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CASE REPORT

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Hyperammonemia in a girl who inherited a likely pathogenic variant of the ornithine transcarbamylase gene from her asymptomatic father—A peculiar pattern of X-linked recessive inheritance

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Abstract

A three-year-old Chinese girl presented with hyperammonemia was diagnosed biochemically and genetically (heterozygous for a novel likely pathogenic missense variant c.476T>A) as having ornithine transcarbamylase (OTC) deficiency, a rare X-linked recessive urea cycle disorders. Extensive family genetic screening eventually revealed paternal gonadosomatic mosaicism.

KEYWORDS

genetic mosaicism, hyperammonemia, inborn errors of metabolism, ornithine transcarbamylase deficiency

1 | INTRODUCTION

Ornithine transcarbamylase (OTC) deficiency (MIM# 311250) is a urea cycle disorder (UCD) caused by pathogenic variants in OTC gene (MIM*300461, chromosome Xp11.4) inherited in X-linked recessive manner, typically affecting hemizygote male and some of the heterozygote female with skewed X-chromosome inactivation. OTC deficiency typically presents with hyperammonemia with elevated glutamine and low-to-normal citrulline in plasma amino acids tests and elevated orotic acid and uracil in urine metabolic profiling. Cascade screening by genetic study is important to study inheritance pattern and offer appropriate genetic counseling for potentially at-risk family members. Here, we present a case of OTC deficiency in a Chinese family with unusual X-linked recessive inheritance pattern complicated by gonadosomatic mosaicism.

2 | CASE HISTORY

A three-year-old Chinese girl with unremarkable past health presented with abnormal behavior and confusion after an episode of upper respiratory tract infection. Parents were non-consanguineous; family history was unremarkable for inherited disease. The parents and a 6-year-old older sister were healthy and asymptomatic. She had preferred vegetables and starchy foods and never liked meat.

Blood test revealed moderate hyperammonemia (198 μmol/L, reference intervals: 21–50 μmol/L) with respiratory alkalosis. Plasma amino acid profile showed elevated glutamine (1208 μmol/L, reference intervals: 355–725 μmol/L) with normal citrulline (19 μmol/L, reference intervals: 13–46 μmol/L). Liver function test was otherwise unremarkable. The pattern was suggestive of a proximal urea cycle defects, such as N-acetylglutamate

synthetase (NAGS) deficiency, carbamoyl phosphate synthetase I (CPSI) deficiency, or OTC deficiency. Gross elevations of orotic acid and uracil were detected in the urine, which together with the clinical presentation and blood results, were highly suggestive of OTC deficiency. Serum acylcarnitine profile showed no abnormal pattern, making fatty acid oxidation defect unlikely. The patient was rapidly stabilized with intravenous ammonia scavengers and arginine, and subsequently started on oral sodium benzoate, citrulline, and low-protein diet. The biochemical abnormalities gradually improved with treatments.

3 | MOLECULAR FINDINGS

Genetic analysis of the *OTC* gene by Sanger sequencing of all the coding exons for the index patient detected a heterozygous likely pathogenic missense variant, NM_000531.5:c.476T>A p.(Ile159Asn) in exon 5. It was predicted to cause an amino acid change from isoleucine to asparagine at the highly conserved amino acid residue 159 (Figures 1 and 2). In silico prediction tools suggested the variant to be damaging to the protein product (REVEL score 0.949). It has not been previously reported in population database (gnomAD) or clinical database (ClinVar, HGMD). Two other pathogenic missense variants of the *OTC* gene (c.476T>C and c.477T>G) had been reported in the same codon in the past.[1,2] Based on the molecular and biochemical findings, the patient was diagnosed as a heterozygote female affected by OTC deficiency.

Given that OTC deficiency is typically inherited in X-linked recessive manner, targeted screening of the variant by Sanger sequencing was pursued for the proband's mother and older sister. The older sister was also heterozygous for the same variant, but was asymptomatic with normal ammonia level and plasma amino acid profile with no hyperexcretion of urine orotic acid or uracil. Intriguingly, the proband's mother had wild-type *OTC* alleles, that is, did not carry the disease-causing variant (Figure 1).

Genetic and biochemical screening was extended to the proband's father following the unexpected genotype of the mother. The father had been healthy and asymptomatic all along at the age of 48 years old. However, he admitted that he could sometimes be picky with food like his daughter and had occasional episodes of bizarre dreams and nightmares for years. Blood test of the father showed high glutamine level of 1447 μmol/L (reference intervals: 466–798 μmol/L) with a low normal citrulline level of 20 μmol/L (reference intervals: 19–47 μmol/L), with ammonia levels ranging from 51 to 194 umol/L (reference intervals: 15–55 μmol/L). A slight increase in urinary orotic acid and uracil were detected. Targeted genetic testing showed the presence of two different *OTC* alleles, one carrying the disease-causing variant while the other one was the wild-type sequence, in both his blood and urine samples. Multiplex ligation-dependent probe amplification (MLPA) showed that the father had a single copy of X-chromosome. These supported that the father was mosaic for the likely pathogenic *OTC* variant in the somatic cell populations. Although sperm analysis was not performed, given that variant was passed to his daughter, the father is likely gonadosomatic mosaic for the *OTC* variant. As the biochemical findings were suggestive of reduced OTC enzyme activity, he was conservatively managed as OTC deficiency as he could be at risk for decompensation in times of severe illness or stress.[3] He was started on

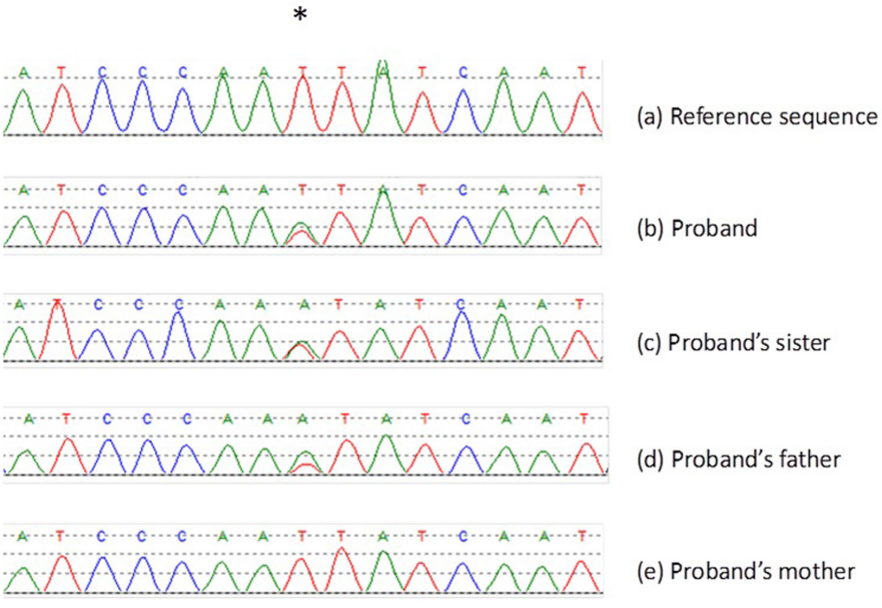

FIGURE 1 Results of Sanger sequencing of the OTC gene for the proband and her family members, where the asterisk (*) denotes nucleotide position 476.

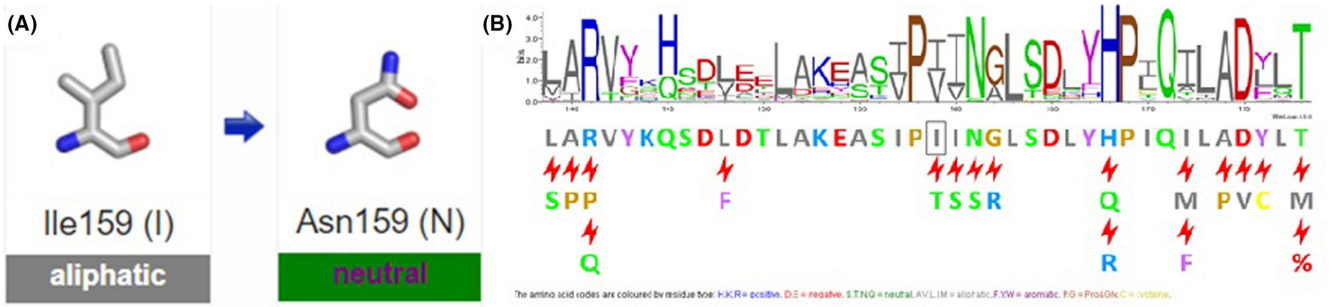

FIGURE 2 (A) Predicted amino acid change at residue 159 from Isoleucine, which has an aliphatic hydrophobic side chain, to Asparagine, which has a neutral side chain. The CADD score for the amino acid change up to 27.7, which indicates that change is likely deleterious to the protein function. (B) This sequence logo shows the alternative residues found at each position in a sequence alignment of related proteins. The amino acid codes are colored by residue property, as shown in the key at the bottom of the page. The boxed position in the protein sequence is the residue 159 of concerned, with up to 20 residues either side. The amino acid change from I (Isoleucine) to N (asparagine) indicates a change from aliphatic side chain to neutral side chain, a change that physio chemically resembling the known pathogenic variant I159T previously reported. Pictorial illustration was generated by VarSite (EMBL-EBI, Wellcome Genome Campus, Hinxton, Cambridgeshire).

sodium benzoate and citrulline supplement and advised to avoid protein-rich foods or prolonged fasting. Family screening was also pursed for the proband's paternal grandmother, and she did not carry the variant.

4 | DISCUSSION

The urea cycle is the principal metabolic pathway for the clearance of waste nitrogen produced from protein turnover. Inherited defects in the enzyme or transporter involved would lead to urea cycle disorders (UCD), clinically characterized by hyperammonemic crisis with triad of encephalopathy, respiratory alkalosis, and hyperammonemia. Up to now, seven UCDs have been described: carbamoyl phosphate synthetase I deficiency (MIM# 237300), OTC deficiency (MIM# 311250), classic citrullinemia (MIM# 215700), argininosuccinic aciduria (MIM# 207900), argininemia (MIM# 207800), N-acetylglutamate synthase deficiency (MIM# 237310), hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (MIM# 238970), and citrullinemia type II (MIM# 605814 & 603,471). OTC deficiency is the commonest among all UCD and is the only one with X-linked recessive inheritance. The OTC enzyme catalyzes the formation of citrulline from carbamyl phosphate and ornithine. Most patients are hemizygous males who usually present as neonates with symptoms due to toxic effects of ammonia on the brain, causing high mortality and morbidity. Approximately 20% of female heterozygote develop symptoms as a result of X-chromosome inactivation with favorable expression of the mutant allele.[3,4] Heterozygous female carriers and males with partial OTC deficiency could present beyond infancy and childhood, even in late adulthood.[4]

The family presented in this case report had a peculiar pattern of X-linked recessive inheritance of OTC deficiency complicated by paternal gonadosomatic mosaicism. Gonadosomatic mosaicism refers to the presence of two or more cell populations with distinct genotypes in both gonadal and somatic cells, usually as a result of a mutational event that occurs post-conceptually during early embryogenesis and before the differentiation of the primordial germ cells, thereby affecting both somatic and gonadal cells. It is likely that the index patient and his older sister inherited the likely pathogenic *OTC* variant from the father's mosaic gonadal cells carrying the variant. Gonadosomatic mosaicism has been described in various genetic disease with autosomal dominant or X-linked recessive inheritance. Olga et al. previously reported a case of OTC deficiency in a 4-year-old female proband who was heterozygous for a pathogenic splice site variant (c.78-1G>A), which her asymptomatic father was gonadosomatic mosaic for the variant.[5] Male OTC deficiency patient who was somatic mosaic for *OTC* pathogenic variants was reported to exhibit milder phenotype with late disease onset.[6] In our case, the mosaic father exhibited mild biochemical evidence of OTC deficiency.

Extensive family genotype screening is crucial to delineate inheritance pattern. In family screening for disease with known X-linked recessive inheritance, quite often only the mother and sibling(s) would be screened, the variant may be assumed to have occurred de novo in the index patient during early embryogenesis, if it was not detected in the mother. Recurrence risk is much higher in the setting of parental gonadal mosaicism, up to 512-fold (female parent of origin) to 3312-fold (male parent of origin), comparing to a 0.1% recurrence risk if the mosaic status is unknown.[7] Gonadal mosaicism should therefore be suspected if multiple offspring were found to carry the

same disease-causing variants while the parent(s) appear not to be a carrier by genetic study on somatic cell population, for example, genetic testing by peripheral blood taking. In this case, somatic mosaicism was demonstrated in the father's urine and blood sample, the mosaic level is close to two-third for the likely pathogenic variant based on the peak height ratio by Sanger sequencing. It should be emphasized that conventional technique such as Sanger sequencing is unable to detect low-level mosaicism below a threshold of 15%–20%. Newer deep sequencing technology now permits a higher sensitivity for the detection of low-level mosaicism; the overall occurrence of low-level parental gonadosomatic mosaicism is now estimated at about 0.5%–8.3%.[8] Demonstration of gonadosomatic mosaicism provides key information for genetic counseling on future recurrence risk and family planning. Mosaicism level in peripheral blood, saliva, urine sample often correlated poorly with disease severity, early detection of mosaic parents or siblings allow proper clinical assessment and management. In a number of X-linked recessive disease, as in the case of OTC deficiency, some of the heterozygous female may manifest clinically, and can range from mildly to severely affected depending on the favorable versus unfavorable X-chromosome inactivation, which is a form of functional mosaicism, and is well demonstrated by the different phenotypes of the index patient and her older sister in this report. Although the older sister appears to be unaffected and not requiring any active treatment, she might still be at certain risk for hyperammonemia during severe illness or stress, including child birth.[9]

5 | CONCLUSION

Urea cycle disorders, including OTC deficiency, should be considered for both male and female patients in the clinical triad of encephalopathy, respiratory alkalosis, and hyperammonemia. Here, we report a family with an unusual pattern of X-linked recessive inheritance of OTC deficiency as a result of paternal gonadosomatic mosaicism and random X-chromosome inactivation. Thorough and careful genetic analysis for proband and all at-risk family members are important to identify and treat affected family members and delineate inheritance pattern for proper genetic counseling.

AUTHOR CONTRIBUTIONS

Toby Chun Hei Chan prepared a first version of manuscript draft, performed detailed literature research and coordinated the whole process of preparation of the manuscript. Hoi Ning Cheung was involved in the preparation of the first draft and illustrative figure. Jasmine Chow reviewed the draft and took part in the management of the patient. Mei Tik Leung reviewed and revised the draft. Sammy Pak Lam Chen reviewed and revised the draft. Chi Chung Shek reviewed and revised the draft. All authors were involved in the preparation of this manuscript. All authors read and approved.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study is in compliance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

INFORMED CONSENT

Written informed consent was obtained from all the parents and the family members involved.

DISCLAIMER

This manuscript, or part of it, has neither been published nor is currently under consideration by any other journal.

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