ORIGINAL ARTICLE

Clinical Significance of UGT1A1 Genetic Analysis in Chinese Neonates with Severe Hyperbilirubinemia

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Received Apr 13, 2015; received in revised form Aug 12, 2015; accepted Aug 14, 2015
Available online 2 December 2015

Key Words
G6PD deficiency; genetic diagnosis; neonatal hyperbilirubinemia; thalassemia; UGT1A1 variant

Background: Neonatal hyperbilirubinemia is common in Asia, and the importance of genetically determined conditions has been recently recognized. The aim of this study was to assess the clinical utility of genetic testing in Chinese neonates with severe hyperbilirubinemia.

Methods: Fifty-eight term infants with bilirubin level \( \geq 20 \text{ mg/dL} \) (342 \( \mu \text{mol/L} \)), and 65 controls were enrolled in the study. Variation status of UGT1A1, G6PD, and thalassemia genes in our study cohort was determined by direct sequencing or genotype assays.

Results: Among these case infants, seven were confirmed with G6PD deficiency, four were heterozygous for \( \alpha- \) or \( \beta- \) thalassemia, and forty-four were detected with at least one heterozygous UGT1A1 functional variant, including nine homozygous for UGT1A1 variation. As well as the predominant c.211G>A (Gly71Arg) variant, three UGT1A1 coding variants [c.1091C>T (Pro364-Leu), c.1352C>T (pro451leu), and c.1456C>T (Tyr486Asp)] were observed in our case neonates. The results of multivariate logistic regressions, adjusted for covariates, revealed odds ratios for neonates who carried heterozygous, homozygous variation at nucleotide 211 of UGT1A1, and G6PD deficiency of 3.47 (1.26–9.55), 12.46 (1.09–142.7), and 12.87 (1.32–135.87) compared with those having the wild genotype and normal G6PD activity, respectively.

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1. Introduction

Severe neonatal hyperbilirubinemia [total serum bilirubin (TSB) level ≥ 20 mg/dL or > 342 μmol/L] is frequently manifested as a pediatric complex trait or disorder, which is still prevalent (1%) in the newborn population today.1,2 Although most cases are benign and do not result in serious consequences, a small number of infants will develop hazardous levels of bilirubin that pose a direct threat of brain damage, and which may result in neuro-developmental abnormalities, such as hearing loss, athetosis, and, rarely, intellectual deficits.3–5 East Asian ancestry encompassing population across mainland China, Hong Kong, Japan, Macau, Korea, and Taiwan was listed as a major risk factor for severe hyperbilirubinemia in the 2004 American Academy of Pediatrics clinical practice guideline.6 It was proposed that higher incidence of hemolytic anemia, such as ABO alloimmunization and G6PD deficiency, may predispose this population to be sensitive to neonatal hyperbilirubinemia, and to an overall increased risk for a TSB of ≥ 20 mg/dL (342 μmol/L).7 However, the etiology is still listed as “idiopathic” and not sufficiently explored in the majority of clinically reported cases.

Genetic diagnosis has cast a new and fascinating light on this complex disorder. The main feature in neonatal jaundice may be the imbalance between increased bilirubin production and decreased conjugation rates. There is increasing evidence showing that genetic variants in the key bilirubin metabolism gene in humans, hepatic bilirubin conjugating isoenzyme uridine diphosphoglucuronosyl transferase 1A1 (UGT1A1), as described classically for Crigler-Najjar type I and II syndromes and reported for Gilbert’s syndrome.8–10 were associated with increased incidence and severity of hyperbilirubinemia in combination with hemolytic disorder.11–15 In this study, we investigated the variation status of UGT1A1, G6PD, and thalassemia genes in neonates with severe hyperbilirubinemia in the Chaozhou region of southern China, where the prevalence of G6PD deficiency and thalassemia was 2% and ~6–8%, respectively.16,17 We presumed that UGT1A1 variation, G6PD deficiency, and thalassemia may be more frequent in these neonates with severe hyperbilirubinemia, and that this may contribute to their development of severe hyperbilirubinemia.

2. Methods

2.1. Study participants and sample collection

This was a retrospective case–control study conducted in the pediatric center of a single hospital (Chaozhou Central Hospital, affiliated with Southern Medical College, Chaozhou, Taiwan). All study neonates were enrolled from those admitted to the study center from November 2011 to July 2014. Eligible infants were term infants with a gestational age of > 37 weeks, a birth weight ≥ 2500 g, and no major birth abnormalities or serious illness.

Blood samples for genotyping were obtained from the surplus ethylenediaminetetraacetic acid anti-coagulated whole-blood sample, which was prospectively collected and stored −20°C after completion of the clinical diagnosis. Clinical records, including the birth date, gender, birth weight, delivery method, gestational age, feeding method, TSB levels, and peak bilirubin levels before phototherapy were reviewed.

Severe neonatal hyperbilirubinemia was defined as a TSB concentration > 20 mg/dL (342 μmol/L).2 The recorded peak TSB was used to divide the enrolled participants into case and control groups. The case group included jaundiced infants with a maximum TSB > 20 mg/dL and aged ≤ 14 days. Neonates with known clinical risk factors for developing neonatal hyperbilirubinemia, such as a positive Coombs’ test, cephalohematoma, sepsis, perinatal asphyxia, or major organ abnormality, were excluded. Control infants were term infants without major abnormality or illness, who were admitted to the study center for reasons other than jaundice during the same period, and with a TSB not requiring phototherapy according to the updated clinical guidelines by the China Neonatal Association.18

The study was approved by the Institute Ethics Committee of Chaozhou Central Hospital. Since the data were analyzed anonymously and blood samples for this study were used after the completion of clinical diagnostic work (blood routine test), the committee approved a waiver of written consent.  

2.2. Analysis of UGT1A1 polymorphism

Samples from jaundiced babies were subjected to direct sequencing of the UGT1A1 genes. Samples from babies in the control group were only subjected for 6(c.211G>A, p.Arg71Gly) polymorphism detection, may be taken into consideration for early diagnosis and treatment of severe hyperbilirubinemic newborns in southern China. 

Conclusion: Besides G6PD-deficiency screening, UGT1A1 genetic analysis, and especially the UGT1A1*6(c.211G>A, p.Arg71Gly) polymorphism detection, may be taken into consideration for early diagnosis and treatment of severe hyperbilirubinemic newborns in southern China.
Analyser (Applied BioSystems, Foster City, CA, USA), and the size of the amplicons determined by using the software GeneMapper 4.0 (Applied BioSystems). The sequence results further confirmed the sizes of (TA)ₙ repeats as determined by fluorescence labeling. Primer sequences for (TA)ₙ-repeat analysis were as follows: F: FAM-ACGTGACACAGCTAAACATTAACT; R: CCAGCATGGGACACC-ACGT.

The *6(c.211G>A, p.Arg71Gly) polymorphism in the control group neonates was determined by our novel high-resolution-melting (HRM) method. Primers used for this PCR and HRM analysis were: F: CACCTGACGCCTCGTTGTAC; R: CTCTTTACATCCCTCCCTTG.

2.3. G6PD gene analysis

G6PD-deficient neonates, as determined by clinically approved G6PD Enzyme Quantification Assay (Guangzhou Micky Medical Instrument Co., Guangdong, China), were further subjected to molecular analysis. A reverse dot blot assay kit (Yaneng Biotechnology Limited Corp., Shenzhen, China) was used for genotyping the mutations in G6PD-deficient neonates. The assay was capable of detecting six common mutations (c.95A>G, c.871G>A, c.1004C>T, c.1024C>T, c.1376G>T, and c.1388G>A) in the Chinese G6PD-deficient population.

2.4. Thalassemia analysis

All the jaundiced babies were subjected to thalassemia gene analysis using the thalassemia detection kit (HybriBio Biotechnology Limited Corp., Chaozhou, China). The procedure for this analysis was detailed in our previous work.²⁰

2.5. Data analysis

A Hardy-Weinberg equilibrium (HWE) test for the two common variants in the UGT1A1 locus was performed. Differences in the categorical variables within the two groups were compared by Chi-square test or Fisher’s exact test, while continuous variables were analyzed using the Student t test or Mann–Whitney U nonparametric test. Multiple logistic regression analysis was performed to evaluate the independence of genetic variants of UGT1A1 and G6PD genes associated with the development of severe hyperbilirubinemia. Association of the development of severe hyperbilirubinemia was adjusted for covariates, including gender, birth weight, gestational age, and feeding practice. All analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A p < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Fifty-eight term infants with TSB ≥ 20 mg/dL and 65 controls were enrolled in the study. They were all term infants admitted to a hospital on approximately the 7th day of life (range, 1–14 days). Clinical features of these participants are summarized in Table 1. Of the selected eight factors obtained from chart records, gestational age, birth weight, feeding way, and G6PD deficiency showed statistically significant differences between the case and control groups. Mean birth weight was 3082 ± 418 g in the case group, and 3270 ± 368 g in the control group. Although we excluded late preterm infants, the gestational age still differed between the two groups, with 38.9 ± 1.4 weeks versus 39.6 ± 0.1 weeks (p < 0.001) for the case and control groups, respectively. Furthermore, case infants received breastfeeding more often than control infants, and more neonates in the case group were observed having G6PD deficiency.

3.2. Determination of gene variations for case versus control

3.2.1. G6PD deficiency

G6PD deficiency was confirmed in seven of 58 neonates in the case group, and one in 65 neonates in the control group. All seven severe hyperbilirubinemia neonates identified with decreased G6PD enzyme activity were males. Four kinds of mutations were detected, including c.95A>G (n = 1), c.1024 C>T (n = 1), c.1376 G>C (n = 3), and c.1388 G>A (n = 2). One male neonate in the control group identified with a c.95A>G variation in G6PD exon 2 did not develop jaundice.

3.2.2. UGT1A1 variation

The frequencies of TATA-box polymorphism and the *6(c.211G>A, p.Arg71Gly) variant in UGT1A1 showed statistically significant differences in distribution between the

| Table 1 Demographic and clinical features of neonates in case and control groups. |
|---------------------------------|------------------|---|
| Sex                            | Case (n = 58)    | Control (n = 65) |
| Male                           | 35(60.3)        | 41(63.1)        | NS |
| Female                         | 23(39.7)        | 24(36.9)        |    |
| Gestational age (wk)           | 38.9 ± 1.4      | 39.6 ± 0.1      | 0.004|
| Birth weight (kg)              | 3.08 ± 0.42     | 3.27 ± 0.37     | 0.012|
| Maximum TSB levels (μmol/L)    | 389.6 (343.8–547.6) | 64.0 (14.9–146.1) | <0.001|
| Breast fed                     | 30(51.7)        | 20(30.8)        | 0.018|
| Breast and formula             | 14(24.1)        | 20(30.8)        | NS |
| Formula                        | 9(15.5)         | 13(20.0)        | NS |
| Unknown                        | 5(8.6)          | 12(18.5)        | NS |
| Birth delivery                 |                  |                 | NS |
| Vaginal                        | 35(60.3)        | 38(58.5)        |    |
| Cesarean                       | 23(39.7)        | 27(41.5)        |    |
| G6PD deficiency                | 7(12.1)         | 1(1.5)          | 0.026|
| Twin gestation                 | 2(3.4)          | 0               |    |

Data are presented as n (%), mean ± standard deviation, or median (95% Confidence Interval). NS = no significance.
case and control groups (Table 2). Neither variant showed significant deviation from HWE in either case or control group neonates. As expected, more neonates in the case group were observed to have the c.211 variants (\( p < 0.001 \)). No homozygote of the (TA)\(_7\) repeat was found in our study cohort. Interestingly, more heterozygotes of the (TA)\(_7\) repeat variant were observed in the control group.

In addition to the variation in the UGT1A1 promoter region \([\text{A(TA)}_{\text{n}}/\text{TAA/}A/\text{(TA)}_{\text{n}}/\text{TAA (6/7)}]\), four variant sites within the coding region of this gene were identified in the case group, including UGT1A1*6(c.211G->A, p.Arg71Gly), *73(c.1091C->T, p.Pro364Leu), rs114982090 (c.1352C->T, p.pro451leu), and *7(c.1456C->T, p.Tyr486Asp; Figure 1).

HRM analysis was established for rapid genotyping of the c.211 mutations in all samples. As shown in Figure 2, heterozygous mutation could be easily distinguished from wild-type samples based on differences in the melting-curve shape. For the melting-curve shapes of homozygous mutations, which were similar to those of wild-type, homozygous mutations were detected by a modified HRM-analysis strategy as described in our previous study.\(^{16,21}\) All 58 case samples were correctly genotyped as compared with the sequence results. Therefore, we believed that HRM may be used as a rapid method for a large-scale investigation of UGT1A1 gene polymorphism.

### 3.2.3. Thalassemia detection

Four patients in the case group were identified with globin gene mutations, including two with \( \alpha \)-thalassemia and two with \( \beta \)-thalassemia, giving a rate of 6.9% in our studied case participants and identical to the figure reported in previous studies of this region.\(^{17}\) The genotypes of the four thalassemia carriers were \( -\alpha^3.7/\alpha \alpha, \alpha^2\alpha/\alpha \alpha, \beta^41.42/\beta, \) and \( \beta^{654}/\beta \), respectively.

### 3.3. Association of UGT1A1 variation and G6PD deficiency with severe neonatal hyperbilirubinemia

After controlling differences in birth weight, gestational age, and feeding method, the nucleotide variant at position 211 of UGT1A1 and G6PD deficiency still showed association with the development of severe hyperbilirubinemia. Specifically, neonates who carried heterozygous, homozygous variation at nucleotide position 211 of UGT1A1, and G6PD deficiency had a 3.47(1.26 \( e \) 9.55)-, 12.46(1.09 \( e \) 142.7)-, and 12.87(1.32 \( e \) 135.87)-fold risk of hyperbilirubinemia as compared with those having the wild genotype and normal G6PD activity, respectively (Table 3).

All the case neonates were treated with phototherapy. Most were discharged without complication, except for three infants who showed signs of bilirubin encephalopathy. The maximum recorded TSB for the three neonates was 547.9 \( \mu \)mol/L, 390.8 \( \mu \)mol/L, and 340.8 \( \mu \)mol/L, respectively.

### Table 2 Genotype frequency of the (TA)\(_n\)-repeat polymorphism and *6(c.211G->A, p.Arg71Gly) variant of UGT1A1 case versus control groups.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case (n, %)</th>
<th>Control (n, %)</th>
<th>Total (n, %)</th>
<th>( p ) (H-E)</th>
<th>( p ) (Genotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TA)(_n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA(_6)/TA(_6)</td>
<td>50 (86.2)</td>
<td>45 (69.2)</td>
<td>95 (77.2)</td>
<td>0.13</td>
<td>0.025</td>
</tr>
<tr>
<td>TA(_6)/TA(_7)</td>
<td>8 (13.8)</td>
<td>20 (30.8)</td>
<td>28 (22.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA(_7)/TA(_7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G211A variation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>24 (41.4)</td>
<td>51 (78.5)</td>
<td>75 (61.0)</td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G/A</td>
<td>25 (43.1)</td>
<td>13 (20.0)</td>
<td>38 (30.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>9 (15.5)</td>
<td>1 (1.5)</td>
<td>10 (8.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as \( n (\%) \).
4. Discussion

Neonatal hyperbilirubinemia is common across Asia, including China (34.4% of term neonates in China). Hazardous hyperbilirubinemia remains not rare, especially in some areas of south China. In the present study, we explored G6PD, UGT1A1, and thalassemia gene variant expression in severely jaundiced neonates from southern China. Our results revealed that much of the observed severe hyperbilirubinemia could be attributed to variations at the UGT1A1 and G6PD loci. Additionally, we established a HRM analysis that could be used for rapid and accurate screening of the most frequent UGT1A1 mutation, the c.211G>A (UGTA*6) variant.

To the best of our knowledge, the present study was the first to evaluate the respective effects of the three independent known genetic modifiers, selected as the strongest reported to date, in a homogenous cohort of severe hyperbilirubinemia neonates in mainland China. In a previous study, Huang et al investigated this issue in Taiwanese neonates. Recently, Zhou et al studied the effect of selected polymorphisms in two bilirubin metabolism genes (Ho-1 and UGT1A1) in breast-fed neonates from mainland China, but they only considered neonates with mild/moderate jaundice. The present study extended the analysis by including three main genetic modifiers involved in both bilirubin production (G6PD and thalassemia) and metabolism (UGT1A1), in a homogenous cohort of severe hyperbilirubinemia neonates from southern China.

Table 3  Associations between independent risk factors and severe neonate hyperbilirubinemia: multivariate logistic regression analysis.

<table>
<thead>
<tr>
<th>G6PD deficiency</th>
<th>Case</th>
<th>Control</th>
<th>Adjusted OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>43 (87.8)</td>
<td>51 (98.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (12.2)</td>
<td>1 (1.9)</td>
<td>12.87 (1.32–135.87)</td>
<td>0.0082</td>
</tr>
<tr>
<td>G211A variation</td>
<td>Wild type</td>
<td>22 (44.9)</td>
<td>39 (75)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>c.211 heterozygote</td>
<td>21 (42.9)</td>
<td>12 (23.1)</td>
<td>3.48 (1.26–9.55)</td>
</tr>
<tr>
<td></td>
<td>c.211 homozygote</td>
<td>6 (12.2)</td>
<td>1 (1.9)</td>
<td>12.46 (1.09–142.7)</td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise indicated.
*Adjusting for gender, birth weight, feeding way, gestational age.
CI = confidence interval; OR = odds ratio.
Therefore, we believe the results from the present work may support those in the clinical setting. Our results emphasized the need to perform UGT1A1 and G6PD analysis as an aid for neonatal hyperbilirubinemia management, as well as family and prenatal genetic counseling of Chinese descendants in this region.

Of the genes involved in bilirubin metabolism, UGT1A1 has been the most widely studied, given its essential role in hepatic bilirubin glucuronidation. The c.211G>A (UGT1A1*6) polymorphism was the most frequent UGT1A1 variant in the East Asian population. The association of UGT1A1*6 and neonatal hyperbilirubinemia has been well studied and documented.12,24–28 Our detailed analysis confirmed the strong association of this independent predictor with the risk for severe hyperbilirubinemia in our study cohort.

In addition to UGT1A1*6, TATA polymorphisms in the UGT1A1 promoter, described as the common cause of Gilbert’s syndrome in the Caucasian population,8,26 were not associated with the increased risk of neonatal hyperbilirubinemia in our study cohort. Many previous studies also observed that the frequency of the A(TA)7TAA allele in the promoter region of UGT1A1 was substantially lower in the Asian population, and most failed to find its correlation with neonatal hyperbilirubinemia in this population.25 Some studies even achieved the reverse results, i.e., both recent studies in Chinese and Japanese breast-feeding neonates observed that heterozygous (TA)7 mutation significantly decreased, rather than increased, the risk of hyperbilirubinemia.25,26 The present study also observed that more neonates in the control group were heterozygous for the (TA)7 mutation, although the association decreased after adjusting the covariate. The precise role of the TATA polymorphism in hyperbilirubinemia merits further study.

The other three kinds of UGT1A1 coding variants found in our case group neonates were *73(c.1091C>T, p.Pro364Leu), rs114982090 (c.1352C>T, p.pro451Leu), and *7(c.1456C>T, p.Tyr486Asp), with each reportedly associated with a significant reduction in UGT1A1 enzyme activity and a Gilbert’s syndrome phenotype in previous studies12,24–30, except for c.1352C>T (pro451Leu), whose role in UGT1A1 isoenzyme activity has not yet been studied using laboratory methods. Alternatively, using a bioinformatics approach, rs114982090 (c.1352C>T, p.pro451Leu) was predicted to be a deleterious nsSNP by two algorithms, sorting intolerant from tolerant (SIFT) and polymorphism phenotyping (PolyPhen).31

G6PD deficiency is an important cause of severe neonatal hyperbilirubinemia and kernicterus. Neonate screening for G6PD deficiency has been established in many countries with high disease prevalence as recommended by the World Health Organization.32 Consistent with most previous studies, our study revealed a strong association between G6PD deficiency and significant hyperbilirubinemia in neonates.

Previous studies also indicated that heterozygous female patients reported as enzymatically normal might still be at risk.33–35 For this consideration, molecular diagnosis favoring the detection of heterozygotes can be a supplement to regular newborn screening, and useful for premarital and prenatal diagnosis of G6PD deficiency.

Thalassemia is another common heritable hemolytic disorder in Southeast Asia.36 All α-thalassemia patients identified in our study cohort were silent/mild thalassemia carriers, reflecting defects consisting of one or two mutations in α-globin or heterozygous for β-globin mutation, which were not associated with hemolysis and severe hyperbilirubinemia risk in neonates. As previously mentioned, co-inheritance of thalassemia and Gilbert’s syndrome was reported to elevate bilirubin levels in α-thalassemia traits and β-thalassemia heterozygotes.14,15 Co-expression across these genes has been commonly observed and might contribute to clinical severity. Fifty percent of G6PD-deficient neonates co-inherited with at least one UGT1A1 variant. All the four thalassemia neonates combined with either G6PD deficiency or UGT1A1 variation. Our sample size did not allow us to fully characterize the complexity of the interactions among these potential contributors. However, the degree of genetic heterogeneity and variant co-expression observed in this cohort underscored the likely complex polygenic nature of neonatal hyperbilirubinemia.

Except for the genetic risk factors, breast feeding was the most frequently confirmed demographic risk factor observed in association with hyperbilirubinemia. Furthermore, increasing evidence suggests that there may be an additive effect between UGT1A1 variation and breast-feeding in neonatal hyperbilirubinemia risk.37–39 However, the mechanism underlying this phenomenon remains elusive. Moreover, it should also be noted that in > 20% of severe hyperbilirubinemia infants in this study no etiology was found. This finding suggested that other genetic and/or environmental factors beyond this study might also contribute to the development of neonatal hyperbilirubinemia.

One limitation of the study was the retrospective sampling, which shaped the clinical distribution of the cohort and the sample size, and may have limited our ability to definitively identify common variants with relatively small effect sizes of the expected type. Therefore, a wide range of estimated confidence-interval values was obtained from the regression analysis of homozygous variations at nucleotide position 211 of UGT1A1, as well as G6PD deficiency, for neonatal hyperbilirubinemia risk, though the relative risk value for the homozygous c.211 variant and G6PD deficiency was much higher as compared with the heterozygous variation at nucleotide position 211 of UGT1A1.

In conclusion, in addition to G6PD-deficiency screening, UGT1A1 genetic analysis, especially detection of the UGT1A1*6(c.211G > A, p.Arg71Gly) polymorphism, may serve as a diagnostic aid for individuals with significant hyperbilirubinemia. UGT1A1*6 polymorphism screening should be taken into consideration for early diagnosis and treatment of severe hyperbilirubinemia in Chinese newborns.

Conflicts of interest

The authors declare that they have no conflicts of interest.
Acknowledgments

We thank the Medical Research Fund of Guangdong Province (B2013444 and A2014902) and the Science and Technology Research Fund of Guangdong Province (2012B031800001) for their financial support.

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