Appendix S1

SUPPLEMENTARY MATERIAL

Study methods

Immunological assessment was performed by methods described previously (S1). Briefly, flow cytometry was applied for lymphocyte subsets analysis, enzyme immunoassay for complement activity measurement and photometric immunochemistry for the evaluation of Ig levels. Lymphocyte stimulation was tested with flow cytometry, as well as with a standard 3H-thymidine incorporation method (S2). Maternal engraftment was excluded by a standard fluorescence in situ hybridization (FISH) assay.

Skin immunostaining and microscopy. Skin biopsies were taken from the patient for diagnostic purposes and processed for formalin-fixed paraffin-embedded sections according to standard procedures. Histopathological analyses were performed by experienced dermatopathologists at the Department of Dermatology, Helsinki University Hospital. DSP expression was studied with anti-Desmoplakin rabbit antibody (Sigma Life Science, HPA045840, dilution 1:200), DSG-1 with a monoclonal anti-Desmoglein 1 mouse antibody (Progen Biotechnik GmbH Mab to Desmoglein 1, clone Dsg 1-P23, 652110, dilution 1:1000) and KRT10 with an anti-Keratin 10 mouse antibody (Thermo Fisher Scientific, MS-611-P, dilution 1:1200) after antigen retrieval with microwave treatment. The bound antibody was visualized with Vector Universal ImmPRESS reagent kit.

Electron microscopy. Skin biopsies were fixed with 2.5% glutaraldehyde-4% formaldehyde in 0.1 M phosphate buffer for 12 h minimum. After washing, tissue specimens were treated with 1% osmium tetroxide and 1% uranyl acetate and subsequently embedded into Epon resin. Finally, ultrathin 60 nm sections were placed on copper grids and sequentially stained with 1% uranyl acetate and lead citrate solutions. Sections were viewed and photographed using Tecnai G2 Spirit electron microscope.

Hair analysis. Hair samples were taken from the patient and analysed with a light microscope.

Oesophagus and gastric biopsies. Oesophagogastroduodenoscopy was performed by a paediatric endoscopist. During the procedure, at least 2 biopsies were taken from antrum, corpus, oesophagus and duodenum.

Whole-exome sequencing and variant analysis. Clinical whole-exome sequencing was performed for the patient at Blueprint Genetics (Helsinki, Finland). Total genomic DNA was extracted from EDTA blood.

The SureSelect Human All Exome V6 kit (Agilent Technologies, Santa Clara, CA, USA) was used for exome capture and sequencing was performed at BGI (Hong Kong) using the HiSeq 4000 platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the human reference genome hg19 (GRCh37) using Burrows-Wheeler Aligner (S3). Sequence variants were called using GATK HaplotypeCaller (S4). Variants were annotated using Variant Effect Predictor (S5). Annotated variants were prioritized based on their population frequency, consequence, presence in clinical variant databases and gene-phenotype associations.

Protein modelling. RaptorX (17) and Swiss-model (18) were used for protein modelling to predict conformational changes cause by the variant.

Literature search. PubMed search was performed for the terms "SAM syndrome", "severe dermatitis", "multiple allergies", "metabolic wasting", "erythroderma", "failure to thrive", "infections" combined with desmosomal genes "*DSG1*" and "*DSP*". Articles were selected that describe patients with confirmed variants in desmosomal genes and a phenotype similar to our patient's, as well as those describing patients with SR6 region DSP variants.

Statistics. Statistical analyses were performed with IBM SPSS Statistics software Version 23 and Fisher's exact test was implicated to compare categorical variables.

Cytokine measurements were performed using serum of the patient sampled at 5 different time-points. IL-17A, IL-17F, IL-12p70 and IL-23 were measured using the ultrasensitive Single Molecule Array (Simoa, Quanterix, Lexington, USA) technology (S6).

SUPPLEMENTARY REFERENCES

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