Palmoplantar keratoderma of the Gamborg-Nielsen type (PPK-GN) is a rare autosomal recessive skin disorder described in patients from Sweden. Mal de Meleda (MDM) is also a rare autosomal recessive inherited PPK first reported in 5 families from the island of Meleda. The two conditions phenotypically overlap and are characterised by palmoplantar erythematous hyperkeratotic plaques. The genetic background giving rise to PPK-GN has hitherto been unknown, whereas MDM is known to be caused by mutations in the gene encoding secreted Ly-6/uPAR-related protein 1, SLURP-1. In the present study we scrutinised individuals affected by PPK-GN for mutations in the SLURP1 gene and identified 2 different mutations. Fourteen Swedish patients were homozygous for a previously described mutation, c.43T>C, while one individual was a compound heterozygote with one copy of a novel mutation, c.280T>A, in addition to one copy of the c.43T>C mutation. Hereby we confirm that PPK-GN is an allelic variant of MDM.

Key words: SLURP1; mal de Meleda; palmoplantar keratoderma; Gamborg-Nielsen; missense mutation.

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Palmoplantar keratoderma of the Gamborg-Nielsen type (PPK-GN) or PPK of Norrbotten recessive type (OMIM 244850) was described as a diffuse PPK with autosomal recessive inheritance in patients from the northernmost county of Sweden by Gamborg Nielsen in 1985 (1). PPK-GN manifests with pronounced, often transgressive hyperkeratosis of palms and soles and an erythematous border next to the hyperkeratotic skin, tapered fingers are also observed. Mal de Meleda (MDM; OMIM 248300) or keratosis palmoplantaris transgradiens of Siemens is an autosomal recessive skin disorder first described in 1898 by Neumann (2) in patients from the island of Mljet (Meleda) in Dalmatia, Croatia. MDM is clinically characterised by symmetric transgressive PPK, and sometimes associated with lichenoid or keratotic plaques over joints, redness in the palms and soles, brachydactyly, cone-shaped fingers, pseudoainhum and nail abnormalities with pachyonychia. The progressive lesions can lead to reduced mobility of hands and feet because of contractions (2–8).

PPK-GN shows a similar, but less severe phenotype than most often seen in MDM, i.e. milder hyperkeratosis and no nail dystrophies or lichenoid plaques and no pachydermia or distant keratosis except for knuckle pads in some affected individuals (9). Histological features of PPK-GN are prominent hyperkeratosis and a transit region with a broadened granular layer. However, morphologically this transformation delay is less pronounced in PPK-GN than in MDM. Ultrastructural analyses also showed differences between MDM and PPK-GN in the affected epidermis suggesting the two disorders are not identical (9).

Linkage of MDM to the distal long arm of chromosome 8 was found in 1998 (3) and in 2001 it was established that individuals affected by MDM were found to carry mutations in the SLURP1 gene (10) that encodes secreted lymphocyte antigen 6/urokinase-type plasminogen activator receptor related protein-1.

A Dutch patient with a MDM phenotype but lacking mutations in the SLURP1 gene was described in 2002 (11) and an individual with PPK of the Nagashima-type was also found to be devoid of mutations in the SLURP1 gene in 2008 (12). The Nagashima-type of keratoderma is characterised by a transgressive and non-progressive PPK inherited in an autosomal recessive manner but with a milder phenotype than seen in classical MDM (12).

The aim of this study was to investigate if 15 Swedish patients affected by PPK-GN carry mutations in the SLURP1 gene.
RESULTS

Mutation analyses and clinical characteristics

Fourteen of the 15 individuals affected by PPK-GN were homozygous for a previously described mutation in exon 1 of SLURP1, c.43T>C, that results in a change of tryptophan to arginine, p.Trp15Arg (14). The parents of the affected individuals were all heterozygous carriers of this mutation (data not shown). The 14 affected individuals showed a marked, sharply demarcated, and waxy, usually yellowish PPK. Hyperkeratosis was also present on the back of fingers and toes, especially distally and around the joints. The hyperkeratosis was surrounded by erythema and patches of thinner erythematous skin were often interspersed in the hyperkeratotic skin. Fingers were often tapered towards the tips and occasionally constricting bands were present on the fingers. Maceration between toes was frequent and in some cases interdigital maceration was also observed. Complaints of painful fissures and foul-smelling hyperhidrosis among the patients were common. Most affected individuals had on-going or past histories of complicating fungal infections. Generally, the initial manifestation of PPK appeared during the first year of life, the skin changes then progressed until adulthood, sometimes with continuing progression during adult life but rare occasions of regression were also noted (Fig. 1).

In one of the 15 investigated patients, a novel missense mutation, c.280 T>A in exon 3 of SLURP1 (Fig. S1) was found in one allele. This transversion causes a change of the amino acid cysteine in position 94 to serine, p.Cys94Ser. None of the 100 control alleles sequenced harboured the C.280T>A mutation. The other SLURP1 allele in the patient with the novel mutation carried the same recurrent missense mutation as the other patients, c.43T>C (Fig. S1). One parent of the patient was shown to carry the mutation c.280T>A (Fig. S1) and the other parent the c.43T>C mutation (Fig. S1). The patient is a 2-year-old boy, the only child of unrelated parents from the southern part of Sweden with no family history of skin disease. The boy was born at term after an uneventful pregnancy. Dry palms and soles were noted at birth, and at 4 months definite thickness, scaling and redness had developed and progressed. When immersed in water the skin became “spongy” and whitish. Pruritus often developed at night-time but there were no blisters and no skin lesions were observed elsewhere. He was referred to the Genodermatosis Clinic of Uppsala University Hospital under the diagnosis of epidermolysis bullosa simplex or keratoderma. He showed massive keratoderma, hyperhidrosis and focal peeling, but no blisters (Fig. 2) and had no specific treatment. A tentative diagnosis of recessive PPK-GN or epidermolysis keratoderma was made, but analysis of

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Fig. 1. The palms of a 43-year-old woman with palmoplantar keratoderma of the Gamborg-Nielsen type homozygous for the recurrent c.43T>C mutation in the SLURP1 gene. The picture shows a marked, sharply demarcated palmar keratoderma with a waxy appearance.
SLURP1 mutations in Swedish keratoderma

The KRT9 gene did not reveal any mutation and thereby excluded the latter diagnosis.

Sequence alignments

Multiple sequence alignment of the SLUrP-1 protein was performed in order to estimate inter-species conservation of certain segments and to identify regions shared by other members of the Ly-6/uPAr family of proteins. The members of the uPAR family of proteins were not identical excluding the conserved cysteins that participate in disulphide bonds. Alignment of the human SLURP-1 sequence to other members of the Ly-6/uPAR protein family (hPSCA, hCD59, hE48 and huPAR) showed that the amino acid corresponding to the position of the novel p.Cys94Ser alteration is conserved in the vast majority of proteins (data not shown). Alignment of the human SLURP-1 sequence to 10 other species (Chimp., Macaque, Rat, Mouse, Dog, Cat, Cow, Opossum, Chicken and Tetraodon) also showed conservation of the cysteine corresponding to position 94 in the human SLURP-1 (data not shown).

DISCUSSION

SLURP-1 protein is involved in keratinocyte differentiation (15) and alterations of the protein can disturb normal skin development as has been found in patients with MDM (8, 10, 14, 16–22). The SLURP-1 protein is encoded by the 3 exons of the SLURP1 gene (previously ARS) and contains a signal peptide as well as conserved cysteines important in forming disulphide bonds that are critical for the function of the protein. Human SLURP-1 is a member of the large Ly-6/uPAR protein superfamily; proteins that contain 8–10 highly conserved cysteines that form disulphide bonds.

In this study we have genotyped 15 Swedish individuals from families with autosomal recessive PPK-GN.

Fourteen persons were found to be homozygous for a c.43T>C (p.Trp15Arg) mutation in the SLURP1 gene and as expected all parents of the affected individuals were heterozygous carriers. Since 13 affected individuals from 7 families originating from the 2 northernmost counties of Sweden have been found to carry identical homozygous haplotypes around the SLURP1 gene loci on chromosome 8qter (data not shown) a common founder for the mutation in this population is very probable. The c.43T>C mutation has been described previously in several different populations (8, 14, 16). The T to C transition introduces a positively charged arginine residue into the conserved non-polar signal sequence and the altered protein is predicted to have a shortened signal sequence and a weaker cleavage site at position 18 (14).

One of the 15 persons affected by PPK-GN was found to have compound heterozygous mutations in the SLURP1 gene, a novel c.280T>A mutation (p.Cys94Ser) in addition to the recurrent c.43T>C mutation; c.280T>A was not detected in 100 control alleles strengthening the assumption that this is a mutation causing disease and not a polymorphism. Moreover this mutation affects one of the conserved cysteine residues in the SLURP-1 protein that are essential in forming disulphide bridges within the protein, bridges that are critical for normal function of the protein.

So far, 16 distinct SLURP1 gene mutations have been reported in MDM (Table I). The PPK-GN patients in our study appears to have a milder phenotype than described in classical MDM and the mutations found are not identical with those described in the families from the Mjlet island by Fischer et al. 2001 (10). However, our findings confirm that mutations in the SLURP1 gene are responsible also for the milder type of autosomal recessive PPK encountered in Sweden, and that PPK-GN and MDM indeed are allelic disorders.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Consequence of mutation</th>
<th>Reference</th>
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<tr>
<td>c.1A&gt;C</td>
<td>p.Met1Leu</td>
<td>Eckl et al. 2003 (14)</td>
</tr>
<tr>
<td>c.43T&gt;C</td>
<td>p.Trp15Arg</td>
<td>Eckl et al. 2003 (14)</td>
</tr>
<tr>
<td>IVS1 G&gt;A</td>
<td>Altered splice site</td>
<td>Wajid et al. 2009 (19)</td>
</tr>
<tr>
<td>c.82delT</td>
<td>p.Cys28fs32Termin</td>
<td>Fischer et al. 2001 (10)</td>
</tr>
<tr>
<td>c.129C&gt;A</td>
<td>p.Cys43Termin</td>
<td>Muslumanoglu et al. 2006 (20)</td>
</tr>
<tr>
<td>c.212G&gt;A</td>
<td>p.Arg71His</td>
<td>Favre et al. 2007 (17)</td>
</tr>
<tr>
<td>IVS2 G&gt;A</td>
<td>Altered splice site</td>
<td>Fischer et al. 2001 (10)</td>
</tr>
<tr>
<td>c.229T&gt;C</td>
<td>p.Cys77Arg</td>
<td>Charfeddine et al. 2003 (18)</td>
</tr>
<tr>
<td>c.244C&gt;T</td>
<td>p.Pro82Ser</td>
<td>Gruber et al. 2011 (21)</td>
</tr>
<tr>
<td>c.256G&gt;C</td>
<td>p.Gly86Arg</td>
<td>Eckl et al. 2003 (14)</td>
</tr>
<tr>
<td>c.280T&gt;A</td>
<td>p.Cys94Ser</td>
<td>Present study</td>
</tr>
<tr>
<td>c.286C&gt;T</td>
<td>p.Arg96Termin</td>
<td>Fischer et al. 2001 (10)</td>
</tr>
<tr>
<td>c.293T&gt;C</td>
<td>p.Leu98Pro</td>
<td>Yerebakan et al. 2003 (22)</td>
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REFERENCES