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A novel *MBTPS2* start codon mutation causes a mild ichthyosis follicularis with atrichia and photophobia phenotype

F. Chen,[1] J. Wang,[2] Z. Yao[1] and M. Li[1]

[1]*Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; and* [2]*Department of Dermatology, Henan Provincial People's Hospital, Zhengzhou, China*

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Ichthyosis follicularis with atrichia and photophobia (IFAP; MIM 308205) syndrome is a rare, X-linked, oculocutaneous human disorder, which is caused by mutations in the gene *MBTPS2*. We report a Chinese family with one affected child, whose parents were not affected.

A 5-year-old boy presented with the IFAP triad of symptoms: ichthyotic scaling, complete lack of hair and mild photophobia. His parents were not related, and there was no similar illness history or familial history of atopy.

The skin manifestations included mild xerosis with follicular hyperkeratosis, which gave a mild thorn-like sensation with palpation (Fig. 1). Complete atrichia affected the scalp, eyebrows and eyelashes. Pachyonychia, angular cheilitis and perianal psoriasiform lesions were present. Ophthalmic examination indicated that the patient had mild photophobia. There was no evidence of seizures, mental retardation, chronic rhinitis, diarrhoea, epilepsy, or a propensity to chronic infections or inguinal hernia. The patient's weight and height, verbal communication ability and psychomotor development were all within normal limits, and his hearing was adequate.

Following informed consent, DNA was taken from the proband and his clinically unaffected parents for mutation analysis by next-generation and Sanger sequencing, using a gene probe consisting of 541 genetic loci of genodermatoses. This analysis revealed a heterozygous start codon mutation, c.2T>C, in the *MBTPS2* gene, which results in the mutation p.M1?, changing the start codon and preventing the initiation signal of polypeptide chain synthesis (Fig. 2a). No mutation was detected in either of the parents (Fig. 2b,c), and the mutation was not detected in 100 unrelated healthy Chinese individuals (200 alleles) by Sanger sequencing. The mutation was also absent from the public database, suggesting that the mutation was most likely the deleterious mutation in this patient.

IFAP syndrome is generally accepted as a rare X-linked recessive genodermatosis caused by mutations in *MBTPS2*.[1] The MBTPS2 protein is essential for cholesterol homeostasis and endoplasmic reticulum stress response. Deficiency in cholesterol homeostasis in the stratum corneum could contribute to barrier function abnormalities, which in turn could lead to disturbed differentiation of epidermal structures, resulting in the IFAP phenotype.[2,3]

The clinical severity of the IFAP phenotype has large variation. X linkage was predicted because the full phenotype is found in males only. It has been reported that female carriers with missense *MBTPS2* mutations may present with a variable phenotype ranging from severely affected to total absence of IFAP symptoms. Moreover, a female patient with IFAP who had congenital diffuse hypotrichosis was found to harbour no *MBTPS2* mutation, suggesting genetic heterogeneity of IFAP, and the possible existence of an autosomal inheritance form.

In conclusion, we report a patient presenting with a clinical constellation of follicularis ichthyosis, nonscarring alopecia, photophobia, pachyonychia, perianal and perioral psoriasiform lesions, which was highly suggestive of IFAP syndrome. The proband's mother denied having any symptoms reminiscent of IFAP. Screening of all genes in the candidate disease gene region identified only one potential disease-causing variant, a heterozygous change c.2T>C in

*Correspondence: Dr Ming Li, Department of Dermatology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China.
E-mail: liming01@xinhuamed.com.cn

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FC and JW contributed equally to this work and are joint first authors.

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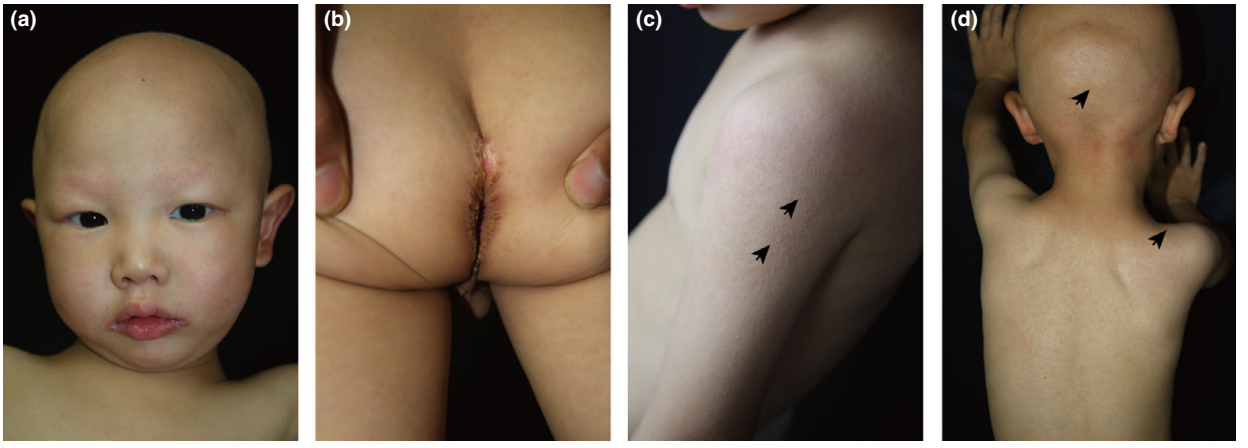

Figure 1 Clinical features of ichthyosis follicularis with atrichia and photophobia syndrome in a 5-year-old Chinese boy: (a) mild photophobia, angular cheilitis and complete atrichia affecting the scalp, eyebrows and eyelashes; (b) psoriasiform lesions over the perianal area; and (c) mild keratotic follicular papules prominent on the proband's arm and trunk (arrow).

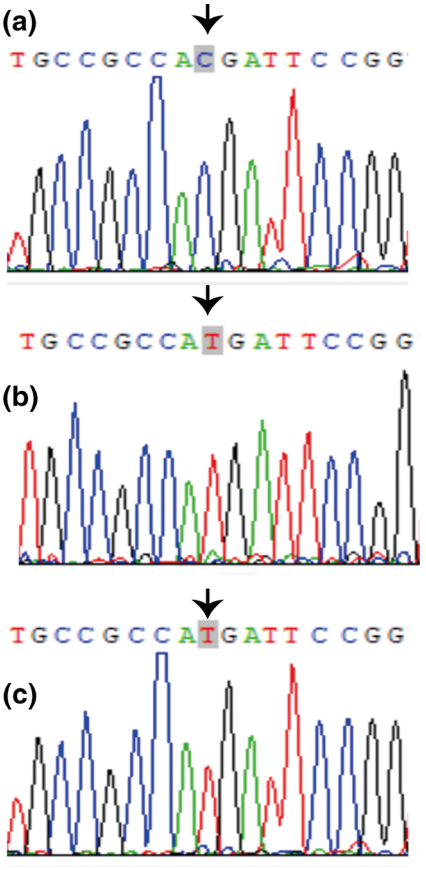

Figure 2 (a) Sequence chromatogram showing a heterozygous c.2T>C mutation in *MBTPS2* 5-year-old Chinese boy with ichthyosis follicularis with atrichia and photophobia syndrome, affecting the start codon (arrow shows the mutated base). Sequence chromatograms of (b) the proband's father and (c) the proband's mother were normal.

MBTPS2. As the mutation in *MBTPS2* was located in the start codon and was therefore predicted to abolish translation initiation, but the clinical phenotype was moderate, we hypothesize that an alternative start codon might be used for translation initiation or another protein might be used to compensate for the functions of MBTPS2. This Chinese sporadic paediatric case of IFAP syndrome adds new clinical and genetic information on this condition.

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CPD questions

Learning objective

To demonstrate an understanding of the clinical and genetic features of ichthyosis follicularis with atrichia and photophobia.

Question 1

Which of the following is the most appropriate first-line genetic test to confirm a new case of ichthyosis follicularis with atrichia and photophobia?

(a) Next-generation sequencing.
(b) Sanger sequencing.
(c) Whole exome sequencing.
(d) Whole genome sequencing.
(e) Multiplex ligation-dependent probe amplification.

Question 2

Which of the following is not characteristic of ichthyosis follicularis with atrichia and photophobia?

(a) X-linked inheritance.
(b) Ichthyosis follicularis.
(c) Autosomal dominant-negative inheritance.
(d) Atrichia.
(e) Photophobia.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.