A novel Oncostatin M receptor mutation in familial primary localised cutaneous amyloidosis

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Primary localised cutaneous amyloidosis (PLCA) is a chronic disorder, characterised by small flat topped papules or brown-grey macules, which are intensely itchy \(^1\). Underpinning the clinical manifestations is the deposition of beta-sheets of extracellular protein in the papillary dermis, thought to arise from degenerate protein from basal keratinocytes, immunoglobulins and normal serum amyloid P component. Most cases are sporadic, with autosomal dominant inheritance responsible for about 10% of cases, and although common in South American and Asian populations \(^1-4\), it is rare amongst Caucasians.

Mutations in the \textit{OSMR} and IL31RA genes have been previously reported in patients with PLCA \(^1-5\). The \textit{OSMR} gene encodes oncostatin M receptor \(\beta\) (OSMR-\(\beta\)), a member of the IL-6 type cytokine receptor family that binds IL-31 and oncostatin-M (OSM). Overexpression of IL-31 in mice has been shown to cause itchy dermatitis and thought to contribute to pruritic skin conditions in humans, such as nodular prurigo. OSM has a role in keratinocyte function, mediating differentiation, proliferation, inflammation and migration and once bound to the OSM type 2 receptor, it can induce apoptosis \(^5\). The exact function and downstream signalling of OSMR-\(\beta\), as well as its role in PLCA, has yet to be fully identified but a reduction in OSMR-\(\beta\) signalling could explain the increased apoptosis of basal cell keratinocytes associated with PLCA.

A 35 year old Caucasian male presented with pruritic papules on his lower leg since adolescence (Fig. 1a). A skin biopsy of a lesion, from the patient and his mother, both demonstrated extracellular protein deposits were seen in the papillary dermis, which was congo red and thioflavin T positive (Fig. 1b,c). Written informed consent was obtained from the patient, mother and wife for a genetic study. OSMR gene sequencing identified a
heterozygous single point nucleotide mutation in exon 10, c.1715G>A, p.R438K (Fig. 1d), in the affected but not the unaffected individual. Protein homology and amino acid identity indicate that amino acids p.R438 is conserved across several species (Fig. 1e), the incorporation of a basic lysine into the fibronectin III (FNIII) repeat of the extracellular component of the OSMR would alter the protein 3D structure and so may affect ligand binding.

In conclusion, OSMR mutations associated with PLCA that have been described in the non-cytokine binding FNIII repeats that form the extracellular “hinge” beneath the cytokine binding portion of the protein. The novel mutation described herein resides in the third such non-cytokine binding FNIII (Fig. 1f), highlighting the importance of the hinge in modulating receptor ligand interaction and signal transduction.
References


Figure Legends

Figure 1. (a) Numerous firm skin coloured papules on the lower limbs. Skin histology demonstrated a mild acanthosis, with dermal deposit which was congo red positive (b) and demonstrated thioflavin T stain fluorescence (c). (d) Electropherogram of sequencing by forward (and reverse) primers identified a heterozygous mutation c.1715G>A in affected family members, leading to a change in amino acid p.R438K at a conserved site (e), representing a novel mutational site in the predicted protein (f).