Recurrent splice-site mutation in MBTPS2 underlying IFAP syndrome with Olmsted syndrome-like features in a Chinese patient

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doi:10.1111/ced.12248

Summary

Mutations in MBTPS2 have been reported to cause a broad phenotypic spectrum of X-linked genodermatoses, including IFAP (ichthyosis follicularis; atrichia and photophobia) syndrome (OMIM 308205) with or without BRESHECK (brain anomalies, retardation of mentality and growth, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear deformity and deafness, eye hypoplasia, cleft palate, cryptorchidism, and kidney dysplasia/hypoplasia) syndrome, keratosis follicularis spinulosa decalvans (KFSD; OMIM 308800) and an X-linked form of Olmsted syndrome. We report a recurrent intronic mutation in MBTPS2 (c.671-9T＞G) in a Chinese patient with the typical triad of IFAP syndrome (i.e. ichthyosis, atrichia and photophobia), along with pachyonychia, palmoplantar and periorificial keratoderma, which were reminiscent of Olmsted syndrome. Interestingly, this mutation was previously reported in two cases of IFAP without keratoderma, which suggests clinical heterogeneity of the same mutation in MBTPS2. The concomitance of Olmsted syndrome-like features in this patient with IFAP may challenge the existence of the X-linked form of Olmsted syndrome as an independent condition.

Mutations in the gene encoding for membrane-bound transcription factor protease site 2 (MBTPS2) have been reported to cause a broad phenotypic spectrum of X-linked genodermatoses, including IFAP (ichthyosis follicularis; atrichia and photophobia) syndrome (OMIM 308205) and an X-linked form of Olmsted syndrome. We report a patient with features of IFAP and other Olmsted syndrome-like conditions.

Report

The proband was a 22-year-old man of Chinese Han ethnicity, who had been born at 35 weeks of gestation, after an uneventful pregnancy. Non-scarring total alopecia had been present since birth (Fig. 1b). At the age of 3 years, lamellar desquamation on his limbs had been noted, which later progressed to the whole body, with the pretibial region being most severely affected. He developed photophobia as a result of corneal scarring and neovascularisation as a school-child (around the age of 7–10 years). Palmoplantar keratoderma extended to involve the dorsa of the palms and soles, along with the nails, and there was prominent pachyonychia, which resulted in flexion contracture of the left third finger when he was 14 years old (Fig. 1c). Mild hyperkeratosis developed around the periorificial regions of the coccyx and the angles of the lips (Fig. 1b,d). He underwent two inguinal hernia repairs at the ages of 8 and 19 years.

At his presentation to us (aged 22 years), he was found to have short stature (145 cm) and low body weight (33 kg), but his psychomotor development was normal. On histopathological examination of the ichthyosiform lesions, nonspecific features were seen, with orthohyperkeratosis and acanthosis, and there was an

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Conflict of interest: none declared.
Accepted for publication 16 August 2013
inflammatory infiltrate in the upper dermis. The patient’s mother exhibited milder hyperkeratosis affecting her right distal limbs in a linear mosaic pattern following the lines of Blaschko (Fig. 1e), whereas his sister and father were clinically unaffected (Fig. 1a).

In summary, this patient exhibited a clinical constellation of ichthyosis, alopecia, photophobia, short stature, inguinal hernia, palmoplantar and periorificial keratoderma, and pachyonychia, which could be features of a range of genodermatoses, including IFAP, Olmsted syndrome, Clouston syndrome, pachyonychia congenita or keratitis–ichthyosis–deafness (KID) syndrome. It was also possible that this might be a new undescribed condition, and thus we decided to carry out exome sequencing.1

The study was approved by the clinical research ethics committee of Peking University First Hospital, and all the family members provided written informed consent for participation.

Blood samples were collected, and genomic DNA was extracted from peripheral blood leucocytes using a commercial kit (TIANamp Genomic DNA Kit, Tiangen, Beijing, China) according to the manufacturer’s instructions. Exome sequencing was then carried out. In brief, the exome was captured and enriched using an exome library (SeqCap EZ Human Exome Library, version 3.0; Roche NimbleGen, Madison, WI, USA) and then sequenced on a Hiseq 2000 platform (Illumina, San Diego, CA, USA) in accordance with the manufacturer’s instructions. A total amount of 11.1 Gb raw data was obtained, with an average of >100-fold coverage depth. Of this, about 5.1 Gb data was mapped to the target region which was >44 Mb in length, and 98,015 single nucleotide variants and 7,094 small insertions and deletions (indels) were annotated. Sequence variants were filtered against three public databases (dbSNP134, 1000 Genomes Project, HapMap8) and the BGI inhouse exome database. Under the assumption of X-linked inheritance, we focused on the variants of chromosome X, and noted a variant in the MBTPS2 gene (c.671-9T>G), encoding for membrane-bound transcription factor protease site 2 (MBTPS2), which was predicted to be a splice-site mutation. Sequencing confirmed that this mutation was hemizygous in the proband and heterozygous in his mother (who had milder symptoms) (Fig. 2), consistent with
X-linked recessive inheritance. We did not find this mutation in the patient’s father or sister, or in 200 unrelated ethnically matched healthy individuals. No variants in the TRPV3 (Olmsted syndrome), GJB2 (underlying KID syndrome), GJB6 (Clouston syndrome), KRT6A, KRT6B, KRT16 or KRT17 (pachyonychia congenita) genes were detected in the proband’s exome sequencing data.

The intronic mutation c.671-9T>G in MBTPS2 was previously reported by Oeffner et al. in two patients with IFAP. Mutation c.671-9T>G was predicted to disrupt the intronic splicing enhancer, leading to skipping of exon 6 in mRNA transcription, as was shown in that study by minigene assay in vitro, and confirmed by reverse transcription PCR using patient cells in vivo. Consequently, mutation c.671-9T>G probably results in frameshift and finally premature termination of MBTPS2 (p.Ile225LeufsX25). The two patients in that study exhibited hernia, short stature and thickened dystrophic nails, in addition to the classic IFAP triad (ichthyosis, atrichia and photophobia), which were also present in our patient. However, unlike our patient they did not show palmoplantar or periorificial keratoderma, indicating the clinical heterogeneity of this mutation. All these three cases with mutation c.671-9T>G had different ethnic backgrounds, suggesting that this might be a mutation hotspot of MBTPS2. Accordingly, more attention should be paid to the exon–intron boundaries of MBTPS2 during mutation screening.

MBTPS2, the protein encoded by the MBTPS2 gene, is a zinc metalloproteinase essential for cholesterol homeostasis and endoplasmic reticulum stress response. Mutations in MBTPS2, which reduce but do not deplete the functionality of the protein, are associated with IFAP syndrome with or without BRESHECK (brain anomalies, retardation of mentality and growth, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear deformity and deafness, eye hypoplasia, cleft palate, cryptorchidism, and kidney dysplasia/hypoplasia) syndrome, keratosis follicularis spinulosa decalvans syndrome (KFSD; OMIM308800) and an X-linked form of Olmsted syndrome. All these disorders are inherited in an X-linked manner, with full-blown clinical features in affected males, and absence of or milder features in female carriers, which, if they are present, follow the lines of Blaschko. Although the phenotype varies considerably between each of these disorders, there is clinical overlap between them.

The clinical phenotype of IFAP varies considerably, with a large number of additional features described, including hyperkeratotic nails, palmoplantar keratosis,
neurological abnormalities, inguinal hernia, finger hyperextension, and failure to thrive. Ichthyosis follicularis is not a constant presentation. In severe cases of IFAP, lamellar desquamation or well-demarcated psoriasiform plaques predominate on the limbs. Olmsted syndrome is characterized by bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques. Frequent further features include intolerable itch sensation, alopecia and nail dystrophy. Recently, gain-of-function mutations in the TRPV3 gene were reported to cause Olmsted syndrome. After genetic testing, we diagnosed the family as having IFAP with Olmsted syndrome-like features. Intriguingly, a recently published literature described two male relatives with an X-linked form of Olmsted syndrome who harboured a missense mutation in MBTPS2. However, it remains to be elucidated whether the X-linked form of Olmsted syndrome represents an independent condition or merely a severe form of IFAP, as shown in our case.

In conclusion, we report a recurrent splice-site mutation of MBTPS2 in a Chinese family with IFAP and Olmsted syndrome-like features. This study highlights the facilitation of exome sequencing in gene diagnosis of complicated cases, and expands the clinical spectrum of MBTPS2-related disorders.

Learning points

- Olmsted syndrome is characterized by palmoplantar and periorificial keratoderma, whereas the IFAP triad includes ichthyosis follicularis, atrichia and photophobia.
- The clinical phenotype of IFAP varies considerably, and many additional features have been described.
- The intronic mutation c.671-9T>G may be a mutation hotspot of MBTPS2 with clinical heterogeneity.
- Exome sequencing facilitates the process of gene diagnosis in complicated cases.

Acknowledgements

We thank the patient and his family members for participating in this study. This work was supported by the National Natural Science Foundation of China (81071289 and 81201220).

References