

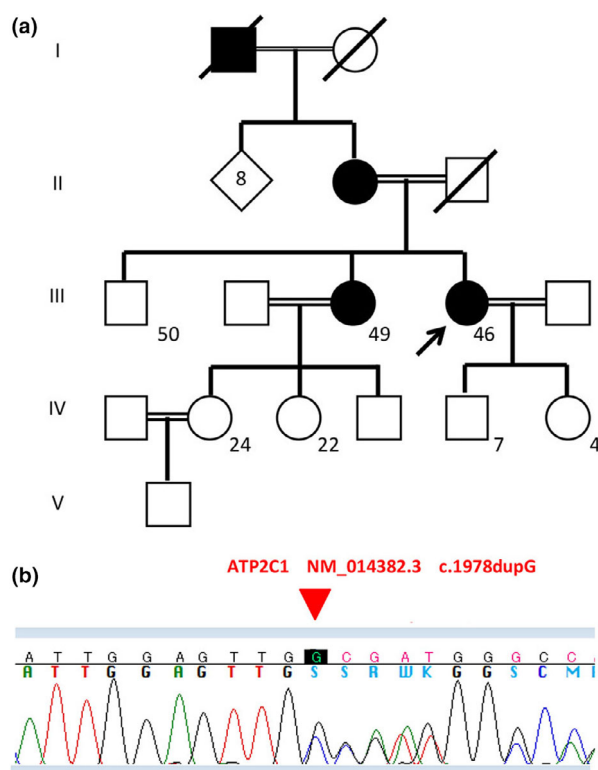


Figure 2 (a) Family tree. White square: normal male; white circle, normal female; black square, male with symptoms of Hailey-Hailey disease (HHD); black circle, female with symptoms of HHD; arrow, the patient described in this report. (b) Sanger sequencing of the *ATP2C1* gene, showing a heterogeneous mutation at c.1978dupG, resulting in the change p.A660Gfs*21 in the patient. The same mutation was present in the patient's mother and elder sister. Upper characters are the reference sequence.

This variant has not been reported previously for *ATP2C1*. Although over 200 mutations in this gene have been reported to date,³ no reports have clarified the correlations between the site and type of gene mutation and differences in clinical symptoms.⁴ It is also unclear why the clinical symptoms of HHD are solely isolated to the skin, despite *ATP2C1* being expressed in all tissues.⁵ Accumulation of gene mutations and clinical reports will facilitate further elucidation of disease pathogenesis and the development of more effective treatments for HHD.

S. Itsukage,¹ N. Kambe,^{1,2} Y. Ueki,¹ C. Sato³ and H. Nakano⁴

¹Departments of, Department of, Dermatology, Kansai Medical University, Hirakata, Osaka, Japan; ³Department of, Pathology and Laboratory Medicine, Kansai Medical University, Hirakata, Osaka, Japan; ²Department of Dermatology, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, Japan and ⁴Department of

Dermatology, Hirosaki University School of Medicine, Hirosaki, Aomori, Japan

E-mail: nkambe@kuhp.kyoto-u.ac.jp

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Successful treatment with dupilumab of an adult with Netherton syndrome

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Netherton syndrome (NS), also known as ichthyosis linearis circumflexa, is a rare autosomal recessive disorder. NS is caused by pathogenic loss-of-function variants in the serine protease inhibitor of the Kazal type 5 gene (*SPINK5*), which compromise the function of the lymphoepithelial Kazal inhibitor type 1 (LEKTI-1) protein. The unopposed serine protease activity due to reduced LEKTI-1 inhibition in NS, leads to premature degradation of corneodesmosomes, causing decreased stratum corneum cohesion and thinning. Reduced inhibition of kallikreins also leads to release of thymic stromal lymphopoietin and T helper (Th)2 cytokines as well as activation of Langerhans cells, which in turn further perpetuate the skin barrier dysfunction and cause inflammation.

NS mimics atopic dermatitis (AD) or psoriasis in infancy and early childhood, potentially resulting in a wrong diagnosis. Children with NS may often develop allergic manifestations with high levels of IgE and presence of AD-like inflammation.

At present, there are no specific treatments available for patients with NS. Dupilumab is a fully human monoclonal antibody against the interleukin (IL)-4 α receptor

subunit, and thereby limits signalling from IL-4 and IL-13. Both IL-4 and IL-13 are crucial cytokines in the Th2 pathways, and are key players in atopic diseases including asthma and AD.

A 43-year-old man with sustained and severe clinical diagnosed NS, and a history of asthma, iatrogenic adrenal insufficiency, actinic keratoses and squamous cell carcinoma has been followed up and managed in our department since birth. The disease severity of NS had been constant since childhood. Previous systemic medical treatments for NS included corticosteroids, methotrexate, mycophenolate mofetil, azathioprine and ultraviolet therapy, which had all failed, and topical treatment with corticosteroids and calcineurin inhibitors.

Following written informed consent from the patient, a genetic study was performed. Whole genome sequencing of DNA isolated from full blood revealed the heterozygous presence of the known pathogenic *SPINK5* (NM_001127698.1) mutation consisting of a 2-bp deletion, c.316_317delGA, predicted to introduce a premature stop codon, p.(Asp106Trpfs*7). We assumed there was a second pathogenic variant located outside the *SPINK5* coding region, but this has yet to be analysed. We also identified several rare

heterozygous intronic variants. cDNA analysis is presently ongoing, to explore the potential effect on RNA splicing.

We initiated treatment with dupilumab injections, starting with a loading dose of 600 mg followed by 300 mg every second week. At baseline, the Eczema Area and Severity Index (EASI) score was 22.6, Dermatology Life Quality Index (DLQI) was 19 and Patient Oriented Eczema Measure (POEM) was 15. Blood samples showed leucocytes $13.8 \times 10^9/L$ (normal range $3.5\text{--}8.8 \times 10^9/L$) and total IgE 13 600 kIU/L (normal < 120 kIU/L). At the 4-week follow-up, EASI was reduced to 5.3, DLQI to 2 and POEM to 9, while leucocytes had dropped to $9.3 \times 10^9/L$ and total IgE to 9150 kIU/L (Fig. 1). After 6 months of treatment, the NS is still reduced to a minimum.

Our case report supports that IL-4 receptor antagonism may dramatically reduce cutaneous inflammation in NS.¹ However, the levels of IL-13, a prominent Th2 cytokine, in skin and blood were similar in patients with NS and healthy controls in recent studies.^{2,3} Similarly, the increase in some Th2 chemokine markers (e.g. CCL-18) is significantly lower in patients with NS than in patients with AD.^{2,4} Moreover, Th2 suppression, via protease-activated receptor 2/thymic stromal lymphopoietin (TSLP)



Figure 1 Clinical response to dupilumab (a) at baseline, before treatment; (b) at follow-up 4 weeks after treatment initiation.

blockade in an NS mouse model, showed no reduction in cutaneous inflammation, which would further argue against a significant Th2 skew in NS and a treatment benefit of dupilumab.⁵ However, the unopposed serine protease activity and reduced inhibition of kallikreins together with eosinophilic activation, increased numbers of mast cells and elevated levels of TSLP in NS stimulate differentiation of Th0 to Th2 cells.^{6,7} This initiates the development of lesions similar to those observed in AD. Interestingly, the reduced levels of Th2 cytokines in some patients with NS could be explained by downregulation via Th17 pathways.⁴ IL-17, IL-19 and Th17/IL-23 pathways were upregulated in skin and blood of 15 patients with NS aged 6–43 years, and IL-17 levels were higher than in patients with AD.^{2–4} It is possible that the inflammation is different in patients with NS than patients with AD; they may have a different skew of Th2 and Th17 pathways and this relative skew might change with age.

The exact immune activation in NS is currently unclear. Which biologic treatment, if any, that is best suited to individual patients with NS remains to be defined. One study including three patients with NS observed increased Th1 marker levels in patients with NS similar to that of patients with AD and patients with psoriasis.² A recent case report demonstrated a clinical effect of treatment with ustekinumab, which is an IL-12/-23 antibody, in a 15-year-old girl with NS.⁸ Importantly, anti-inflammatory treatment cannot treat the primary skin barrier defect, and patients with NS need to continue applying emollients daily.

We conclude that treatment with dupilumab in our adult patient with NS led to the dramatic reduction in EASI. Further studies are needed to evaluate the immune profile of patients with NS.

**T. H. Andreassen,^{1,2}  H. G. Karstensen,³  M. Duno,³ 
U. Lei,¹  C. Zachariae¹  and J. P. Thyssen^{1,2} **

¹Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; ²CORGIS, Copenhagen Research Group for Inflammatory Skin, Hellerup, Denmark and ³Department of Clinical Genetics, Rigshospitalet, University Hospital Copenhagen, Hellerup, Denmark

E-mail: jacob.p.thyssen@regionh.dk

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Methodological considerations when exploring the impact of social media health promotional materials

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Linked article: Guckian J *et al.* *Clin Exp Dermatol* 2020; **45**: 295–301

We read with interest the recent article in *Clinical and Experimental Dermatology* by Guckian and colleagues, exploring the impact of social media as a potential influence on the patient journey from recognizing a suspicious skin lesion to attending a melanoma screening clinic.¹

Social media and its impact on medicine is a novel research area and is receiving increased attention owing to the rising influence of social media on people's lives and in turn, their decision-making. However, there is limited availability of statistical data regarding user demographics and their social media usage within the academic literature. Such information is found within market research companies who collect and use this data, or within the social media platform itself. This is a challenge when studying the influence of social media within the medical context, as the market share of social media platforms vary according to user age, sex and location. Data regarding demographic usage of particular social media platforms and the type of interaction they prefer is vital to align