Correspondence

New variant in deficiency of interleukin-36 receptor antagonist syndrome (DITRA)

Dear Editor,

Deficiency of interleukin-36 receptor antagonist (DITRA) syndrome is an autoinflammatory disease caused by loss of function mutations in the interleukin-36 receptor. These patients present generalized pustular psoriasis (GPP) associated with systemic symptoms. We report the case of a boy suffering from DITRA syndrome and a novel mutation in the *IL36RN* gene.

We report the case of a 5-year-old boy who presented, since the age of 1 month, a succession of flares of generalized pustular eruptions associated with fever and inflammatory syndrome, each lasting a few days up to a week. He is the ninth child of a family of 10 healthy children, born to nonconsanguineous parents. Clinical examination showed multiple coalescing pustular lesions on an erythemato-squamous background affecting approximately 90% of the body surface (Fig. 1). Biopsy showed a hyperplastic psoriasiform epidermis devoid of granular layer, associated with an extensive neutrophilic exocytosis leading to a formation of spongiform subcorneal pustules. The underlying superficial dermis contained a perivascular inflammatory infiltrate of neutrophils accompanied by lymphocytes and histiocytes (Fig. 2), confirming the diagnosis of GPP.

Genetic analysis by mass sequencing in parallel on 4427 genes panel (SeqCap EZ Choice XL NimbleGen Roche) showed the presence of a paternal c.143G > A, p.(Arg48Gln) variant and a maternal c.227C > T, p.(Pro76Leu) variant in the *IL36RN* gene. Biallelic anomalies of the *IL36RN* gene are responsible for DITRA syndrome (OMIM: 614204).

DITRA syndrome is a life-threatening autoinflammatory disease first described by Marrakchi et al.[1] Homozygous or compound heterozygous loss-of-function mutations responsible for DITRA may be inherited or arise de novo, and both missense and nonsense pathogenic variants have been reported.[2] The c.227C > T (p. Pro76Leu) variant has already been described as pathogenic. The c.143G > A, p.(Arg48Gln) has never been reported in the literature and is considered as likely pathogenic. Indeed, it is located in the disulfide bond domain "disulfide bond_8-154" where most non VUS variants reported are pathologic (PM1), it is found in a single individual at the heterozygous state in the gnomAD database and never at the homozygous state (PM2), and it is detected in trans with a known pathogenic mutation (PM3). A variant affecting the same amino acid has already been reported as pathogenic c.142C > T (p. Arg48Trp) (PM5),[2] the rate of neutral missense variant in the *IL36RN* gene is low, and most reported pathogenic variants are missense

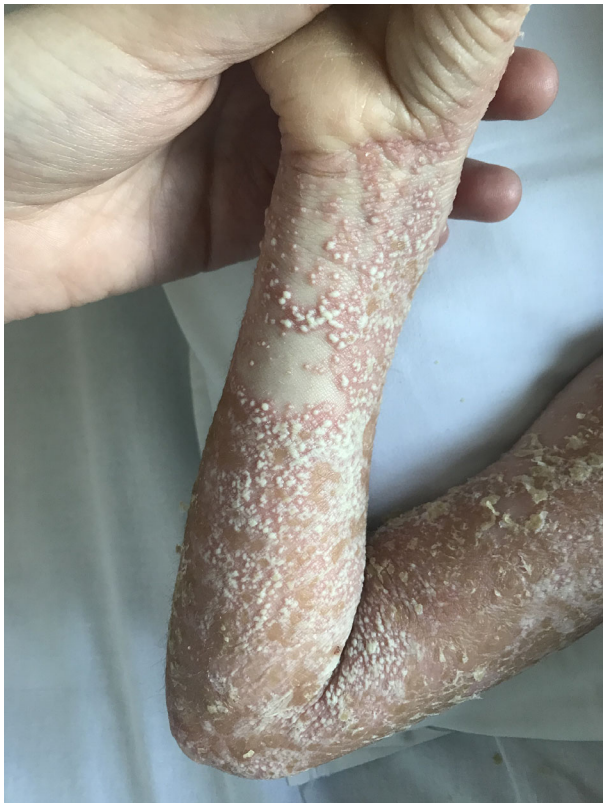

Figure 1 Generalized pustular eruption

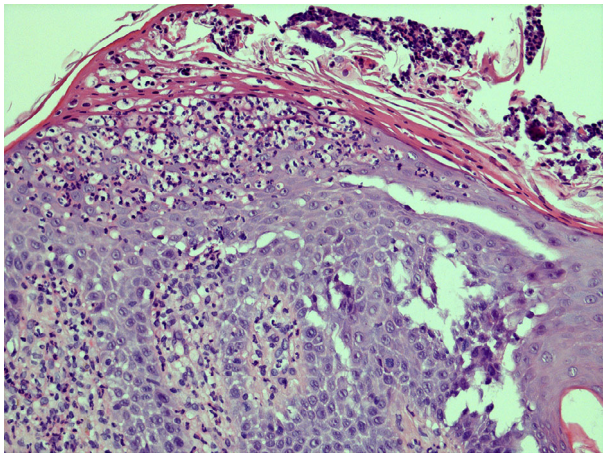

Figure 2 Subcorneal pustule (Hematoxylin and eosin, ×20)

(PP2). Only three other pathogenic/likely pathogenic variants are reported in Clinvar, and five others are found through literature.[3,4]

IL36RN, located on chromosome 2, encodes for the interleukin-36 receptor antagonist (IL-36Ra), a competitive inhibitor of IL-36 receptor. Loss of functional IL-36Ra leads to an unrestrained IL-36 activity which activates the nuclear factor-κB and mitogen-activated protein kinase pathways.[2] This overexpression of proinflammatory cytokines enhances the production of IL-8,[2] responsible for a neutrophilic infiltration. The age of onset of DITRA occurs during childhood. This condition can be life threatening, and rashes can be complicated by sepsis.[1] Mortality rate is estimated around 4–7%.[3]

Treatment guidelines do not exist specifically for DITRA syndrome because of its rarity; however, case reports and series show a good response to methotrexate, oral retinoids,[5] anti-TNF (etanercept, adalimumab, infliximab), or IL17 (secukinumab) and IL12/23 inhibitors (ustekinumab).[3] To date, there does not seem to be any link between genotype and response to treatment or evolution.

DITRA is a life-threatening autoinflammatory disease associating GPP and systemic symptoms. We report here a novel c.143G > A (p. Arg48Gln) likely pathogenic variant.

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Conflict of interest: None.

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References

1 Marrakchi S, Guigue P, Renshaw BR, *et al*. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011; **365**: 620–628.
2 Tauber M, Bal E, Pei X-Y, *et al*. IL36RN mutations affect protein expression and function: a basis for genotype-phenotype correlation in pustular diseases. *J Invest Dermatol* 2016; **136**: 1811–1819.
3 Hospach T, Glowatzki F, Blankenburg F, *et al*. Scoping review of biological treatment of deficiency of interleukin-36 receptor antagonist (DITRA) in children and adolescents. *Pediatr Rheumatol Online J* 2019; **17**: 37.
4 Bal E, Lim AC, Shen M, *et al*. Mutation in IL36RN impairs the processing and regulatory function of the interleukin-36-receptor antagonist and is associated with DITRA syndrome. *Exp Dermatol* 2019; **28**: 1114–1117.
5 Cuperus E, Koevoets R, van der Smagt JJ, *et al*. Juvenile interleukin-36 receptor antagonist deficiency (DITRA) with c.80T>C (p.Leu27Pro) mutation successfully treated with etanercept and acitretin. *JAAD Case Rep* 2018; **4**: 192–195.