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## ABOUT COVER

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CASE REPORT

# Hemizygous deletion in the *OTC* gene results in ornithine transcarbamylase deficiency: A case report

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**Author contributions:** Wang LP, Cao YT, and Chen J jointly conceived the study and contributed to the study design, initial writing, and revision of the manuscript; Luo HZ collected the patient data; Wang LP and Song M performed the molecular experiments; Yang ZZ and Yang F reviewed variant interpretation; all authors contributed to the manuscript and approved the submitted version.

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## Abstract

### *BACKGROUND*

Ornithine transcarbamylase deficiency (OTCD) is a common ornithine cycle disorder, and *OTC* gene variation is the main pathogenic factor of this disease. This study explored and validated a variant in the *OTC* gene.

### *CASE SUMMARY*

The neonate exhibited high blood ammonia, lactic acid, and homocysteine levels on the fifth day after birth. A novel deletion variant in the *OTC* gene [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324GlnfsTer16] was uncovered by exome sequencing. The variant caused a protein-coding frameshift and resulted in early translation termination at the 16$^{th}$ amino acid after the variant site.

### *CONCLUSION*

Our results provide a novel pathogenic variant in *OTC* and related clinical features for further OTCD screening and clinical consultation.

**Key Words:** *OTC*; Ornithine transcarbamylase deficiency; Deletion variant; Exome sequencing; Early translation termination; Case report



**Core Tip:** In this study, we introduce one boy with ornithine transcarbamylase deficiency caused by an unreported hemizygous variant of *OTC* gene. Our study delivered the importance of *OTC* gene testing in metabolism disease. We believe that our study will inspire more doctors to apply genetics testing when facing complex

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## INTRODUCTION

Ornithine transcarbamylase deficiency (OTCD, OMIM: 311250), also known as hyperammonemia type II, is an X-linked genetic disorder of the ornithine cycle (urea cycle)[1]. The incidence of OTCD is approximately 1/80000–1/56500. OTCD is the most common type of ornithine circulation disorder and accounts for 50%-66% of total ornithine circulation disorders. Both neonates and adults can be affected by complex clinical symptoms of this disorder, with varying degrees of severity. Due to this lack of specificity, OTCD is often misdiagnosed[1-3]. OTCD has a high mortality rate in neonates, and survivors often have varying degrees of neurological sequelae. Early diagnosis, individualized diet, medication, and liver transplantation are the main strategies for reducing the mortality and disability rates of patients with OTCD.

The *OTC* gene (OMIM: 300461) is located on chromosome Xp11.4, contains 10 exons and 9 introns, and encodes a 354 amino acid protein. The *OTC* gene is highly expressed in the liver[4]. Pathogenic variants in the *OTC* gene lead to a reduction or absence of *OTC* enzyme activity and the shutdown of citrulline synthesis and the ornithine cycle, resulting in an ammonia metabolism disorder and an increase in levels of ammonia in the blood[5]. Excessive accumulation of ammonia is highly toxic to the central nervous system, interferes with the energy metabolism of brain cells, and causes cytotoxic cerebral edema and acute or chronic traumatic encephalopathy as well as neuropsychiatric damage[5].

Based on the time of onset, patients with OTCD are divided into neonatal onset and late onset (age of onset > 28 d) groups[6]. Enzyme activity between the two groups is notably different. In the neonatal onset group, enzyme activity is completely reduced, and in the late onset group, enzyme activity is partially reduced. Most patients with neonatal-onset OTCD are males with hemizygous variants[7]. They demonstrate no symptoms at birth but gradually refuse to feed and begin to exhibit symptoms of vomiting, irritability, hyperventilation, and lethargy within a few hours to days after birth. Onset is sudden with rapid and complex clinical features, such as convulsions, coma, hypothermia, and respiratory failure[8]. Due to the lack of specificity in clinical features, patients are often misdiagnosed with neonatal sepsis, neonatal hypoxic-ischemic encephalopathy, birth injury, food poisoning, acute gastroenteritis, encephalitis, epilepsy, encephalopathy combined with visceral steatosis (Wright's syndrome), neurodegenerative disease, or schizophrenia. Elevated ammonia in the blood is a main abnormal indicator in patients with OTCD, and *OTC* gene variants are another crucial factor in the diagnosis of OTCD[9]. To date, over 530 variants in the *OTC* gene have been reported, but no hotspot mutations have been found. Therefore, the collection of as many pathogenic variants as possible is important for clinical diagnosis and screening.

This study involved a male neonate with a pathogenic variant in *OTC*. We comprehensively investigated the clinical features and enzymatic activity through genetic testing.

## CASE PRESENTATION

### *Chief complaints*

A five-day-old boy who did not feed and showed no movement or responsiveness was referred to our department for further treatment.

### History of present illness

The proband was delivered *via* cesarean section due to "fetal distress" at 40 wk. There was no meconium-stained amniotic fluid, no abnormalities in the umbilical cord, and no premature rupture of membranes. His birth weight was 2350 g, and his Apgar score was normal. He was diagnosed as a "low birth weight infant with gastrointestinal bleeding" and showed improvement after unknown treatment. The amount of ordinary formula milk fed was increased gradually until he consumed 30 mL of milk at each feeding. Five days later, he stopped feeding, showed no movement, and exhibited poor responsiveness, which was accompanied by an abnormal increase in muscle tone, shortness of breath, moaning, foaming at the mouth, screaming, pumping, vomiting, abdominal distention, and blood in the stool.

### Physical examination

Physical examination revealed a low body temperature (35 °C), low blood pressure (35/15 mmHg), bradycardia (97/min), and lack of spontaneous breathing.

### Laboratory examinations

The final blood glucose level of the patient was 2.6 mmol/L. He had high blood ammonia [461.0 μmol/L (ref: 18–72)], high lactic acid [10.80 mmo1/L (ref: 1.06–2.09)], and high homocysteine [29.21 μmol/L (ref: < 15)] levels (Table 1).

A hemizygous variant in the *OTC* [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324GlnfsTer16] gene was identified by exome sequencing. The variant caused a 10-bp deletion and early translation termination in the *OTC* gene. Sanger sequencing confirmed that this variant was inherited from his mother (Figure 1). The variant was absent in public databases (gnomAD, Exome Aggregation Consortium, or 1000 Genomes). The variant was classified as likely pathogenic according to the ACMG guidelines (Table 2). Pathogenic variants in other genes associated with hyperammonemia have not yet been identified. We reported this variant in the ClinVar database (accession number: VCV001256051).

## FINAL DIAGNOSIS

The male infant patient was diagnosed with OTCD caused by an *OTC* mutation.

## TREATMENT

After admission, we ensured that the patient's airway was unblocked, warmed the body, monitored vital signs, assisted breathing with the use of a ventilator, and corrected the blood pH with the administration of sodium bicarbonate. Meropenem and penicillin were utilized to combat infection, phenobarbital for spasms, dopamine for circulation, and 10% glucose to maintain the stability of the internal environment.

Arginine was used to reduce blood ammonia, and levocarnitine was used to promote metabolism. Lidocaine was used for nonparoxysmal ventricular arrhythmia, which was indicated by an electrocardiogram.

## OUTCOME AND FOLLOW-UP

The patient remained in a coma since admission with weak heart sounds. After active rescue and treatment, the patient's condition remained critical, with no remission or spontaneous breathing. His blood pressure, oxygen saturation, and heart rate were unstable; there was no response to stimulation. The patient was still in a coma when discharged and died soon after.

## DISCUSSION

OTCD diagnosis is mainly based on clinical symptoms, blood ammonia levels, and other general biochemical tests, such as blood amino acids, urine organic acids, and genetic tests. For suspected cases, such as those in which patients present intermittent or progressive encephalopathy and high blood ammonia levels with unknown causes,

**Table 1 Main clinical examination results of proband**

| Item | Result | Ref. |
|---|---|---|
| Body temperature | 35 ℃ | 36–37 ℃ |
| Blood pressure | 35/15 mmHg | 66–75/45 mmHg |
| Heart rate | 97/min | 120–140/min |
| Blood ammonia | 461.0 μmol/L | 18–72 μmol/L |
| Lactic acid | 10.80 mmo1/L | 1.06–2.09 mmo1/L |
| Homocysteine | 29.21 μmol/L | < 15 μmol/L |

**Table 2 Classification of the variants in *OTC* according to ACMG**

| Gene | Variant | Inheritance | MAF | | | SIFT | Polyphen2 | Mutation taster | Evidence | ACMG category |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ExAc | gnomAD | 1000 genomes | | | | | |
| *OTC* | c.970_979del TTCCCAGAGG | Hemi | NE | NE | NE | - | - | - | PS2 + PM2_supporting + PP3 | Likely pathogenic |

Transcript: NM_000531.5; MAF: Minor allele frequency; NE: Not existing.

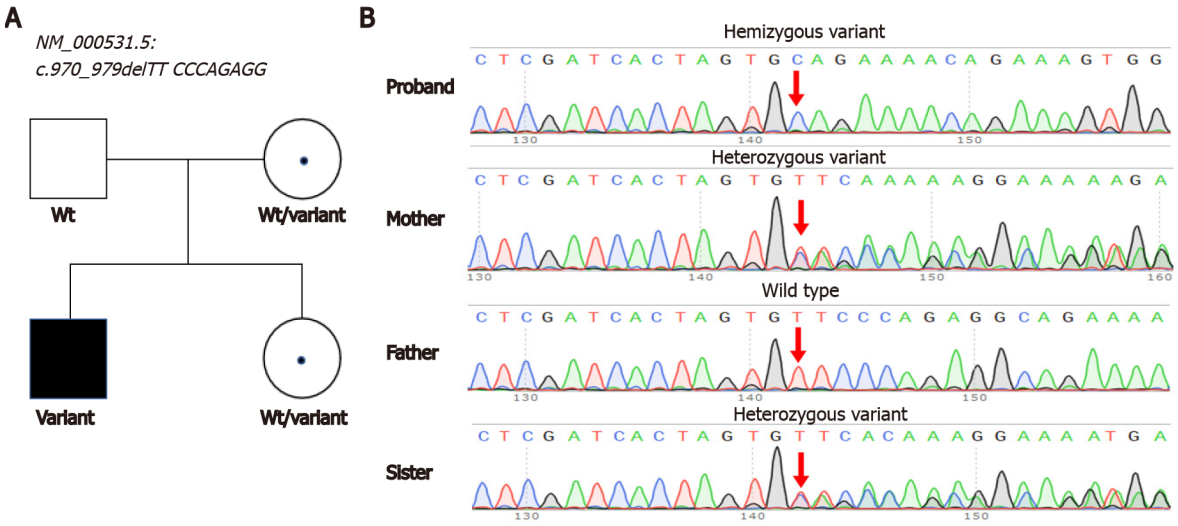


**Figure 1 The genogram of proband and parents.** A: Mutation analysis of the *OTC* gene; B: The father was hemizygous for *OTC*, the mother and sister were heterozygous for *OTC*, and the proband was hemizygous for *OTC*. The red arrow represents the mutation site.

blood amino acid analysis and urine organic acid analysis should be performed as early as possible. If blood citrate is reduced or normal and urine whey acid or uracil is increased[9], OTCD diagnosis can be confirmed by combining these results with genetic testing. For neonates whose blood amino acid screening by tandem mass spectrometry indicates reduced citrulline levels, dynamic observation should be carried out, and urine organic acid and genetic tests should be performed.

The clinical symptoms and related examinations of OTCD patients lack specificity and should be differentiated from those of hyperammonemia caused by other factors, including different ornithine circulatory disorders; miscellaneous genetic metabolic diseases, including organic acid hematic disease, fatty acid oxidation disorder, beta oxygen defects, high insulin, and hepatic encephalopathy; severe liver damage; exogenous toxicity (*e.g.*, carbamidine); and drugs (*e.g.*, valproic acid). All these factors can elevate blood ammonia levels and should be identified according to the patient's medical history and clinical symptoms[9]. Genetic testing of the *OTC* gene is another crucial factor in the diagnosis of this disease.

Liver transplantation is regarded as an effective treatment for OTCD. For patients with neonatal onset, liver transplantation should be performed at the earliest identification of disease. Surgery is recommended between three months (and/or body weight > 5 kg) and one year[9]. Once OTCD is suspected, clinical examinations for blood ammonia, blood amino acids, and urine organic acids should be performed rapidly in a specialized metabolic laboratory. Our case shows high blood ammonia [461.0 μmol/L (ref: 18-72)], high lactic acid [10.80 mmo1/L (ref: 1.06-2.09)], and high homocysteine [29.21 μmol/L (ref: < 15)] levels. After interpreting the sequencing results, we confirmed the diagnosis of OTCD in this patient.

Genetic testing is a crucial method for the diagnosis of OTCD. As a routine practice of next-generation sequencing (NGS), high-throughput sequencing will rapidly uncover many pathogenic variants in neonates who are suspected to have OTCD with abnormal hyperammonemia. Array CGH or multiplex ligation-dependent probe amplification fails to detect *OTC* gene deficiency in SNVs or microinsertions and deletions in patients[10,11], whereas NGS has the advantage of detecting these variations. Our study uncovered an unreported variant in the *OTC* gene [NM_000531.5, c.970_979delTTCCCAGAGG, p.Phe324GlnfsTer16], which caused the early termination of OTC. Our results provide a reference for the accurate diagnosis of patients with the same variant. A previous study reported that approximately 15% of female carriers become symptomatic[12]. Our findings also suggest heterozygote detection of at-risk female relatives as a promising direction for further investigation.

## CONCLUSION

In our case study of one individual, a rare variant in the *OTC* gene was identified and confirmed by Sanger sequencing. This finding broadens the *OTC* variant spectrum and provides evidence for further OTCD screening and clinical consultation.

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