Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin.
Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin

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Background: Severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome is a recently recognized syndrome caused by mutations in the desmoglein 1 gene (DSG1). To date, only 3 families have been reported.

Objective: We studied a new case of SAM syndrome known to have no mutations in DSG1 to detail the clinical,

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Mendelian skin diseases that include atopic dermatitis (AD) or AD-like dermatitis, food allergies, or both as part of their phenotype potentially offer significant insights into disease pathogenesis. The best examples of insights into AD pathogenesis from Mendelian disease are Netherton syndrome (Mendelian Inheritance in Man [MIM] #256500) and ichthyosis vulgaris (MIM #146700). The discovery of mutations in the serine protease inhibitor Kazal-type 5 gene (SPINK5) as causative for Netherton syndrome highlighted the role of excessive stratum corneum protease activity in patients with AD, and identification of mutations in the filaggrin gene (FLG) in patients with ichthyosis vulgaris has been transformative in our understanding of the importance of the skin barrier in patients with AD and those with allergic sensitization. Other rare genodermatoses, such as “type B” peeling skin syndrome, which is attributed to mutations in the corneodesmosin gene (CSDN), reinforce the importance of stratum corneum cohesion in the pathogenesis of AD. In 2013, a new syndrome designated severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome was attributed to loss-of-function mutations in the desmosomal plaque protein desmoglein 1 (desmoglein 1 gene [DSG1]). Four cases of SAM syndrome...
have now been reported, all caused by DSG1 mutations.7,8 Here we report the first case of SAM syndrome (MIM #613508) attributed to a missense mutation affecting the plakin domain of the desmoplakin gene (DSP).

METHODS

Clinical history

We report the case of a white boy, now aged 6 years, with SAM syndrome. The patient is the first child of Irish, nonconsanguineous healthy parents. He was born at 39 weeks and 5 days' gestation by means of an emergency cesarean section because of fetal bradycardia after rupture of the membranes. He weighed 3.18 kg at birth (25th percentile). The perinatal history was suggestive of a colloidion membrane. Erythroderma with "skin scaling and peeling" was reported to be present from the first weeks of life. He was referred to our department at 6 months of age. He had marked erythroderma, ichthyosiform erythroderma, palmoplantar keratoderma (PPK) with nail dystrophy, and diffuse peeling. His hair started to grow when he was 6 years old and is a wooly hair phenotype. Also, he has had ongoing poor periodontal health, with marked hypodontia.

The patient was atopic, with multiple food allergies. Blood investigations were consistent with atopy, with persistent eosinophilia (0.4-0.5 X 10^9/L) and increased IgE levels (611 kU/L). Analysis of specific IgEs confirmed sensitization to egg, peanut, and wheat, despite having no oral exposure to these foods.

Histopathologic findings

Skin biopsies performed when the patient was 3 and 16 months of age showed similar findings (Fig 2, A). There was hyperkeratosis and parakeratosis overlying an acanthotic epidermis. The granular layer was absent, and there was no evidence of acantholysis. A superficial dermal inflammatory infiltrate composed of lymphocytes, admixed neutrophils, and histiocytes was present (Fig 2, B). A skin biopsy of the pustular eruption performed when the patient was 26 months of age showed a florid pustular dermatosis superimposed on the previously reported histologic findings (Fig 2, B). The pustule was intraepidermal and restricted to the stratum corneum. Hair microscopy was noncontributory, and notably, there was no trichorrhexis invaginata. Esophageal biopsies were done when the patient was 10 and 16 months old. They showed separation, detachment, and acantholytic sloughing of the superficial squamous epithelial cells in the absence of any significant inflammatory process or spongiosis (Fig 2, C).

Molecular genetics analysis

Whole-exome sequencing (WES) was performed in the proband with the Agilent SureSelect v4 capture kit (Agilent Technologies, Santa Clara, Calif) and sequenced on an Illumina HiSeq 2000 (Illumina, San Diego, Calif; GenePool, Edinburgh, United Kingdom). The resulting 88.7M 100-bp PE sequencing reads were aligned to the human genome (Ensembl release 68) with Bowtie2 (version 2.02; 98.8% aligned).9 Read duplicates were removed with Picard Tools (version 1.79; http://picard.sourceforge.net), and variants were called by using the UnifiedGenotyper in GATK-lite (version 2.2-8) according to the GATK best practices.1 The 69,732 called variants were annotated with the Variant Effect Predictor (version 72),1 and any variants with the following consequences were filtered out: downstream_gene_variant, upstream_gene_variant, synonymous_variant, intronic_variant, and intron_variant. Filtered data were put in a MySQL database, allowing querying through a Django interface. The desmoplakin variant p.His568Pro was confirmed by means of Sanger sequencing with the primers and conditions previously reported for exon 14 of the DSP gene.12 Array comparative genome hybridization (aCGH) was carried out with the Cytoscan 750K high-density oligo array (Affymetrix UK, High Wycombe, United Kingdom), according to the manufacturer’s recommended conditions (analysis performed under contract by the South East Scotland Cytogenetics Laboratory, Western General Hospital, Edinburgh, United Kingdom).

Ultrastructure

Skin biopsy specimens were prefixed in half-strength Karnovsky fixative, followed by postfixation in reduced 1% OsO4 containing 1.5% potassium ferrocyanide. After embedding in an Epon epoxy resin, ultrathin sections (600 Å) were mounted on Formvar-coated grids, counterstained with uranyl acetate and lead nitrate, and examined in a Jeol JEM 100 CX electron microscope (60 kV).

Immunohistochemistry of skin biopsy specimens

Four-micrometer paraffin-embedded sections were baked overnight at 60°C and deparaffinized with xylene, followed by a gradient of ethanol.
washes. Sections were permeabilized with 0.5% Triton X-100. Antigen retrieval was done by heating sections to 95°C for 15 minutes in 0.01 mol/L citrate buffer (pH 6.0). Slides were blocked in 1% BSA and 2% normal goat serum and incubated for 1 hour at 37°C. Primary antibodies were diluted in 1% BSA and 2% normal goat serum and incubated overnight at +4°C. Mouse mAbs used were as follows: 4B2 (desmoglein 1; diluted 1:100) and 115F (desmoplakin, a gift from David Garrod; diluted 1:100). Polyclonal antibodies used were as follows: keratin 10 (a gift from Julie Segre; diluted 1:2000) and 1407 (plakoglobin, diluted 1:2000). Secondary staining was done with Alexa Fluor–conjugated antibodies to mouse, rabbit, or chicken (Life Technologies, Grand Island, NY) diluted 1:300 in 1% BSA and 2% normal goat serum for 30 minutes at 37°C. All washes were done with PBS. Coverslips were mounted with polyvinyl alcohol for microscopic analysis by using a DMR Leica microscope (×40 NA 1.0 Plan-Fluotar Plan-Apochromat objective) and a charge-coupled device camera (Orca 100 model CA7 42-95; Hamamatsu Photonics, Hamamatsu City, Japan). 4′,6-Diamidino-2-phenylindole was added during the secondary antibody incubation at a final concentration of 2 μg/mL.

RESULTS
Molecular genetics

Initial mutation screening of the proband’s genomic DNA isolated from peripheral blood was unremarkable. This included Sanger sequencing of the entire coding sequences of SPINK5 and ADAM metallopeptidase domain 17 (ADAM17), as well as 8 genes known to cause autosomal recessive congenital ichthyosis (NIPAL4, CYP4F22, ALOXE3, ALOXE12B, TGM1, PNPLAI, ABCLA2, CERS3, FATP4, and ABHID5) and pustular psoriasis (CARD14 and IL36RN). Results of DNA repair studies were entirely normal. The patient had a normal male karyotype, and aCGH showed no major deletions or duplications.

The proband’s DNA was then subjected to WES. Given the known association of DSG1 mutations in prior cases of SAM syndrome, we screened WES variant data for mutations in DSG1 and related desmosomal genes. Repetitive analysis was initially focused on the DSG1 gene, which was previously reported to be causative in patients with SAM syndrome. No potentially pathogenic variants were identified in the DSG1 gene, and therefore genes encoding other desmosomal proteins were examined. Only nonpathogenic single nucleotide polymorphisms (SNPs) that have been found in healthy populations by the 1000 Genomes Project were identified in the desmosomal protein genes listed in Table I, with the exception of the novel point mutation c.1757A>C in DSP (encoding desmoplakin) predicting the amino acid substitution mutation p.His586Pro in the desmoplakin polypeptide.

The mutation was confirmed by means of Sanger sequencing (Fig 3, A and B) and excluded from 100 unrelated, ethnically matched healthy control subjects (200 alleles) by using Sanger sequencing. The mutation was not detected in the proband’s parents, indicating that it represents a de novo change. This mutation lies within the plakin domain of desmoplakin, which is shared by other members of the plakin protein family (Fig 3, C). The crystal structure of residues 175 to 630 of desmoplakin was described by Choi and Weis. Histidine 586 is located in an α-helix within spectrin repeat 6, a structure that is conserved in bullous pemphigoid antigen 1 and plectin. Histidine is a hydrophilic charged amino acid, whereas proline is a hydrophobic residue, and therefore this is a nonconservative amino acid substitution. More importantly, proline introduces a strong turn structure within polypeptide chains, and therefore this variant is strongly predicted to completely disrupt the conserved α-helix within desmoplakin’s spectrin repeat 6.

As an incidental finding, both the proband and his father were heterozygous for a c.6208G>A missense SNP in DSP, predicting the protein change p.Asp2070Asn (Table I). This SNP (rs41302885) was absent in maternal DNA. SNP rs41302885 has been found at a low frequency in healthy populations, with
minor allele frequencies of 0.0026 (1000 Genomes Project; http://www.ncbi.nlm.nih.gov/SNP/) and 0.0033 (Exome Variant Server; http://evs.gs.washington.edu). Therefore this variant, like those seen in other desmosomal genes (Table I), is predicted to be a nonpathogenic polymorphism.

High-density aCGH was performed to exclude the presence of a second compound heterozygous genomic mutation that might be missed by both WES and targeted PCR-based sequencing, such as deletion or duplication of 1 or more exons. The Affymetrix 750K array used had full probe coverage for all exons of the DSP and DSG1 genes. No copy number changes were observed for either gene by using high-density aCGH. Consistent with this result, the coverage of WES sequence reads across the DSP gene was not significantly different from that of matched control samples (data not shown). Thus all molecular genetics data are consistent with the de novo missense mutation p.His586Pro in DSP being the causative genetic lesion.

**Ultrastructural analysis**

In normal human epidermis keratin filaments make looping attachments with the inner plaques of desmosomes.\(^1\) Electron microscopy of the patient’s skin (Fig 4) showed a striking disassociation between keratin filament bundles (asterisks in the control tissue image) and desmosomes in the spinous layer of the epidermis, where desmosomes are most clearly visualized (Fig 4, A and B). The desmosomal inner plaques were much less electron dense and appeared poorly formed compared with desmosomes observed in normal control skin (Fig 4, C and D). The stratum corneum also displayed striking structural abnormalities (Fig 5), including marked attenuation of cornified envelopes (Fig 5, J, double arrows), a virtual absence of

**TABLE I. Desmosome protein variants**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Missense SNP</th>
<th>Zygosity</th>
<th>dbSNP no.</th>
<th>Minor allele frequency (1000 Genomes Project)</th>
</tr>
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<tbody>
<tr>
<td>DSP</td>
<td>Desmoplakin</td>
<td>p.Asp2070T &gt;p.His586Pro</td>
<td>Het</td>
<td>rs41302885</td>
<td>0.0026</td>
</tr>
<tr>
<td>DSG1</td>
<td>Desmoglein 1</td>
<td>p.Met111Val</td>
<td>Hom</td>
<td>rs1426310</td>
<td>0.3626</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desmoglein 2</td>
<td>p.Ile293Val</td>
<td>Het</td>
<td>rs2230234</td>
<td>0.0323</td>
</tr>
<tr>
<td>DSG3</td>
<td>Desmoglein 3</td>
<td>p.Arg773Lys</td>
<td>Het</td>
<td>rs2278792</td>
<td>0.2400</td>
</tr>
<tr>
<td>DSG4</td>
<td>Desmoglein 4</td>
<td>p.Ile644Leu</td>
<td>Hom</td>
<td>rs4799570</td>
<td>0.0341</td>
</tr>
<tr>
<td>DSC1</td>
<td>Desmocollin 1</td>
<td>p.Met659Thr</td>
<td>Het</td>
<td>rs28620831</td>
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</tr>
<tr>
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<td>Het</td>
<td>rs985861</td>
<td>0.0933</td>
</tr>
<tr>
<td>DSC3</td>
<td>Desmocollin 3</td>
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<td>Het</td>
<td>rs1893963</td>
<td>0.1965</td>
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<tr>
<td>JUP</td>
<td>Plakoglobin</td>
<td>p.Arg142His</td>
<td>Het</td>
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<td>PKP1</td>
<td>Plakophilin 1</td>
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<tr>
<td>PKP2</td>
<td>Plakophilin 2</td>
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<td></td>
<td></td>
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<tr>
<td>PKP3</td>
<td>Plakophilin 3</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKP4</td>
<td>Plakophilin 4</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSDD</td>
<td>Corneodesmosin</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EVPL</td>
<td>Envoplakin</td>
<td>p.Gln433Arg</td>
<td>Het</td>
<td>rs2071192</td>
<td>0.3241</td>
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<tr>
<td>EVPLL</td>
<td>Envoplakin-like</td>
<td>p.Ser4Asn</td>
<td>Het</td>
<td>rs570145</td>
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<tr>
<td>PPL</td>
<td>Periplakin</td>
<td>p.Arg819Ser</td>
<td>Hom</td>
<td>rs2734742</td>
<td>0.0617</td>
</tr>
</tbody>
</table>

Het, Heterozygous; Hom, homozygous.
Variables in boldface are disease causing.
corneodesmosomes, and abnormalities in the postsecretory maturation (Fig 5, C) and organization of secreted lamellar body contents (Fig 5, B, and E-G).

**Immunohistochemistry**

Immunofluorescence analysis revealed aberrant desmoplakin staining, appearing as large accumulations or aggregates (Fig 6, A and B). Striking reductions in both desmoglein 1 and keratin 10 staining were observed (Fig 6, E-H). What DSG1 remained appeared in aggregates. Plakoglobin distribution appeared less perturbed, with largely plasma membrane–associated staining punctuated by fluorescence-bright regions that colocalized in some cases with desmoplakin aggregates (Fig 6, C and D).

**DISCUSSION**

Intercellular junction complexes are a diverse group of organelles that function to provide adherence and communication between individual cells, as well as contributing to the
integrity of larger tissues. These intercellular junctions include desmosomes, adherens junctions, tight junctions, and gap junctions. Desmosomes are intercellular attachment and anchoring sites for the intermediate filament cytoskeleton. Electron microscopic studies have characterized their ultrastructure as containing the intermediate filament-associated inner plaque, an electron-dense outer plaque, the plasma membrane, and the electron-dense midline in the extracellular domain.

Desmosomes are composed of several transmembrane and intracellular molecules. The transmembrane proteins facilitating intercellular adhesion are desmosomal cadherins, desmogleins, and desmocollins. Intracellular domains are attached to the intermediate filaments through a range of linker molecules, including desmoplakin, plakoglobin, and plakophilins.

Desmosomal structures are widely expressed in epithelia, including the intestinal mucosa, gall bladder, uterus and oviduct, liver, pancreas, stomach, salivary and thyroid glands, and epithelial cells of the nephron, but they are most abundant in tissues that experience mechanical stress, such as the skin and myocardium. Not only do desmosomes provide resistance to the strong mechanical forces applied to skin and cardiac muscle and therefore contribute to tissue cohesiveness, they also have a role in cell signaling and skin barrier functionality. These important functions explain, in part, the diverse range of disease phenotypes observed in patients with desmosomal diseases. Genetic abnormalities in desmosomal components result in a variety of skin and cardiac diseases.

Desmoplakin is an obligate component of functional desmosomes and is highly expressed in the heart, epidermis, and hair follicles. Desmoplakin associates with intermediate filaments through its C-terminus and interacts with plakophilins and plakoglobin through its N-terminus to target the desmoplakin-keratin complex to the desmosomal inner plaque. Desmoplakin haploinsufficiency has been reported to cause autosomal dominant type II striae PPK without any other skin, hair, or extracutaneous features. This clinical phenotype suggests that a 50% expression level of desmoplakin is sufficient for epidermal functioning in most body sites but not for the palms and soles, which are subject to considerable mechanical stress. Recessive mutations in desmoplakin result in severe phenotypes. Carvajal syndrome is characterized by striae PPK, woolly hair, and left ventricular cardiomyopathy. Skin fragility/woolly hair syndrome is also caused by recessive mutations in DSP. Reported cases included compound heterozygosity for a nonsense/missense combination of mutations. The clinical phenotype described in the reports was a focal and diffuse PPK, hyperkeratotic plaques on the trunk and limbs, and varying degrees of alopecia but no apparent cardiomyopathy. Heterozygous carriers of these mutations displayed no phenotypic abnormalities. Lethal acantholytic epidermolysis bullosa has been reported in a neonate presenting as complete alopecia, neonatal teeth, nail loss, extensive skin erosion, and neonatal death. The infant had compound heterozygosity for a recessive nonsense and frameshift DSP mutation, resulting in deletion of the intermediate filament-binding sites in the desmoplakin tail domain.

**FIG 4.** Ultrastructural abnormalities. **A,** Abundant keratin filaments (asterisks) anchored to desmosomes (arrows) in the cytoplasm of a spinous cell in normal human epidermis. **B,** Note the scarcity of keratin filaments at the same level in the proband. **C,** Common desmosomal structure with normal inner dense plaque (arrowheads) in a human control sample. **D,** In contrast, a poorly formed inner dense plaque lacking evidence of keratin filament attachment was observed in the proband.
Our case is the first reported case of SAM syndrome caused by a DSP mutation. The recently reported families with SAM syndrome had biallelic loss-of-function mutations in DSG1.7,8 Desmoglein 1 is a member of the desmosomal cadherins and strongly expressed in the granular and spinous layers of the epidermis18,19 and hair follicles.20 Heterozygous mutations in DSG1 cause type I striate PPK. Homozygous DSG1 mutations were reported to cause the severe phenotype of SAM syndrome.7 The first reported cases were
The described phenotype was congenital erythroderma; skin erosions and scaling; yellowish papules and plaques at the periphery of the palms, along the fingers, and over weight-bearing areas of the feet; and hypotrichosis. From early infancy, they had markedly increased IgE levels, severe food allergies, and recurrent infections with severe metabolic wasting. Minor cardiac developmental defects were noted in 2 patients, which is in keeping with the association between desmosomal diseases and cardiac conditions. Two of the patients also had esophageal involvement, which was similar to our patient. The fourth reported case, the only child of healthy unrelated parents, had a milder phenotype with PPK, dermatitis, and multiple allergies but had normal hair and was otherwise well. 8 Samuelov et al demonstrated that DSG1 deficiency was associated with increased expression of genes encoding the allergy-related cytokines thymic stromal lymphopoietin, IL-5, and TNF. It is notable that our patient and other patients with SAM syndrome had esophageal involvement; our patient had separation and detachment of the esophageal superficial squamous cells, and another patient with SAM syndrome had typical eosinophilic esophagitis. 7 Similar to SAM syndrome, eosinophilic esophagitis is characterized by allergic inflammation of the esophageal mucosa, immune sensitization to foods, and impaired esophageal barrier function. 26 Recent data have suggested a functional role for DSG1 and its dysregulation in the pathophysiology of eosinophilic esophagitis. Furthermore, the loss of DSG1 expression might potentiate allergic inflammation through induction of proinflammatory mediators. 15,27 Our patient showed a marked reduction in desmoglein 1 protein expression, as shown by immunohistochemical staining of the skin (Fig 6), despite not having a DSG1 mutation. This reduction in expression might be due, at least in part, to disruption of stable complexes comprising both DSP and DSG1. The primary structure of desmoplakin has 3 distinct regions: the 1056-amino-acid N-terminal domain, an 890-residue central coiled-coil domain, and a 925-residue C-terminal intermediate filament binding domain (Fig 3, C). 14 Yeast two-hybrid assays and communoprecipitation experiments showed that desmoplakin’s N-terminal 584-amino-acid region is necessary and sufficient to target desmoplakin to the inner desmosomal plaque through its association with armadillo proteins. 14,21 It is likely that replacement of histidine with proline in close proximity to this region disrupts protein conformation and possibly armadillo protein binding, leading to defects in DSP localization and function. More recently, the microtubule plus tip protein end-binding protein 1 was identified as a binding partner for this same region of desmoplakin. 27 In addition, the observed loss of DSG1 that occurs secondary to desmoplakin defects might be a causative factor in decreasing keratin expression because DSG1 suppresses the extracellular signal-regulated kinase signaling required to promote differentiation, including expression of genes important for barrier formation. 28,29 Thus DSG1 not only maintains adhesion in the upper epidermis but also instructs an early epidermal differentiation program on stratification. 30 The attenuation of differentiation might also lead to loss of expression of other epidermal proteins, therefore further exacerbating the barrier defect. Because DSG1 expression or localization is affected in all cases of SAM syndrome, it is unclear whether it is the loss of DSG1 or DSP at intercellular junctions that might be causative in the disease.

Although FLG mutations are the most significant mutations associated with AD, many other genes involved in skin barrier function have been implicated, including SNPs in the SPINK5 gene. 31 Homozygous or compound heterozygous loss-of-function mutations in the SPINK5 gene result in the autosomal recessive disorder Netherton syndrome, with severe AD and allergy. 4 Furthermore, proteomic profiling of skin from patients with AD has found that multiple other proteins related to the skin barrier were expressed at significantly lower levels in lesional compared with nonlesional sites of patients with AD. These
proteins included filagrin 2, corneodesmosin, desmoglein 1, desmocollin 1, and transglutaminase 3. Nonlesional AD skin might also partially share the lesional skin phenotype. It has been shown that nonlesional skin has reduced expression of filaggrin and filagrin-like proteins, as well as increased expression of immune genes.

The pathomechanisms of AD are complex and include interplay between epidermal structural abnormalities and immune dysregulation. However, there are several lines of evidence supporting the role of an aberrant skin barrier in the development of atopic diseases and allergy. The compromised skin barrier might allow enhanced allergen exposure to the cutaneous immune system, enhanced Th2 responses, and development of allergies. Alternatively, or in addition, the structural protein-deficient epithelium might be proinflammatory and primed for the development of allergy.

We report a fifth case of SAM syndrome and the first case caused by desmoplakin mutations. SAM syndrome substantiates the role of heritable skin barrier defects, particularly in desmosomal proteins, in the pathogenesis of atopic disease. The pathomechanisms of SAM syndrome require further investigation and might provide valuable insights into the development of atopic diseases.

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**Clinical implications:** Three families with SAM syndrome have been reported, all with mutations in **DSG1**. We report a fifth case, the first linked to a **DSP** mutation. In patients with SAM syndrome, mutations in **DSG1**, **DSP**, and other desmosomal proteins should be considered.

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