Novel Mutations in the 3β-hydroxy-Δ5-C27-steroid Dehydrogenase Gene (*HSD3B7*) in a Patient with Neonatal Cholestasis

He-Yu Huang[1], Hua Zhou[1], Hong Wang[2], Ya-Xian Chen[1], Feng Fang[1]

[1]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China
[2]Department of Internal Medicine, Genetic Diagnostic Centre, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

Key words: *HSD3B7*; Mutation; Neonatal Cholestasis

Bile acid synthetic defect (BASD) is a rare category of genetic disorders that are responsible for approximately 2% of persistent cholestasis in infants.[1] Until date, four enzymes responsible for congenital defects of bile acid synthesis (CBAS) have been identified. 3β-hydroxy-Δ5-C27-steroid dehydrogenase (3β-HSD), the deficiency of which can cause CBAS1 (OMIM No. 607765), is encoded by the gene *HSD3B7* and works in the second step of transforming the steroid into primary bile acids.

An infant (1 month and 9-day-old) was brought to our hospital by her parents with an indication of lasting jaundice. The baby had been delivered by spontaneous vaginal delivery without complications at the full-term gestation week, weighing 3300 g. Jaundice had appeared just 2 days after birth and persisted after 8 days. Her temperature at that time was normal, the stool sample had a light yellow color, and there was no sign of diarrhea or steatorrhea. After 3 days of treatment in another hospital, the patient was referred to our hospital because of hyperbilirubinemia and liver dysfunction. Initial physical examination on admission showed hepatomegaly (about 4 cm below the rib) and obvious jaundice.

After admission, we conducted a thorough examination to determine the cause for cholestasis. The ultrasound scan indicated no particular sign of intrahepatic or extrahepatic bile duct malformation or obstruction. Tests for conventional pathogens in infants had no significant positive findings; these were as follows: Anti-Cytomegalovirus (CMV), anti-Rubella virus, and anti-Herpes simplex virus (HSV) I: IgM−, IgG+; anti-*Toxoplasma gondii* and anti-HSV II: IgM−, IgG−; anti-*Parvovirus* B19: IgM−; shell viral assay for urine human CMV detection: –; blood Epstein–Barr virus DNA: –; hepatitis A, B, C, and E virus antibodies: –; human immunodeficiency virus antibody: –; and syphilis antibody: –. Urine sample analysis by gas chromatography-mass spectrometry (GC-MS) ruled out several organic acidurias. Blood sample acylcarnitine and amino acid profiles did not support the diagnosis of fatty acid or amino acid metabolic diseases. Peculiarly, in spite of high aminotransferase (alanine aminotransferase [ALT] 174 U/L, aspartate aminotransferase [AST] 195 U/L) and bilirubin (total bilirubin [TBIL] 106.0 μmol/L, direct bilirubin [DBIL] 78.30 μmol/L) levels, the patient had normal γ-glutamyltransferase (GGT, 24 U/L) and total bile acid (2.2 μmol/L) concentrations, which led us to consider the possibility of BASD.

With the parents' consent, we ran a genetic test of the patient and her parents for a set of genes responsible for neonatal cholestasis. The potential influence of the detected mutations on protein function was estimated using Sorting Intolerant from Tolerant (SIFT) (http://sift.jcvi.org/www/SIFT_BLink_submit.html) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph 2/) software.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.172603

Address for correspondence: Prof. Feng Fang, Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China
E-Mail: ffang@tjh.tjmu.edu.cn

Received: 28-09-2015 **Edited by:** Yuan-Yuan Ji
How to cite this article: Huang HY, Zhou H, Wang H, Chen YX, Fang F. Novel Mutations in the 3β-hydroxy-Δ5-C27-steroid Dehydrogenase Gene (HSD3B7) in a Patient with Neonatal Cholestasis. Chin Med J 2016;129:98-100.

Two compound heterozygous *HSD3B7* gene mutations and a single *SLC25A13* gene mutation were identified in the patient. Sequencing of the patient and parental homologous regions revealed the maternally inherited mutation c.503G>A (p.Trp168Ter) and the paternally inherited mutation c.683G>A (p.Arg228Gln) [Figure 1]. The *SLC25A13* mutation c.852-855delTATG (p.Met285fs) was inherited from her mother, but the allele gene was normal.

The c.503G>A (p.Trp168Ter) mutation in exon 5 causes an abrupt termination of 3β-HSD transcription. The c.683G>A (p.Arg228Gln) mutation in exon 6 was predicated to have a probable damaging influence on protein function (PolyPhen score 1; SIFT score 0.05). Both *HSD3B7* mutations mentioned above have not been identified either in 100 normal subjects studied by us or in Chinese members of the 1000 Genomes Project and other human populations. The *SLC25A13* mutation causes neonatal intrahepatic cholestasis due to citrin deficiency (NICCD; MIM No. 605814). The patient inherited the *SLC25A13* mutation from her mother and a normal *SLC25A13* gene from her father, so she had no aminoacidemia, which is typical for NICCD.

The patient's genetic results ultimately led to the diagnosis of CBAS1; however, the parents declined our proposal of liver biopsy. Ursodeoxycholic acid (UDCA) treatment (62.5 mg, b.i.d) had been initiated on the 2nd day of admission to relieve her clinical symptoms. After the establishment of CBAS1 diagnosis, we planned to switch to chenodeoxycholic acid (CDCA) treatment, but the parents demanded an early discharge and received CDCA treatment (41.66 mg, b.i.d) at another hospital. By the time of discharge from our hospital, the patient showed an improvement of liver function (ALT: 34 U/L, AST: 143 U/L, TBIL: 93.6 μmol/L, DBIL: 78.00 μmol/L; decreased aminotransferase and bilirubin; increased albumin, prealbumin, and globulin). At follow-up 2 weeks later by telephone, the parents informed that jaundice had completely faded, and the aminotransferase level had returned to normal.

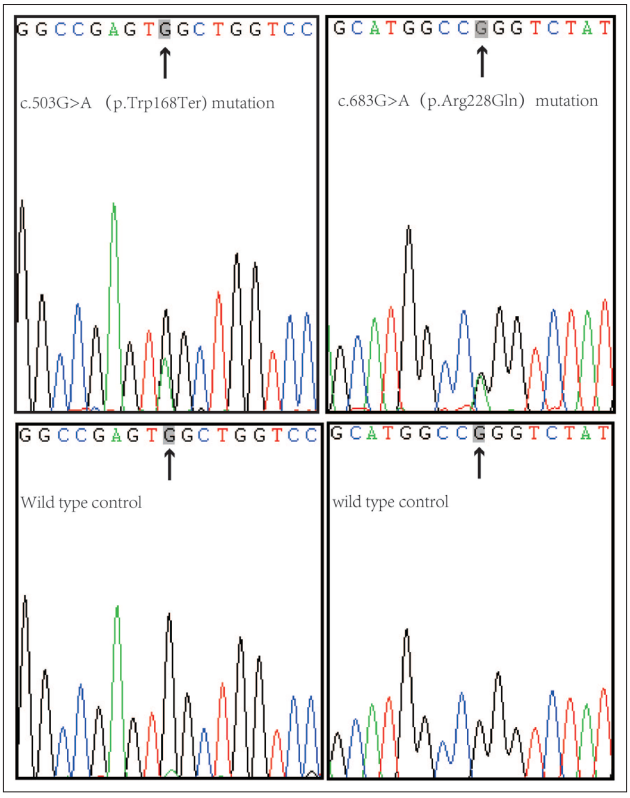

Figure 1: Sequence analysis of exons of the *HSD3B7* gene of the patient. Two identified mutations were c.503G>A (p.Trp168Ter) in exon 5 and c.683G>A (p.Arg228Gln) mutation in exon 6. The patient inherited the aforementioned two mutations from her parents as the compound heterozygote. The nucleotide exchange and insertion are marked by arrows.

CBAS1 due to *HSD3B7* mutations often has an early onset; in rare cases, adults with liver dysfunction turn out to be 3β-HSD deficient. 3β-HSD enzyme dysfunction can lead to bile acid biosynthesis errors, which will cause primary bile acid (cholic acid [CA] and CDCAs) deficiency and atypical bile acid and sterol accumulation. Lack of primary bile acids results in bile acid flow reduction, which in turn leads to fat and fat-soluble vitamin malabsorption. The atypical metabolites can be toxic to liver cells, resulting in liver dysfunction. Although the clinical manifestations in patients (including cholestasis, bleeding tendency, rickets, failure to thrive, etc.)[2] are varied, the GGT and total bile acid concentrations are usually within normal range.[3] Liver biopsy often shows giant cell hepatitis, and at late stages, bridging fibrosis and micronodular cirrhosis can also be seen.[2] Bile acid analysis of serum and urine using GC-MS or fast atom bombardment MS (FAB-MS) is a conventional way to screen BASD, but this test is currently not available in China.

CDCA or CA treatments have been recommended by some doctors on the basis of clinical data, where patients who received treatment at an early age remained asymptomatic for many years and could develop normally. CA seems to be a better choice than CDCA, because, at late disease stages, CDCA may have toxic effects on hepatic cells.[3] Gonzales *et al*. investigated the long-term effect of oral CA for hereditary defects of primary bile acid synthesis and suggested it was safe and effective for 3β-HSD-deficient patients.[4] UDCA treatment can have limited benefits, but it has little effect in reducing the harmful intermediate metabolites in urine[5] and can even cause liver damage.

Our patient was admitted for cholestasis, the common causes of which had been excluded after a thorough examination. Her GGT and total bile acid levels stayed normal after admission, which reminded us of BASD. Because serum and urine bile acid analyses by GC-MS and FAB-MS were not available, we tested for cholestasis-related gene mutations instead. We identified two novel *HSD3B7* gene mutations in our patient, which could be a new underlying pathogenesis of 3β-HSD deficiency.

BASD accounts for about 2% of neonatal cholestasis cases, and early primary bile acid replacement treatment can achieve good results.[5] For cholestasis with normal GGT and total bile acid concentrations, the possibility of BASD should be considered and confirmed with genetic testing. Even though initial UDCA treatment can have some beneficial effects, it is important to investigate further instead of immediately concluding a diagnosis of idiopathic cholestasis. Once confirmed, the UDCA must be stopped immediately and be replaced with primary bile acids.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bove KE, Heubi JE, Balistreri WF, Setchell KD. Bile acid synthetic defects and liver disease: A comprehensive review. Pediatr Dev Pathol 2004;7:315-34.
2. Grijalva J, Vakili K. Neonatal liver physiology. Semin Pediatr Surg 2013;22:185-9. doi:10.1053/j.sempedsurg. 2013.10.006.
3. Subramaniam P, Clayton PT, Portmann BC, Mieli-Vergani G, Hadzic N. Variable clinical spectrum of the most common inborn error of bile acid metabolism-3beta-hydroxy-Delta 5-C27-steroid dehydrogenase deficiency. J Pediatr Gastroenterol Nutr 2010;50:61-6. doi: 10.1097/MPG.0b013e3181b47b34.
4. Gonzales E, Gerhardt MF, Fabre M, Setchell KD, Davit-Spraul A, Vincent I, *et al.* Oral cholic acid for hereditary defects of primary bile acid synthesis: A safe and effective long-term therapy. Gastroenterology 2009;137:1310-20.e1-3. doi: 10.1053/j.gastro.2009.07.043.
5. Mizuochi T, Kimura A, Ueki I, Takahashi T, Hashimoto T, Takao A, *et al.* Molecular genetic and bile acid profiles in two Japanese patients with 3beta-hydroxy-DELTA5-C27-steroid dehydrogenase/isomerase deficiency. Pediatr Res 2010;68:258-63. doi: 10.1203/00006450-201011001-00505.