

## Heterozygous *PDGFRB* Mutation in a Three-generation Family with Autosomal Dominant Infantile Myfibromatosis

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Infantile myfibromatosis (IM; MIM#228550) is a rare disorder of myfibroblastic proliferation and is one of the most common causes of benign fibrous tumour of infancy (1). IM is categorized into solitary, multicentric and generalized forms, with solitary IM being the most common. While solitary IM is characterized by the presence of a single cutaneous nodule, multicentric IM involves the skin, subcutaneous tissues, muscles and bones. Both forms of IM regress spontaneously during childhood. Generalized IM is characterized by visceral involvement, and may have a poor outcome. Although IM is mainly sporadic, 30 families suggestive of autosomal dominant (AD) or autosomal recessive (AR) inheritance have been reported. Recently, heterozygous mutations in *PDGFRB* and *NOTCH3* have been reported in 13 families with AD IM (2, 3). We report here, a 3-generation family with multicentric AD IM and a novel *PDGFRB* mutation (c.1679C>T; p.P560L).

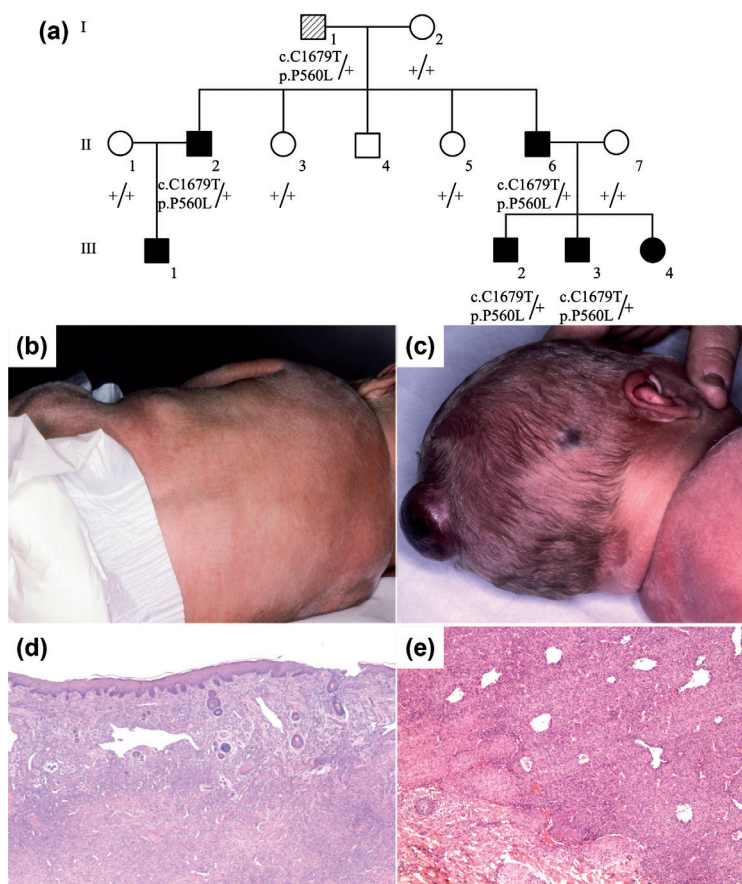
### CASE REPORT

A male patient (III-2) was referred at birth due to the presence of 4 firm, flesh-coloured subcutaneous nodules; 2 on the scalp, 1 on the left shoulder and 1 on the back (Fig. 1a–c). Histopathology of the dorsal nodule biopsy was consistent with a diagnosis of IM (Fig. 1d, e). Systemic monitoring showed multiple skeletal involvement and a 3-cm nodule of the left psoas muscle, partially infiltrating the spinal canal. No visceral lesions were found. Spontaneous, complete and uncomplicated regression occurred during the first 2 years of life.

The patient belongs to a French family of Spanish origin. Six of his relatives presented with AD multicentric IM (Fig. 1a, Table S1<sup>†</sup>). Of note, individual III-3 had a solitary IM subcutaneous nodule 5 years after complete regression of the neonatal lesions. None of the affected relatives presented with skeletal overgrowth, neurological deterioration or dysmorphic features. After obtaining informed consent, DNA extracted from blood leucocytes was analysed by whole exome sequencing for each patient and relative. Re-sequencing of *PDGFRB* identified a heterozygous missense mutation in exon 12 (c.1679C>T;p.P560L), which segregates with the disease in the family, and identified individual I-1 as the founder despite no

history of IM. Variants in *NOTCH3* and *PTPRG* were excluded by whole-exome sequencing.

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**Fig. 1. Familial autosomal dominant infantile myfibromatosis (IM): pedigree, clinical and histopathological pictures.** (a) Pedigree shows autosomal dominant inheritance. At birth, patient III-2 presented with: (b) 2 firm, flesh-coloured nodules on the back; and (c) 2 firm nodules on the scalp with necrotic evolution. Histopathological analyses of a removed dorsal nodule (patient III-2) showed a lesion located in the dermis and upper subcutis composed of both a spindle-shaped cell proliferation and a vascular proliferation. This angiomatous area, mostly seen at the periphery, is composed of more-or-less dilated capillaries arranged in a haemangiopericytoma-like pattern. The deep dermis is more cellular, less vascular and contains fibrosis. It is likely to be a regressing infantile myfibromatosis lesion (d: haematoxylin and eosin (HE)  $\times 25$ ). The periphery is composed of small myfibroblast fascicles arranged as rounded and hyalinized nodules. Beneath the periphery there are vascular channels, some exhibiting staghorn shapes. Between these the cells are poorly differentiated, polygonal or spindle (e: HE $\times 50$ ).

## DISCUSSION

This case report identified a novel pathogenic *PDGFRB* mutation in a family presenting with multicentric AD IM. The mutation involves an amino acid that is particularly well-conserved through mammalian species, which segregates with the disease. No other mutation was detected in whole-exome next-generation sequencing.

Familial IM is frequently multicentric, but may exist as solitary or generalized forms in the same family (2, 3). Because most IM lesions are asymptomatic and regress spontaneously, milder expression in relatives may be overlooked, indicating that familial IM is probably more frequent than reported. The mechanism of regression remains unknown.

Heterozygous mutations in *PDGFRB* have been identified in 13 out of the 14 reported families. To date, 4 mutations, including the one identified here, have been reported in IM, the most frequent being c.1681C>T; p.R561C in exon 12 of *PDGFRB* (2–4). In 4 out of 9 paediatric patients with IM, a second somatic *PDGFRB* mutation was detected in a removed nodule, suggesting that loss of heterozygosity might explain nodule development, as well as the occurrence of both solitary and multicentric forms in the same family. In addition to *PDGFRB*, mutations in *NOTCH3* and *PTPRG* have been reported in AD IM (3, 4). Both *NOTCH3* and *PTPRG* belong to the *PDGFR* signalling pathway (3). *PTPRG* encodes an enzyme that dephosphorylates *PDGFRB*, reducing its activity (5). *NOTCH3* encodes a transmembrane receptor that directly regulates expression of *PDGFRB* (6). *PDGFRB* encodes the  $\beta$ -polypeptide of the platelet-derived growth factor receptor, a tyrosine kinase receptor that promotes growth of mesenchymal cells, including fibroblasts and smooth muscle. Beside IM, several other *PDGFRB* mutations have been ascribed to idiopathic basal ganglia calcification (7), Penttinen syndrome (8), and a distinct overgrowth syndrome with dysmorphic features and neurobehavioral manifestations (9; Table SII<sup>1</sup>). Those mutations in *PDGFRB* involve the juxta-membrane domain of the protein (2, 3, 9) or its tyrosine kinase domain (2, 3, 8).

While loss-of-function mutation of *PDGFRB* causes idiopathic basal ganglia calcification, a gain-of-function mutation is responsible for the other 3 disorders. Moreover, *PDGFRB* activation occurred even in the absence of its ligand. The *PDGFRB* R561C and N666K mutations involved in AD IM, induced cell proliferation and a strong activation of STAT pathway in the absence of the ligand *in vitro* (10). Cells transfected with *PDGFRB* mutant and injected in BALB/c rag2<sup>-/-</sup> mice promoted tumourigenesis *in vivo*. The same authors suggested that P584R mutation causing the overgrowth syndrome (9) activates *PDGFR $\beta$*  to a greater extent than R561C muta-

tion. In Penttinen syndrome, the *PDGFRB* mutations are associated with a ligand-independent hypersensitivity *in vitro* (8). Thus, distinct gain-of-function mutations occurring in the same gene domain are associated with allelic phenotypes with minimal overlap. Therefore the degree of *PDGFRB* activation may modulate differently its downstream signalling pathways, explaining the clinical spectrum observed. A modifier gene or a second hit mutation could also be involved.

Mutations in *PDGFRA* have been associated with several cancers, such as glioblastoma. *PDGFRB* fusions are reported in myeloid neoplasms (11). Non-specific receptor kinase inhibitors targeting the PDGF receptor, such as imatinib or ponatinib, have shown encouraging results in those diseases (11). Interestingly, p.R561C and p.N666K mutants, involved in IM, are sensitive to imatinib and ponatinib *in vitro* (10). Further investigations may assess the potential effect of these drugs on aggressive forms of IM.

The authors declare no conflicts of interest.

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