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SHORT COMMUNICATION

Familial Primary Localized Cutaneous Amyloidosis Results from Either Dominant or Recessive Mutations in *OSMR*

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Primary localized cutaneous amyloidosis (PLCA; MIM 105250) is a chronic itchy skin disorder associated with amyloid deposits in the superficial dermis (1). Clinically, most skin lesions comprise small, flat-topped papules (lichen amyloidosis) or brown-grey macules (macular amyloidosis). Recently, proteins containing a considerable amount of β-sheet structures, such as galectin-7 and actin, have been reported as amyloidogenic in PLCA (2, 3).

Most cases of PLCA are sporadic, but familial cases (FPLCA) with autosomal dominant inheritance also exist (4–6). Pathogenic mutations in *OSMR* and *IL31RA* have been reported as the major cause of FPLCA (5, 7); both of these genes belong to the family of interleukin (IL)-6 family cytokine receptors. *OSMR* encodes oncostatin M receptor-beta (OSMRβ), a component of both the OSM type II receptor and the interleukin (IL)-31 receptor (8, 9), whereas *IL31RA* encodes the IL-31 receptor alpha, which combines with OSMRβ to form the IL-31 receptor (7). To date, 10 heterozygous missense mutations in *OSMR* and 1 heterozygous missense mutation in *IL31RA* have been reported in FPLCA, with all cases showing autosomal dominant inheritance (5–7, 10).

In this study, we examined 2 large pedigrees with FPLCA originating from Pakistan (family A) and Malaysia (family B) (Fig. 1a, b). Unusually, however, the occurrence of FPLCA in both families is consistent with autosomal recessive, rather than dominant, inheritance.

MATERIALS, METHODS AND RESULTS

All individuals provided written informed consent according to a protocol approved by local ethics committees in adherence with the guidelines of the Declaration of Helsinki. The diagnosis of FPLCA was made by dermatologists based on typical clinical skin features. Blood samples were collected from 4 affected and 4 unaffected individuals of family A and 4 affected individuals of family B marked in the respective pedigrees (Fig. 1a, b; "DNA"). Genomic DNA was extracted from peripheral blood leukocytes by standard procedures.

Genome-wide linkage-scan in family A was performed using the Illumina HumanOmniExpress BeadChips (Illumina Inc., San Diego, CA, USA). Analysis of genotype data was carried out using easyLinkage (11). In family A, whole-exome sequencing was performed using DNA samples of 1 affected individual (III-1) (Appendix S1[1]). In family B, whole-exome sequencing

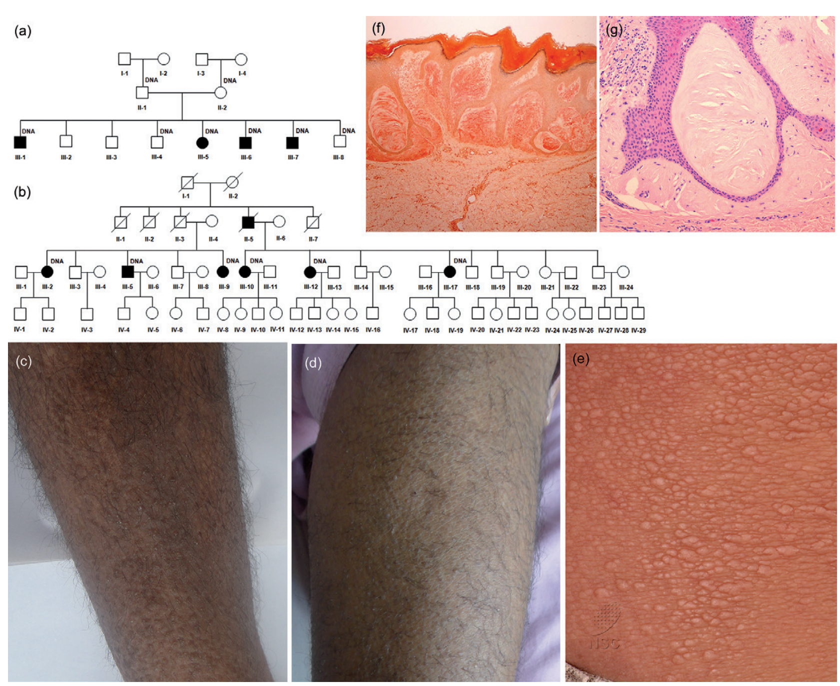

Fig. 1. Pedigree structure, Clinical and histopathological features of familial primary localized cutaneous amyloidosis (FPLCA). Pedigree of (a) family A and (b) family B, showing segregation of the FPLCA phenotype. Affected males and females are indicated by filled squares and circles, respectively. Deceased individuals are indicated by crossed symbols. Symbols with "DNA" represent the samples available for the study. Clinical appearances of FPLCA in an affected individual (III-1) of family A showing hyperpigmented flat papules on (c) the right arm and (d) the lower leg. (e) Clinical features of an affected individual (III-2) of family B showing skin-coloured papules on the lower back. Histopathological examination of skin from an affected individual (III-2) in family B showing amyloid deposition immediately below the epidermis using Congo red staining (f) 40× image resolution, (g) 100× image resolution.

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was performed using DNA samples of 2 affected individuals (III-2, and III-9) using previously reported methods (12).

In family A, all affected siblings showed the first symptoms at the age of 13–14 years. They presented with marked skin lichenification. The hyperpigmented flat papular lesions were itchy and present above the ankles, extending to the shins, thighs and abdominal regions (Fig. 1c, d). There was no history of FPLCA in previous generations. In family B, the age of onset ranged from 18 to 70 years. Symptoms started on the legs and arms with pruritus, followed by brown papules and patches. Later, the papules spread to other areas, involving trunk, limbs, neck and back (Fig. 1e). Histopathology of lesional skin showed amorphous eosinophilic material in the papillary dermis by use of Congo red (Fig. 1f, g). In this pedigree, the inheritance pattern was more complex; part of the pedigree showed probable recessive inheritance in 3 siblings (Fig. 1b, individuals III-2, III-5, and III-9), while autosomal dominant transmission was more likely in other relatives (II-5, III-10, III-12, and III-17).

Thus far, not a single gene/gene locus had been reported for autosomal recessive FPLCA. Therefore, we performed a genome-wide linkage scan with 8 individuals from family A. Analysis of genotype data identified 3 chromosomal regions segregating with the FPLCA phenotype: 1q23.3–q24.2; 5p14.2–q11.2; 14q32.33. The linkage region on chromosome 5 harbours *OSMR* and *IL31RA*, and therefore these genes were sequenced. Sequencing of *IL31RA* did not reveal any pathogenic variant(s), but a homozygous single nucleotide substitution, c.1385A>G; p.Asn462Ser (NM_003999), was detected in exon 11 of *OSMR* (Fig. S1a[1]). Sequencing of all available DNA samples of family A revealed co-segregation of the mutation with disease phenotype. Heterozygous carriers (II-1, II-2, III-4, and III-8) did not show any clinical signs of FPLCA or report symptoms of pruritus, arguing against semi-dominant inheritance. This mutation has not been reported in dbSNP, the 1,000 genomes project or the ESP6500 data-set. To demonstrate that there were no other potentially pathogenic mutations in genes located in regions of linkage, we performed whole-exome sequencing of one additional family member (III-1). Our filtering strategy (Appendix S1[1]) retained only the variant described above in *OSMR*.

Analysis of the exome data in family B revealed a homozygous missense mutation in exon 11 of *OSMR* (c.1538G>A; p.Gly513Asp) in both individuals (Fig. S1b[1]), with the amino acid change predicted to be damaging by bioinformatic analysis with PolyPhen-2 (score 1.000) and SIFT (score 0). Sanger sequencing showed homozygosity for the mutation in individuals III-2, III-5 and III-9, but heterozygosity in subject III-10. Clinically, individual III-10, heterozygous for p.Gly513Asp, had very similar features of FPLCA to the other affected cousins who were homozygous for this mutation, with no differences in age of onset, pattern or severity of the disease. Intriguingly, further history revealed no symptoms in individuals II-3 (deceased) or II-4, who, as parents of 3 homozygous offspring, were likely to be heterozygotes for the mutation. Furthermore, none of the offspring of III-2 or III-5, obligate heterozygotes for p.Gly513Asp, had any features of FPLCA.

DISCUSSION

All the dominant mutations reported for *OSMR* are located within the 2 extracellular fibronectin III-like domains (FNIII domains) that are closest to the transmembranous region of OSMRβ (10). In contrast, both new mutations are located in a more distal FNIII domain (Fig. S1c[1]). Our data further suggest that p.Gly513Asp in family B may act as both a dominant and a recessive mutation, but, at present, it is not known what factors influence the presence or absence of FPLCA in heterozygotes.

The cutaneous amyloid deposits comprise collections of keratins (from basal keratinocytes), serum amyloid P component, apolipoprotein E, galectin-7 and actin (2), with galectin-7 peptides contributing to amyloidogenesis (3), although other amino acid motifs may also be implicated in forming the β-sheets that are an essential part of the pathophysiology of cutaneous amyloidosis (13).

The link between mutations in *OSMR* and the pathogenesis of cutaneous amyloidosis is not fully known. Previous studies have demonstrated that the pathogenic missense mutations in *OSMR* result in aberrant IL-31 signalling (5). Abnormalities in IL-31 signalling may be directly relevant to the key clinical symptom of itch (14), although an additional consequence of alterations in the IL-31 pathway demonstrated for mutations in *OSMR* is a failure to induce expression of monocyte-chemotactic protein-1 (MCP-1) (15). The implications for the pathogenesis of cutaneous amyloidosis could be that a lack of inducible MCP-1 results in less monocyte chemotaxis in patient skin, which leads to altered innate immunity, with reduced scavenger function and accumulation of cellular debris (15). Transcriptomic analysis of RNA from lesional cutaneous amyloidosis skin has also revealed upregulation of keratinocyte proliferation and differentiation markers, downregulation of keratinocyte stem cell markers, and downregulation of anti-apoptotic factors (6). The latter observations are helpful in explaining the clinicopathological features (dyschromia or lichenification with keratinocyte apoptosis) and may be relevant to the pathophysiology of the disease, although the precise mechanisms leading to changes in keratinocyte gene expression are not fully known. In conclusion, this study offers new findings on the molecular genetics and disease relevance of mutations in *OSMR* in FPLCA.

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