European Journal of Medical Genetics 60 (2017) 353–358

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

The spectrum of infantile myofibromatosis includes both non-penetrance and adult recurrence

Keywords:
Infantile myofibromatosis
Myofibroma
PDGFRB gene
NOTCH3 gene

A B S T R A C T

Infantile myofibromatosis is characterized by benign myofibroblastic tumors within skin, muscle, bone or viscera which have a characteristic staining pattern on immunohistochemistry. The condition typically presents in infancy and the tumors often disappear by the third year of life. Mutations in the *PDGFRB* gene and *NOTCH3* genes have been identified in familial forms of the condition. We present two families with molecularly confirmed germline mutations in the *PDGFRB* gene, one demonstrating a phenotype ranging from complete non-penetrance to neonatal lethality; and the other illustrating adult recurrence of the tumors.

1. Introduction

Infantile myofibromatosis [IM] is a disorder characterized by benign myofibroblastic tumors, either solitary or multiple, within skin, subcutaneous tissue, striated muscle or occasionally viscera and bone (Orbach, 2013). The histological appearance is characteristic and shows peripheral spindle cells in a biphasic pattern surrounding central round or polygonal cells, with positive actin and negative desmin staining on immunohistochemistry (Kacar et al., 2012). Myofibromas are most commonly present at birth or appear in patients under the age of two and are most common in the head and neck region (Orbach, 2013). Visceral involvement is associated with poor prognosis (Kacar et al., 2012; Lee et al., 2014). To our knowledge, recurrence of myofibromas in survivors in adulthood has not previously been reported. Sporadic adult-onset myofibromas have been recognized and are most common in the head and neck (Lee et al., 2014; Ramadorai et al., 2010). A recent series by Al-Qattan et al. reported 12 cases of sporadic solitary myofibromas presenting in the hands without evidence of familial transmission (Al-Qattan and Arafah, 2016).

Familial forms of IM exhibiting autosomal dominant and recessive transmission were reported over the past two decades. Martignetti uncovered causative mutations in the *PDGFRB* gene and *NOTCH3* gene in affected families through whole exome sequencing (Martignetti et al., 2013). Simultaneously, Cheung et al. studied 11 patients from four families along with 5 simplex cases with IM, and through whole exome sequencing and RNA-sequencing of tumor tissue identified the recurrent c.1681 C > T p.Arg561Cys *PDGFRB* variant segregating with the disease in affected families (Cheung et al., 2013). Mutations in this gene were absent in germline and tumor DNA in the simplex cases. *PDGFRB* is a tyrosine kinase receptor for platelet derived growth factors stimulating growth of mesenchymal cells (Orbach, 2013; Martignetti et al., 2013). Jin in 2015 identified the role of *PDGFRB* as a *NOTCH3* target gene (Jin et al., 2008). More recently, a mutation in the tumor suppressor gene *NDRG4* has been identified as the cause of autosomal recessively inherited IM in one family (Linhares et al., 2014a), while a *PTPRG* mutation was hypothesized as a modifier contributing to variable expressivity in patients with inherited *PDGFRB* mutations (Linhares et al., 2014a, 2014b).

The mainstay of treatment at present is a watch and wait approach, or surgical resection for cosmetic purposes or in the case of limb or organ threatening tumors (Orbach, 2013). Combination chemotherapy with Vincristine and Dactinomycin has been trialed a small cohort of infants with IM with some success. Recent *in vitro* experiments suggest that cells expressing *PDGFRB* with mutations found in patients with IM do respond to imatinib (Arts et al., 2016), opening the door to trials of this drug in patients with IM.

Here, we report on two families with unique presentations of molecularly confirmed autosomal dominant Infantile Myofibromatosis, including a spectrum of severity in a family with a novel familial *PDGFRB* mutation ranging from neonatal death to apparent non-penetrance. We also report on a family with the recurrent *PDGFRB* c.1681C > T p.Arg561Cys mutation with recurrence of myofibromas in an adult female who had previously had a classic neonatal presentation.

2. Patient data/material

2.1. Ascertainment of patients

Cases were identified through referral to the Clinical Genetics Service of the Hunter New England Local Health District, a service covering a population of 870000 in the city of Newcastle and rural NSW, Australia. Informed consent was obtained for participating individuals.

http://dx.doi.org/10.1016/j.ejmg.2017.02.005
1769-7212/

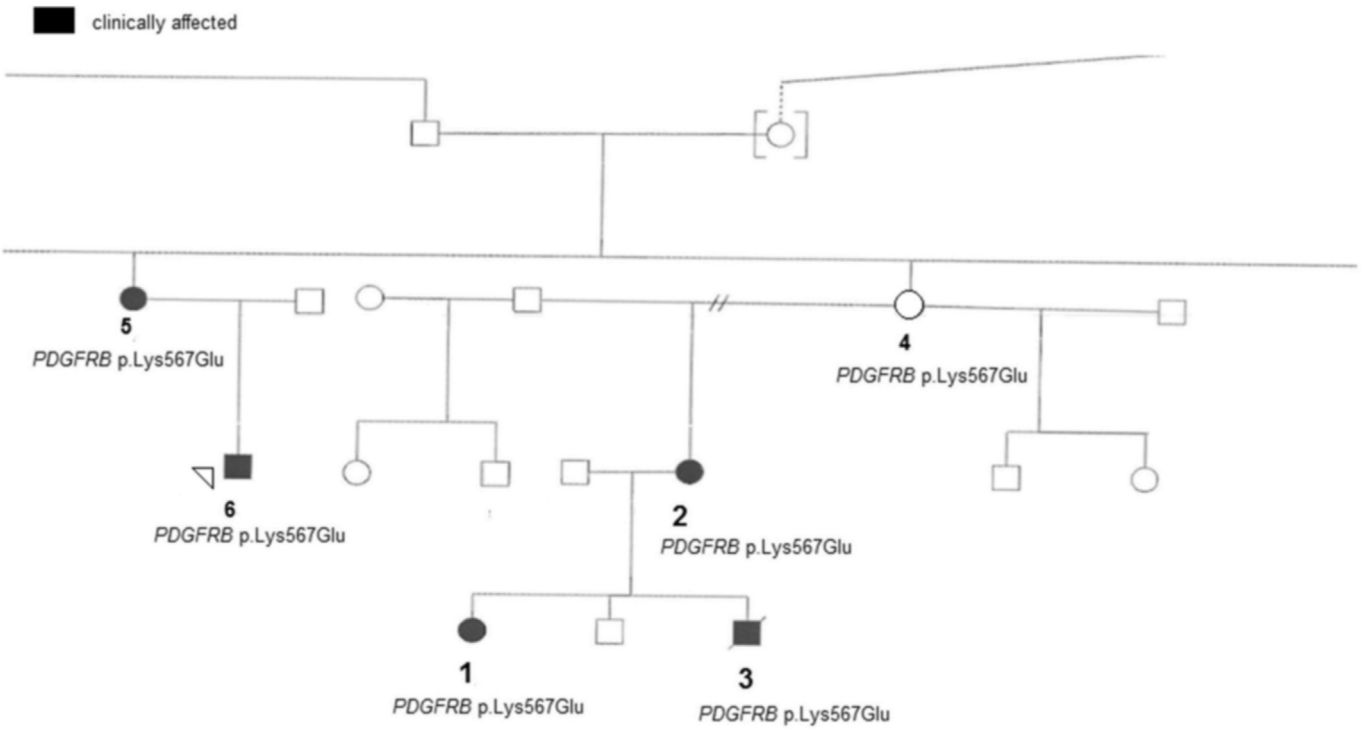

Fig. 1. Family 1 pedigree.

2.2. Laboratory methods

DNA was extracted using the Qiagen QIAamp Kit using the manufacturer's instructions. *PDGFRB* exons were amplified by PCR using the primers detailed in the supplementary table 1. Sanger sequencing of these exons was performed at The McGill University and Génome Québec Innovation Centre. Analysis of the chromatograms was done using Geneious (http://www.geneious.com/).

3. Results

3.1. Clinical evaluation and genetic testing for family 1

The female proband, Patient 1, was diagnosed with a solitary myofibroma at ten months of age after a lesion overlying the right scapula was excised and showed a typical appearance on immunohistochemistry. A lesion on the left lateral outer canthus was present when examined at the age of 3. A subsequent chest X-ray and abdominal ultrasound following resection did not show any evidence of visceral involvement and the patient remained otherwise well with normal growth and development at the age of four.

The mother of the proband, Patient 2, is a healthy 22-year-old. She reported a lump over the medial aspect of her left arm during childhood, which regressed spontaneously; and another bony lump present over the right third metacarpal which had an X-ray appearance of a healing fracture. Neither lesion was biopsied. During her second pregnancy with affected Patient 3, she had a normal nuchal translucency scan and a normal 20 week morphology scan. At 40 weeks she noticed reduced fetal movements and had spontaneous membrane rupture. The fetal cardiotocogram was abnormal and an emergency Caesarian section was performed for failure to progress. An intrapartum ultrasound showed the infant had hydrocephalus complicating a large posterior fossa mass. Patient 3 was intubated at birth for respiratory failure and seizure activity and CT and MRI studies confirmed the tumor with significant underlying mass effect and distortion of brain architecture. The infant died on day 4 of life and histology from the subsequent autopsy confirmed infantile myofibromatosis. The major finding was a 110 × 95 × 80mm solid, well circumscribed mass attached to the dura overlying the temporal bone, with thinned adjacent cortex and distortion of the left hemispheric structure. The histology showed the typical biphasic morphology and immunohistochemistry.

Patient 4 is the mother of Patient 2, aged in her 40s. She had a right sided shoulder lesion biopsied as an infant. This was described as a teratoma although confirmatory results were not available.

Patient 5, the maternal aunt of Patient 2, was never diagnosed with myofibromatosis in infancy but had a lump within the lower mandible which was biopsied and said to be “benign”, although the reports were not available. She was otherwise well, though she has a history of significant joint hypermobility with joint dislocations and mitral valve prolapse, and an incidentally found 22q11.2 microduplication.

Her son, Patient 6, was born at term following an uncomplicated pregnancy at a birth weight of 2890 g [25th percentile]. Shortly after delivery he was found to have a mass behind the right knee. X-ray of the mass and an MRI at 2 weeks of life showed a 2 × 2.6 cm heterogenous lesion with central enhancement and calcification in the medial head of the gastrocnemius. MRI identified an 11 × 6mm mass overlying the right frontal bone, and three additional soft tissue tumors including a mass behind the right ear 0.5cm diameter, a 0.5cm diameter mass behind the left 12th rib and a 0.5cm diameter mass overlying the head of the right triceps. There were no visceral lesions identified and the masses had spontaneously regressed by 3 years of age, at which time he had met normal growth and developmental milestones. A microarray performed in the infant period showed the 22q11.2 microduplication.

A novel mutation in *PDGFRB* [NM_002609.3:c.1699A > G, p.Lys567Glu] was first identified in Patient 6 and confirmed in