>
</tr>
<tr>
<td>Mouth</td>
<td>Red oral mucosa</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Deeply fissured tongue</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Internal organs</td>
<td>Lung disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal-dominant; HMD, hereditary mucoepithelial dysplasia; IFAP, ichthyosis follicularis with atrichia and photophobia; ND, not described.

Modified from Hernández-Martín et al. (2012).
Three-Dimensional Telomeric Fingerprint of Mycosis Fungoides and/or Sézary Syndrome: A Pilot Study

TO THE EDITOR

Mycosis fungoides (MF) is the commonest cutaneous T-cell lymphoma (CTCL). MF is a lifelong, slow-growing CD4+ neoplasm, which may evolve over years from skin patches to plaques and tumors (Swerdlow et al., 2016; Willenze et al., 2019). Outcomes are good in the early stages of the disease with a survival comparable with that of an age-matched cohort (Agar et al., 2010). In later stages, defined as tumors and extracutaneous dissemination, the prognosis is poor owing to organ involvement and immune suppression. Sézary syndrome (SS) is defined by the triad of erythroderma, generalized lymphadenopathy, and a circulating clone of T cells with cerebriform nuclei (Sézary cells). SS accounts for <5% of CTCLs. It is closely related to MF; however, they are considered as separate entities on the basis of clinical presentation, behavior, and the cell of origin. The 5-year overall survival rate for SS is <30% (Swerdlow et al., 2016).

Research on factors that lead MF cells to become more aggressive to transform into leukemic Sézary cells has shown that cytokines such as IL-15 and mutations involving oncogenic signaling pathways (MYC, PTEN, Jak-3/signal transducer and activator of transcription, and p53) play a role in CTCL pathogenesis (Agar et al., 2010; Zhao and Tao, 2018). Biomarkers of clinical aggressiveness in T-cell proliferations are the lymphoid activation marker CD30 (Zain, 2019) and shorter telomeres (Chevret et al., 2014). On the basis of these findings, we hypothesized that the three-dimensional (3D) spatial telomere organization and dynamics might correlate with clinical tumor aggressiveness and CD30 expression (Knecht et al., 2012; Vermolen et al., 2005). Although strong CD30 expression is almost invariably associated with large cell transformation and severe disease, CD30-negative large cell transformation of MF does exist. It would be interesting to see whether CD30-negative transformation behaved as aggressive as CD30 positive and whether they were different with respect to telomere kinematics and loss.

For these experiments, Institutional approval and written informed consent of patients were obtained. Our pilot study of 10 samples (Supplementary Table S1) revealed that 3D telomere analysis combined with clinical staging and CD30 expression represents an innovative approach to MF and/or SS diagnosis. We have used both clinical stage and CD30 expression as markers of more advanced disease. The choice of these parameters is based on published data. There is substantial evidence that clinical stage is one of the best prognostic tools in CTCL (Kim et al., 2003; Olsen et al., 2007; Swerdlow et al., 2016). High CD30 expression by immunohistochemistry has been shown to be an independent poor prognostic marker in non-transformed MF and to be a frequent finding in transformed MF (Edinger et al., 2009).

We are aware that our approach has limitations. For example, telomere loss may also be complemented by a mechanism termed alternative telomere lengthening not analyzed in this study owing to limited material (Sobinoff and Pickett, 2017).

The choice of controls in MF is confounded by the localization of MF to the skin. The use of keratinocytes is limited by their programmed cell death, which may alter their telomere dynamics, and circulating T lymphocytes show a significant variation in age-associated telomere attrition (Lin et al., 2015). Circulating CD4+ T lymphocytes in MF show already shortened telomeres compared with CD4+ circulating lymphocytes of healthy donors (Wu and Hansen, 2001). Therefore, the use of nonmalignant, lymph node tissue-residing CD4+, CD30- lymphocytes from treatment-naive patients with Hodgkin lymphoma was considered the best alternative control. Of note, in Hodgkin lymphoma, the tumor cells make up for only 1–5% of the lymph node cells, the bulk thereof being made of benign, mainly CD4+ lymphocytes.

3D Telomeric quantitative FISH enabled us to perform an in-depth analysis of the 3D telomeric configuration and organization of MF tumor cells. An important parameter pertaining to telomeric signal intensity is the proportion of abnormal telomeres of low intensity (TLIs), the so-called ultrashort telomeres or t-stumps (Baird et al., 2003).