mutation of the \textit{IL36RN} gene. Indeed, psoriasis in DITRA is pustular, is not preceded by PV, and often starts in childhood in the absence of a family history of psoriasis. It may be postulated that pure GPP is a subtype of psoriasis, different from GPP accompanied by PV. This hypothesis is supported by Sugiyura et al. [1]. Among the 14 mutations of the \textit{IL36RN} gene that have been documented, the c.115+6C>T homozygous mutation has been detected in 27 patients [2–9] (table S1). Pan et al. [6] suggested that this same mutation could be a marker for severe and treatment-resistant disease. In our patient, the GPP resisted four lines of treatment. This prompted us to introduce etanercept, which proved to be effective for a period of three years with no flares to date. We speculate that isolated GPP with DITRA has a distinct pathogenesis, moreover, treatment of sporadic GPP may not necessarily be effective in patients with DITRA. The response to treatment could also be different depending on the mutation. There are very few studies on sporadic or non-sporadic GPP in patients with DITRA syndrome and no comparative studies in terms of pathogenesis and treatment. Many treatments exist for sporadic GPP, but data on treatment response for DITRA are limited. We were unable to establish a relationship between the efficacy of treatment, the type of mutation, and the patient’s ethnic origin, and further studies are necessary to establish such an association. The efficacy of TNF-alpha inhibitors as treatment for patients with GPP, as well as DITRA syndrome, has been reported. The mode of action is not clearly understood. The c.115+6T>C mutation is responsible for a splice defect, which results in exon skipping due to a premature stop codon, thus leading to the production of a truncated IL36Ra protein [1]. The result is excessive signalling of IL-36-alpha, -beta, and -gamma; three cytokines belonging to the IFN-beta family of IL-1 involved in the generation of the inflammatory response [10]. The treatments used for GPP are not approved for DITRA, but the efficacy of TNF-alpha inhibitors has been reported. Further studies are necessary to show that TNF-alpha inhibitors are effective as treatment for DITRA.

Supplementary Material

Supplementary material (Table S1) accompanied by the online version of this article is available on http://www.sciencedirect.com and doi:10.1684/ejd.2018.3219.


Valérie BABIC
Sandra MOAWAD
Anne-Claire BURSZTEJN
Jean-Luc SCHMUTZ


A Chinese family with autosomal recessive congenital ichthyosis and Leber congenital amaurosis due to mutations in \textit{PNPLA1} and \text{LCA5}

Autosomal recessive congenital ichthyosis (ARCI) is a rare inheritable skin disorder characterized by abnormal desquamation over the whole body. Mutations in \textit{PNPLA1} are relatively rare in ARCI. In this study, we describe a consanguineous Chinese family with ARCI due to a novel missense mutation in \textit{PNPLA1}, as well as Leber congenital amaurosis due to a novel nonsense mutation in the \textit{LCA5} gene. The proband (IV-2; \textit{figure 1A}) was a 14-year-old boy and the offspring of consanguineous parents from first cousins. He had scales localized on his knee, abdomen, and lower limbs when he was one year old. Diffuse, brown, and linear or circumscribed scales (\textit{figure 1B; left}) became generalized over the whole body after age three. His elder brother (15 years old, IV-1; \textit{figure 1A}) was born as a collodion baby and later developed generalized ichthyosis with mild, fine, and greasy-white scales (\textit{figure 1B; right panel}). Electron microscopy showed massive and compact orthohyperkeratosis of up to more than 40 layers of cornified lamellae with electron-lucent lipid droplets in the lamellae, irregular accumulation of abnormal membranous and vesicular inclusions around nuclei in keratinocytes in the granular layer, and focal and severely attenuated cornified envelope (CE) indicating impaired barrier protection of CE (\textit{figure 1D}). In


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addition, the visual acuity of the two children was very low since four months old. On ophthalmological examinations, both children had poor visual acuity, nystagmus, and sluggish pupillary responses. Ophthalmofundoscopy revealed pale optic papillae and diffuse subretinal flecks (figure 1C). Franceschetti’s oculo-digital sign is characteristic of Leber congenital amaurosis and was positive in both children.

Whole-exome and PCR sequencing revealed a homozygous mutation of c.700C>T in PNPLA1 resulting in a missense mutation of p.Pro234Ser PNPLA1, and a homozygous mutation of c.795T>G (NM_001122769.2) in LCA5 resulting in a nonsense mutation at p.Tyr265* in LCA5 in the proband and his brother (figure 1E). These mutations were heterozygous in their parents. The p.Pro234Ser change in PNPLA1 was predicted to be a disease-causing mutation after we evaluated this change using the VarSome, SIFT and Polyphen-2 software. The three-dimensional model of hPNPLA1 was predicted by SWISS-MODEL using patatin-like phospholipase as the template (SMTL id: 4akx.1). Based on an analysis of structural interaction with the local environment for posi-