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Homozygous *IL36RN* mutation and *NSD1* duplication in a patient with severe pustular psoriasis and symptoms unrelated to deficiency of interleukin-36 receptor antagonist

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DEAR EDITOR, Generalized pustular psoriasis (GPP) is a severe inflammatory skin disease characterized by sudden episodic generalized erythematous eruption with pustules, high-grade fever, leucocytosis/neutrophilia and elevated C-reactive protein.¹ Familial forms of this condition, caused by homozygous mutations of *IL36RN*,^{2–6} are named DITRA (deficiency of interleukin-36 receptor antagonist; OMIM #614204). Interestingly, widespread aseptic pustular rash defines another genetic disorder – due to *IL1RN* mutations – called DIRA (deficiency of interleukin-1 receptor antagonist; OMIM#612852).⁷ However, DIRA has different clinical manifestations from DITRA, including major skeletal anomalies, severe failure to thrive (SFTT) and osteomyelitis.

Here we report a patient with severe neonatal-onset pustular psoriasis, recurrently exacerbated, along with > 38 °C fever associated with a complex developmental syndrome including microcephaly, aortic stenosis, osteomyelitis and SFTT. On family whole-exome sequencing he was shown to carry a recessive *IL36RN* mutation and an *NSD1* microduplication. The methods are described in the Supporting Information.

The patient was the third child of consanguineous healthy parents (first cousins) of Moroccan origin. He was a boy born at 37 weeks of gestation. Critical antenatal aortic stenosis was diagnosed by routine fetal echocardiogram. It was due to a bicuspid aortic valve, which needed early postnatal (1 month of age) surgical commissurotomy (the postoperative period was uneventful). This was a congenital abnormality with no sign of pre- or postnatal aortitis/vasculitis. A postsurgery echocardiographic view is shown in Figure S1 (see Supporting Information), clearly showing aortic stenosis with a thickened dome-shaped aortic valve. His birthweight was 2560 g (–1 SD), length 45 cm (–3 SD) and occipitofrontal circumference (OFC) 33.5 cm (–1.5 SD). Physical examination at birth showed also hypospadias. At the age of 2 months, he presented a recalcitrant erythematous rash initially located at the diaper area, which progressively expanded to localized erythematous squamous plaques with rare pustules (Fig. 1a). In addition, he had recurrent cutaneous erythematous exacerbations with fevers. He had chronic oral lesions (migratory glossitis) (Fig. 1b) and nail changes (Fig. 1c). Routine laboratory investigations showed high C-reactive protein and neutrophilia (14×10^9 cells L^{–1}; normal range 1.5–8.5 $\times 10^9$ cells L^{–1}) during fever flares. IgA and IgM levels were within the normal ranges. No features of immunodeficiency were detected. At the age of 4 months, his weight was 4200 g (–3 SD), his length 62 cm (–4 SD) and OFC 41 cm (–3.5 SD). At the age of 8 months he had an episode of *Staphylococcus aureus* septicaemia with calcaneal osteomyelitis (no other hotspots were detected in a bone scintigraphy; Fig. S1b; see Supporting Information), which was treated by intravenous cloxacillin. Topical corticosteroids, topical tacrolimus and systemic retinoids were ineffective. Escalating doses of anti-interleukin-1 therapy – firstly anakinra, one injection per day, incrementally up to 5 mg kg^{–1} during 3 month, and subsequently canakinumab at 2 mg kg^{–1} then 3 mg kg^{–1} every 8 weeks – did not alleviate the clinical symptoms. At the age of 3 years, he still had SFTT [weight 13.3 kg (–1 SD), length 89 cm (–2.5 SD), OFC 45 cm (–4.6 SD)] and was nourished by gastrostomy. He still had a recalcitrant psoriasis that formed chronic plaque lesions (Fig. 1d) with rare localized pustules and recurrent diffuse erythematous exacerbations with fevers (Fig. 1e). He had no recurrence of osteomyelitis. Skin biopsies showed a psoriasiform dermatosis with mild parakeratosis and spongiform pustules. In addition neutrophils were punctually seen in the dermal papilla, whereas only a few lymphocytes were present in the superficial dermis. This might have been due to the relatively early timing of the biopsy at 4 months of age, and the fact that we biopsied an erythematous plaque (Fig. 1f–i).

Fig 1. Clinical characteristics of the patient and skin histopathology. (a) Localized erythematous squamous plaque with rare pustules. (b) Chronic migratory glossitis. (c) Diffuse erythema on both feet with nail changes. (d) Severe erythematous squamous dermatitis of the head. (e) Diffuse erythematous exacerbation during fever flare with no pustules. (f) Overall and (g) focused views of the skin displaying the psoriasiform hyperplasia of the epidermis and the absence of any lymphocytic infiltration. The epidermis shows a psoriatic edge. The superficial dermis is devoid of any lymphocytes. Within a dermal papilla a neutrophilic infiltrate is visible. Another overall (h) and focused (i) skin view showing the absence of lymphocyte infiltration (h), but with the presence of small numbers of neutrophils within the superficial epidermis sketching a spongiform pustule. The biopsy for (f–i) was realized at 4–5 months of age. Haematoxylin–eosin–safran staining; magnification $\times 100$ (f, h) and $\times 200$ (g, i).

According to the clinical examination, we first suspected a DIRA, but genetic testing for *IL1RN* was negative (data not shown). At the initial time of this study, the implication of *IL36RN* in generalized pustular psoriasis was unknown, so we performed whole-exome sequencing and array comparative genomic hybridization (CGH) of the proband (II1), his healthy brother (II2) and sister (II3) and the consanguineous parents (I1 and I2) (Fig. 2a). Array CGH analysis revealed a microduplication including the *NSD1* gene (5q35.2–q35.3) in the proband and his mother, but not in his father (further explanation in Fig. S2 and Appendix S1; see Supporting Information). By analysing genetic variants of the five family members we identified a known recessive mutation, c.T80C (p.L27P), in *IL36RN* (Fig. 2b). In addition to *IL36RN*, four other genes had homozygous protein-altering variants with no apparent relevance to our complex phenotype (Appendix S1).

In conclusion, we describe a unique phenotype in our patient. The vast majority of his symptoms are consistent with DITRA, but aortic stenosis, microcephaly and perhaps SFTT (which has recently been reported in a genuine case of DITRA, however)⁸ outreach the *IL36RN* deficiency and are likely due to the *NSD1* duplication (although with apparently incomplete penetrance in other members of the family; Fig. S2).⁹ Finally, this study further highlights the power of whole-exome sequencing in dissecting complex clinical phenotypes.

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Fig 2. Family pedigree and electropherograms of the IL36RN gene mutation c.T80C (p.L27P). (a) The solid symbol indicates the affected family member (proband). Open symbols represent unaffected members. Squares correspond to male family members, circles to female family members, slashes to deceased family members and double lines to a consanguineous relationship (in this case, first cousins). (b) I1, heterozygous sequence of the father with genotype T/C; I2, heterozygous sequence of the mother with genotype T/C; II1, homozygous sequence of the proband with genotype C/C; II2, homozygous sequence of the brother with genotype T/T; II3, heterozygous sequence of the sister with genotype T/C.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Supplementary materials and methods.

Fig S1. Aortic stenosis and calcaneal osteomyelitis.

Fig S2. Copy number variation analysis in the region 176 362 766–177 214 102 of chromosome 5.

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Mohs micrographic surgery in the U.K.: are we discriminating against people with blood-borne infections?

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DEAR EDITOR, Mohs micrographic surgery (MMS) is a specialized surgical technique used for precise excision of skin cancer under microscopic control. It has the highest known cure rate of any treatment for nonmelanoma skin cancer and is tissue conserving. MMS is normally carried out using frozen sections, which allows instantaneous assessment of adequacy of excision. We are aware that in the U.K., frozen-section MMS is often not undertaken in patients with blood-borne viruses (BBVs), including HIV and hepatitis B and C, because of a perceived risk to staff. We have examined the scope of this practice and question its basis.

We undertook a survey of members of the British Society for Dermatological Surgery (BSDS), of which the majority of the approximately 62 U.K. Mohs surgeons are members, according to the BSDS. The survey was designed to examine the present practice relating to the use of MMS for people with BBV. We received 28 responses (45%) from 62 Mohs surgeons in the U.K. according to the BSDS. Nineteen (68%) avoided frozen-section MMS in people with BBVs, while nine (32%) did not. Of those 19, the majority (15, 79%) offered formalin-fixed tissue techniques, namely slow Mohs. No respondent routinely screened for BBV prior to MMS. Comments from respondents cited different reasons for not undertaking MMS in such patients, including the difficulty in decontaminating the cryostat, lack of funding for testing for blood-borne infections, the risk to the technician and local laboratory protocols preventing frozen-section MMS being used in patients with a known BBV. No respondent had yet received a complaint from a patient as a result of not offering

MMS. Five respondents had experience with using automated cryostats for MMS tissue processing.

MMS involves several stages, including obtaining, laying down and cutting of specimens, fixing of slides, cover slip placement, viewing slides and reconstruction of the defect. There is the possibility of an occupational exposure injury at each of these stages if a patient has a blood-borne infection. The exact incidence of these injuries is not known;¹ however, in the U.K. the National Audit Office² has stated that sharps injuries were the second most common form of injury reported by National Health Service staff, accounting for 17% of accidents.

Our results illustrate a high degree of variability in practice in the U.K.: more than two-thirds of Mohs surgeons in the U.K. avoid frozen-section MMS, which is at odds with practice in the U.S.A., where 89.8% use standard frozen-section MMS in patients with known BBVs.¹ Formalin-fixed sections can be obtained, but this is a much slower process as the specimens need time to fix (1 h per 0.5 mm thickness), resulting in inconvenience to the patient and prolonged operations, perhaps over several days. Patients with HIV are also at higher risk of nonmelanoma skin cancer, and failure to offer MMS denies these patients access to the most effective treatment.

Risk of transmission during the operative stages, as a result of a sharps injury, may occur; however, the risk is not confined to this stage. Occupational exposure could occur during laying down and cutting of specimens. Even after this the specimens are not fixed in formaldehyde so the slides and coverslips may be a source of transmission of BBVs. Going a step further, the cryostat, Mohs trays and microscopes used during MMS may also be a source of transmission. However, the risk of transmission of a BBV during MMS is unknown,¹ with no cases of transmission of BBV while processing frozen sections found on a literature search. The risk of transmission may be higher with a high viral titre, which of course is actually more likely in patients who have occult infections and are therefore untreated.³

We suggest that current practice in many U.K. MMS units not to offer this treatment to people with BBV could be interpreted as unfair discrimination⁴ and might even be subject to litigation. The lack of a good evidence base and the widespread variability in practice within the U.K., especially in comparison with the U.S.A., suggest there is disagreement about best practice. We suggest that the presence of HIV or hepatitis B or C infection should not influence the selection of frozen-section MMS as a treatment, and that it should be routinely offered to all appropriate patients with application of appropriate precautions to minimize risk. Such precautions should be developed in close collaboration with pathology services. These might include pretesting individual for BBV; the use of double gloves; a no-touch technique; wearing eye protectors, masks or respirators; use of blunt skin hooks, safety scalpels and syringes; an automated cryostat and perhaps placing such patients at the end of surgical lists to allow cryostat decontamination. Finally, contaminated equipment such as