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LETTER TO THE EDITOR

Comment on Zhao et al. "Palmoplantar Keratoderma of the Gamborg-Nielsen Type is Caused by Mutations in the *SLURP1* Gene and Represents a Variant of Mal de Meleda"

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Sir,

As reported recently in *Acta Dermato-Venereologica*, Zhao et al. (1) identified mutations in the SLURP1 gene, encoding the secreted lymphocyte antigen 6/urokinase-type plasminogen activator receptor related protein-1 in patients with palmoplantar keratoderma of the Gamborg-Nielsen type (PPK-GN). They describe 15 patients with a marked, sharply demarcated, and waxy, usually yellowish PPK with an erythematous base, involvement of the dorsal sides of the fingers and toes, interspersions of erythematous skin in the hyperkeratosis and pseudo-ainhum. The clinical phenotype was complicated by hyperhidrosis and foul odour due to fungal superinfection. Symptoms began in the first year of life. The authors did not report skin changes on other parts of the body or mucosal symptoms. They suggest that, given the relatively mild phenotype, PPK-GN should be considered as a distinct entity allelic to Mal de Meleda (MDM) which is also caused by mutations in *SLURP1* (2).

We disagree with this suggestion. To classify a disease as allelic to another genetic disease caused by mutations in the same gene, the symptoms need to be distinct and (partly) non-overlapping, not demonstrate varying severity. For instance, both Papillon–Lefèvre syndrome (PLS, MIM #245000) and Haim–Munk syndrome (HMS, MIM #245010) are caused by mutations in the gene coding for cathepsin C (*CTSC*) (3). Their phenotypes overlap to include PPK and periodontitis, but in Haim–Munk syndrome, arachnodactyly, acroosteolysis, and onychogryphosis also develop. Because of this, HMS is considered a distinct entity allelic to PLS. Clearly, the situation for PPK-GN and MDM is quite different. These 2 conditions represent a spectrum of disease severity, as is seen in most genetic disorders. The cases described by Zhao et al. (1) are not remarkable for being especially mild or otherwise distinct from classic MDM.

To illustrate the point, we recently reported a Dutch cohort of MDM-patients with a phenotype comparable to the patients reported by Zhao et al. (1) All subjects had PPK with transgredient hyperkeratosis, pseudo-ainhum and hyperhidrosis with bacterial superinfection, with no skin symptoms elsewhere or mucosal changes (4). All patients had the p.Trp15Arg mutation in *SLURP1*, as was found in the majority of patients in the study by Zhao et al. (1). A relatively mild phenotype has been reported in a significant number of other studies on MDM, with varying severity of symptoms reported even within families harbouring the same mutation in *SLURP1* (5–9). Table SI[1] semi-quantitatively summarizes the phenotypes reported so far in individual patients with MDM, with a description of disease course, including age, clinical characteristics and *SLURP1* mutations. We added the data from the Dutch and Swedish cohorts. We are aware that drawing firm conclusions from these data is difficult; there are no reports describing large cohorts of patients and we acknowledge that there are no objective measures of MDM severity. That said, there seems to be a wide range of symptom severity, with previously reported cases of MDM being similar to the patients reported by Zhao et al. (1) The data suggest a tendency to a more severe course in older patients, which is consistent with earlier reports that note gradual progression during life. It would be of interest to follow disease progression and variation in a larger cohort of patients in order to obtain a more complete view of phenotypic variation in MDM.

In conclusion, we consider that PPK-GN represents only the mild end of the MDM spectrum. We therefore propose that the classification of PPK-GN as a separate genodermatosis should be abandoned.

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Reply to Nellen et al's Comment on the Classification of Clinical/genetic Variants of Mal de Meleda

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We thank Nellen et al. (1) for their valuable comments on our recent paper in *Acta Dermato-Venereologica* in which we showed for the first time that palmo-plantar keratoderma of the Gamborg-Nielsen type (PPK-GN, OMIM

244850) is caused by recessive mutations in the same gene as Mal de Maleda (MdM; OMIM 248300). Several pedigrees and clinical as well as ultrastructural characteristics of PPK-GN were described by Gamborg-Nielsen and co-workers in the late 1980s as a distinct disorder separate from autosomal dominant PPK, type Bothnia, which is very frequent in northern Sweden (18, 19). Until our recent publication, PPK-GN was considered by many as a distinct disease with as yet unknown aetiology. Our demonstration of recurrent and novel *SLURP-1* mutations in many of the Swedish patients with PPK-GN clearly identified this entity as a mild variant of MdM, indeed similar to what has been found in isolated cases of MdM in several countries, including Holland (4, 6; see Table I).

In their commentary, Nellen et al. dispute our mentioning on the last line of the Discussion (1) that "PPK-GN and MdM indeed are allelic disorders". We agree that this was pushing the distinction too far; perhaps a better phrasing would have been "PPK-GN is an allelic variant of MdM". But PPK-GN is still described in many textbooks and in McKusick's database (MIM) as a distinct entity; so, for both practical and historic reasons it may be of some value to use this eponym in parallel with MdM, at least in Sweden, where over the years many patients have been given the PPK-GN diagnosis based solely on clinical findings and inheritance pattern.

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