Association of Neonatal Hyperbilirubinemia with UGT1A1 Gene Polymorphisms: A Meta-Analysis

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Background: The results of studies on association between the polymorphisms in the coding region and the promoter of uridine diphosphateglucuronosyl transferase 1A1 (UGT1A1) and neonatal hyperbilirubinemia are controversial. This study aimed to determine whether the UGT1A1 gene polymorphisms of Gly71Arg and TATA promoter were significant risk factors associated with neonatal hyperbilirubinemia.

Material/Methods: The PubMed, Cochrane Library, and Embase databases were searched for papers that describe the association between UGT1A1 polymorphisms and neonatal hyperbilirubinemia. Summary odds ratios and 95% confidence intervals (CI) were estimated based on a fixed-effects model or random-effects model, depending on the absence or presence of significant heterogeneity.

Results: A total of 32 eligible studies and 6520 participants were identified. Among them, 24 studies focused on the association of neonatal hyperbilirubinemia with UGT1A1 Gly71Arg polymorphisms, and a significant difference was found for the comparison of AA vs. AG+GG (OR=3.47, 95% CI=2.29–5.28, P<0.0001). We included 19 studies on the association of neonatal hyperbilirubinemia with UGT1A1 TATA promoter polymorphism, which also found a statistically significant difference between 7/7 and 6/7 + 6/6 (OR=2.24, 95% CI=1.29–3.92, P=0.004).

Conclusions: This meta-analysis demonstrated that UGT1A1 polymorphisms (Gly71Arg and TATA promoter) significantly increase the risk of neonatal hyperbilirubinemia.

MeSH Keywords: Hyperbilirubinemia • Infant, Newborn • Polymorphism, Single Nucleotide

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Background

Neonatal hyperbilirubinemia is caused by abnormal metabolism of bilirubin, and is characterized by a syndrome of skin, mucous membrane, and sclera jaundice [1]. While most cases are physiological, when the serum bilirubin concentrations are higher than 12.9 mg/dl in full-term infants and for a prolonged period of time, jaundice is no longer considered physiological [2,3]. In pathological hyperbilirubinemia, increased production of bilirubin, deficiency in hepatic uptake, impaired conjugation of bilirubin, and/or increased enterohepatic circulation of bilirubin are observed [4]. However, there is no identifiable factor in almost half of cases.

It has been suggested that genetic variation could enhance the risk of neonatal hyperbilirubinemia when coexpressed with other iatrogenic conditions [5–7]. Among these, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) was identified to be associated with neonatal hyperbilirubinemia [8,9]. UGT1A1 is the key rate-limiting enzyme in the liver for bilirubin glucuronidation, which is a clearance mechanism for numerous dietary and environmental chemicals, including bilirubin [10,11]. The polymorphisms of the UGT1A1 coding region or the promoter may produce structural or functional enzymatic deficiencies, leading to intermittent elevation of unconjugated serum bilirubin, resulting in hyperbilirubinemia, a syndrome of skin, mucous membrane, and sclera jaundice [4]. Numerous polymorphisms of UGT1A1 have been reported in patients with GS and CNS, including Gly71Arg and TATA promoter [14,15].

The Gly71Arg (G71R) of the UGT1A1 gene has been reported as a genetic risk factor for GS, which might reduce the activity of the enzyme, and then cause mild unconjugated hyperbilirubinemia [16–18]. In addition, the TATA promoter polymorphism has been described as another major cause of neonatal hyperbilirubinemia, which is characterized by an increase of total serum bilirubin as a result of poor enzymatic conjugation by glucuronosyltransferase [6,19,20]. TA sequences in the promoter region vary in length from 5 to 8 repeats, and the (TA)7 (UGT1A1*28) and (TA)8 homozygotes, when compared with (TA)6 homozygote, (TA)6/(TA)7 or (TA)6/(TA)8 heterozygotes, have been considered as causes of hyperbilirubinemic syndromes. The (TA)7 homozygote leads to a 70% reduction in UGT1A1 expression as compared to the (TA)6 carriers [21]. Recent data have also shown that the effects of variants in UGT1A1 gene appear to be variable across populations [22–24]. Therefore, we performed a meta-analysis to assess whether the UGT1A1 polymorphisms are associated with neonatal hyperbilirubinemia. We analyzed the Gly71Arg and TATA promoter polymorphisms of UGT1A1 between cases and controls.

Material and Methods

The present meta-analysis was performed according to PRISMA recommendations [25]. The PubMed, Cochrane Library, and Embase databases were searched independently by 2 investigators to retrieve relevant studies published from January 1, 1998 to October 31, 2014. The search criteria “hyperbilirubinemia”, “UDP-glucuronosyl transferase 1A1 (UGT1A1)”, and “polymorphism” were used in text word searches. The “related articles” function was used to broaden the search. The reference lists of the selected articles were also manually examined to find relevant studies that were not discovered during the database searches.

Exclusion criteria

Exclusion criteria were, A) incomplete raw data, B) repetitive reports, and C) material and methods used were not well described or reliable. We used reliability of the methods for patient selection, molecular typing, and statistical analysis as quality variables to accurately assess the quality measures of interest.

Polymorphisms related to neonatal hyperbilirubinemia were divided into 2 groups according to TATA promoter polymorphism and G71R polymorphism in the UGT1A1 gene. All titles, abstracts, and full papers of potentially relevant studies were assessed for eligibility. When several reports from the same study were published, only the most recent or informative one was included in this meta-analysis. The language was restricted to only English.

Data extraction

Two investigators extracted all variables and outcomes of interest independently. Disagreements were resolved through discussion and consensus. Data on first author and year of publication, neonatal hyperbilirubinemia definition, country of study, numbers of cases and controls, and UGT1A1 gene polymorphism genotyping information were extracted (Table 1).

Quality assessment

The included studies were assessed independently by the 2 reviewers using the Newcastle-Ottawa Scale (NOS) [26]. The NOS employs a star rating system to assess quality from 3 broad perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars, and studies with 7 or more stars were considered to be of high quality.

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Table 1. Characteristics of included studies.

| Author (reference) | Year | Country          | Characteristics of cases                                      | Control(n) | Case(n) |
|---------------------|------|------------------|---------------------------------------------------------------|-------------|---------|
| Akaba et al. [24]   | 1998 | Japan            | STB >17 mg/dl                                                 | 101         | 42      |
| Maruo et al. [18]   | 1999 | Japan            | STB >15 mg/dl                                                 | 50          | 25      |
| Yamamoto et al. [16]| 2002 | Japan            | STB >15 mg/dl in the first 7 days                             | 49          | 23      |
| Huang et al. [14]   | 2002 | Taiwan, China    | STB ≥15 mg/dl within 1 week after birth                      | 218         | 123     |
| Seco et al. [41]    | 2002 | Spain            | STB >15 mg/dl                                                 | 115         | 21      |
| Ulgenalp et al. [4] | 2003 | Turkey           | STB >12.9 mg/dl                                               | 35          | 75      |
| Takeuchi et al. [33]| 2004 | Japan            | STB level >17 mg/dl                                           | 71          | 68      |
| Huang et al. [28]   | 2004 | Taiwan, China    | a peak STB ≥20.0 mg/dl in serum within 10 d of birth          | 100         | 72      |
| Sutomo et al. [34]  | 2004 | Malaysia         | STB >15 mg/dl at day 3                                        | 36          | 32      |
| Kanai et al. [51]   | 2005 | Japan            | STB >15 mg/dl at day 4 and thereafter                        | 116         | 29      |
| Yusoff et al. [48]  | 2005 | Malaysia         | STB >15 mg/dl                                                 | 50          | 55      |
| Ferraris et al. [15]| 2006 | Italy            | STB >17 mg/dl                                                 | 83          | 53      |
| Babaoglu et al. [21]| 2006 | Turkey           | STB >17 mg/dl                                                 | 32          | 74      |
| Muslu et al. [36]   | 2006 | Turkey           | STB >15mg/dl, <7d                                            | 55          | 107     |
| Farheen et al. [26] | 2006 | India            | UCB ≥1.2 mg/dl                                                | 95          | 95      |
| Wong et al. [9]     | 2007 | Malaysia         | STB >15 mg/dl at age 1–2 days or >17 mg/dl at age 3 days and onward | 125         | 74      |
| Watchko et al. [6]  | 2009 | America          | STB >95% high-risk zone                                        | 299         | 153     |
| Chang et al. [27]   | 2009 | Taiwan, China    | STB >5.9 mg/dl beyond 28 days of age                          | 90          | 35      |
| Prachukthum et al. [39]| 2009 | Thailand         | STB >95% as defined by the Bhutani nomogram                    | 86          | 91      |
| Agrawal et al. [7]  | 2009 | India            | STB >18 mg/dl                                                 | 50          | 69      |
| Ergin et al. [19]   | 2010 | Turkey           | STB >17 mg/dl                                                 | 54          | 50      |
| Kilic et al. [40]   | 2010 | Turkey           | STB >12.9 mg/dl, or TSB >8.8 mg/dl at day 14                  | 23          | 47      |
| Narter et al. [38]  | 2011 | Turkey           | STB >15 mg/dl in the first 10 days                            | 70          | 39      |
| Chou et al. [11]    | 2011 | Taiwan, China    | STB >15 mg/dl                                                 | 508         | 180     |
| Long et al. [1]     | 2011 | China            | STB >95% as defined by the Bhutani nomogram                    | 105         | 112     |
| Sato et al. [31]    | 2012 | Japan            | Full-term and breast-fed neonates, STB >10 mg/dl at day 1, >16 mg/dl at day 3, and >20 mg/dl at day 6 | 345         | 56      |
| Silva et al. [35]   | 2012 | India            | STB >15 mg/dl in the first 5 days                             | 180         | 126     |
| Tiwari et al. [50]  | 2013 | India            | STB >95% as defined by the Bhutani nomogram                    | 100         | 100     |
| Wong et al. [9]     | 2013 | Malaysia         | STB >15 mg/dl                                                 | 263         | 52      |
| Travani et al. [32] | 2014 | Italy            | STB >20 mg/dl                                                 | 70          | 70      |
| Tiwari et al. [30]  | 2014 | India            | STB >95% high-risk zone, newborns of ≤2 weeks of age          | 218         | 113     |
| Silva et al. [29]   | 2014 | India            | STB ≥15 mg/dl, ≥35 weeks                                      | 171         | 124     |

STB – serum total bilirubin; UCB – serum unconjugated bilirubin.
### Table 2. Allele frequencies of Gly71Arg UGT1A1 polymorphisms in cases of neonatal hyperbilirubinemia and controls.

| Author          | Country      | Control (n) | Case (n) | A allele frequencies in control group |
|-----------------|--------------|-------------|----------|--------------------------------------|
| Akaba et al. 1998 | Japan        | 76          | 23       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |
| Maruo et al. 1999 | Japan        | 35          | 14       | 11                                  |
| Yamamoto et al. 2002 | Japan       | 33          | 15       | 8                                   |
| Huang et al. 2002  | Taiwan, China| 153         | 62       | 36                                  |
| Takeuchi et al. 2004 | Japan       | 48          | 20       | 3                                   |
| Huang et al. 2004  | Taiwan, China| 80          | 18       | 2                                   |

### Table 3. Meta-analysis of the genotyped and allele distributions of Gly71Arg UGT1A1 polymorphisms for the cases and controls.

| GG   | AA   | GA+AA | GG+AG | AA   | G   | A   |
|------|------|-------|-------|------|-----|-----|
| Model | Fixed | Fixed | Fixed | Fixed | Random | |
| Heterogeneity (I²) | 22.4% | 49.3% | 5.8% | 55.5% |
| OR (95%CI) | 4.01 (2.47 to 6.51) | 2.25 (1.76 to 2.87) | 3.47 (2.29 to 5.28) | 2.17 (1.74 to 2.72) |
| P     | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Figure 1A / Figure 1B / Figure 1C / Figure 1D

OR – odds ratio; 95%CI – 95% confidence interval.
sessing the Hardy-Weinberg equilibrium (HWE) of genotypes were considered significant. Chi-square test was used for analysis with the rest repeatedly to show how conclusions might otherwise, the fixed-effects model was used. All of the results ranges from 0% (complete consistency) to 100% (complete inconsistency). If the I2 value was more than 50%, the random-effects model was chosen to calculate the pooled OR; otherwise, the fixed-effects model was used. All of the results were presented as forest plots. In the sensitivity analysis, we removed each study sequentially and performed meta-analysis with the rest repeatedly to show how conclusions might be affected. The presence of publication bias was assessed.

### Statistical analysis

The statistical analysis was performed using meta-analysis software called “Comprehensive Meta Analysis”. The strength of the association between UGT1A1 gene polymorphisms and neonatal hyperbilirubinemia risk was calculated with the OR and respective 95% CIs. The significance of the pooled OR was determined by the Z test, and P-values of less than 0.05 were considered significant. Chi-square test was used for assessing the Hardy-Weinberg equilibrium (HWE) of genotypes in the control group of each study. Statistical heterogeneity among studies was assessed with the I2 statistics. This value ranges from 0% (complete consistency) to 100% (complete inconsistency). If the I2 value was more than 50%, the random-effects model was chosen to calculate the pooled OR; otherwise, the fixed-effects model was used. All of the results were presented as forest plots. In the sensitivity analysis, we removed each study sequentially and performed meta-analysis with the rest repeatedly to show how conclusions might be affected. The presence of publication bias was assessed.
by a visual inspection of a funnel plot and Egger’s linear regression test.

**Results**

**Literature search**

The initial literature search retrieved 322 relevant articles. We excluded 289 articles for not investigating the topic of interest or insufficient data after carefully screening the titles and abstracts. All studies included were in accordance with NOS scale and were therefore defined as high-quality studies. A total of 32 articles with 2455 cases of neonatal hyperbilirubinemia and 4065 controls were included in the meta-analysis. The characteristics of the included studies are summarized in Table 1. A review of the data extraction revealed 100% agreement between the 2 reviewers.

![Figure 1. Meta-analysis of UGT1A1 Gly71Arg polymorphism and neonatal hyperbilirubinemia. (A) Comparison of A/A vs. G/G; (B) comparison of A/A+G/A vs. G/G; (C) comparison of A/A vs. G/G+G/A; (D) comparison of A allele vs. G allele.](image-url)
Finally, 24 studies focused on the relationship between G71R UGT1A1 polymorphism and neonatal hyperbilirubinemia (Table 2). Table 2 and Table 3 list the genotyped and allele distributions of the G71R for the cases and controls. Although most research has been in East Asian populations, the A allele does not appear to be different among races. The genotype frequencies of the G/A polymorphism were 80.7% (GG), 17.7% (GA), and 1.6% (AA) in controls, and 72.0% (GG), 23.0% (GA), and 5.0% (AA) in hyperbilirubinemia neonates. The A allele frequencies in the control group was 0.104. For allele level comparison, the A allele was found to be associated with a risk of hyperbilirubinemia in terms of the frequency of allele comparison (A vs. G: OR=2.17; 95% CI=1.74–2.72, P <0.0001). For a dominant model of the A allele, the AG + AA

| Author               | Country       | Control (n) | Case (n) | (TA) 7 allele frequencies in control group |
|----------------------|---------------|-------------|----------|-------------------------------------------|
| Maruo et al. 1999    | Japan         | 37          | 11       | 2 23 2 0.15                                |
| Huang et al. 2002    | Taiwan, China | 165         | 52       | 1 102 20 1 0.124                          |
| Seco et al. 2002     | Spain         | 61          | 46       | 8 7 11 3 0.270                            |
| Ulgenalp et al. 2003 | Turkey        | 14          | 19       | 2 35 2 8 0.329                            |
| Takeuchi et al. 2004 | Japan         | 57          | 12       | 2 29 14 25 0.113                          |
| Kanai et al. 2005    | Japan         | 96          | 20       | 0 29 0 0 0.086                            |
| Yussuff et al. 2005  | Turkey        | 32          | 53       | 10 4 15 76 0.384                          |
| Babaoglu et al. 2006 | Turkey        | 18          | 11       | 3 44 25 5 0.266                           |
| Muslu et al. 2006    | Turkey        | 47          | 7        | 1 95 12 0 0.082                           |
| Farheen et al. 2006  | India         | 32          | 53       | 10 4 15 76 0.384                          |
| Watchko et al. 2009  | America       | 129         | 127      | 28 66 62 21 0.322                         |
| Agrawal et al. 2009  | India         | 25          | 21       | 4 8 49 12 0.29                            |
| Ergin et al. 2010    | Turkey        | 48          | 6        | 0 10 34 0 0.060                           |
| Sato et al. 2012     | Japan         | 37          | 53       | 10 49 7 0 0.146                          |
| Tiwari et al. 2013   | India         | 32          | 53       | 10 4 15 76 0.384                          |
| Travan et al. 2014   | Italy         | 26          | 30       | 14 26 31 13 0.414                         |
| Tiwari et al. 2014   | India         | 101         | 93       | 24 38 57 18 0.323                         |
| Silva et al. 2014    | India         | 93          | 63       | 19 36 62 25 0.295                         |
| Total                |               | 1671        | 818      | 148 820 521 242 0.216                    |

Table 5. Meta-analysis of the genotyped and allele distributions of TATA promoter UGT1A1 polymorphisms for the cases and controls.

| Model     | Heterogeneity (I²) | OR (95%CI) | P        | Figure     |
|-----------|--------------------|------------|----------|------------|
| (TA) 6/6  |                   | 70.8%      | 2.71 (1.52 to 4.82) | Figure 2A  |
| (TA) 7/7  | 85.1%              | 73.4%      | 1.56 (1.02 to 2.40) | Figure 2B  |
| (TA) 6/7  | 89.2%              | 1.51 (1.03 to 2.20) | 0.004     | Figure 2C  |
| (TA) 7/7  | 89.2%              | 1.51 (1.03 to 2.20) | 0.035     | Figure 2D  |

OR = odds ratio; 95%CI = 95% confidence interval.

Main analysis

Finally, 24 studies focused on the relationship between G71R UGT1A1 polymorphism and neonatal hyperbilirubinemia (Table 2). Table 2 and Table 3 list the genotyped and allele distributions of the G71R for the cases and controls. Although most research has been in East Asian populations, the A allele does not appear to be different among races. The genotype frequencies of the G/A polymorphism were 80.7% (GG), 17.7% (GA), and 1.6% (AA) in controls, and 72.0% (GG), 23.0% (GA), and 5.0% (AA) in hyperbilirubinemia neonates. The A allele frequencies in the control group was 0.104. For allele level comparison, the A allele was found to be associated with a risk of hyperbilirubinemia in terms of the frequency of allele comparison (A vs. G: OR=2.17; 95% CI=1.74–2.72, P <0.0001). For a dominant model of the A allele, the AG + AA
genotypes were associated with the risk for hyperbilirubinemia (AG + AA vs. GG, OR=2.25, 95% CI=1.76–2.87, P<0.0001). For a recessive model of the A allele, the AA homozygote genotype was associated with susceptibility to hyperbilirubinemia (AA vs. AG+GG, OR=4.01, 95% CI=2.47–6.51, P<0.0001, Heterogeneity=0.558) (Figure 1C). For the extreme genotype, the AA genotype was associated with the risk for hyperbilirubinemia (AA vs. GG, OR=4.16, 95% CI=2.47–6.51, P<0.0001, Heterogeneity=0.224) (Figure 1A) (Table 3).

Quantitative synthesis showed significant differences in the comparisons of GG vs. AA+GA (OR=2.25, P<0.0001, 95% CI=1.76–2.87, Heterogeneity=0.493) (Figure 1B). In addition, comparing the A allele to the G allele in the G71R polymorphism also showed a significant difference (OR=2.17, P<0.0001, 95% CI=1.74–2.72, Heterogeneity=0.555) (Figure 1D).

Nineteen studies focused on the relationships between TATA promoter polymorphism and neonatal hyperbilirubinemia (Table 4). Table 4 and Table 5 list the genotyped and allele distributions of the TATA promoter polymorphisms for the cases and controls. The genotype frequencies of the TATA polymorphisms were 63.4% (6/6), 31.0% (6/7), and 5.6% (7/7) in controls, and 51.8% (6/6), 32.9% (6/7), and 15.3% (7/7) in hyperbilirubinemia neonates. The (TA)7 allele frequencies in the control group was 0.216. For allele level comparison, the (TA)7 allele was associated with an increased risk of hyperbilirubinemia in terms of the frequency of allele comparison ((TA)7 vs. (TA)6, OR=1.51, 95% CI=1.03–2.20, P=0.035, Heterogeneity=0.892) (Figure 2D). For a dominant model of the 6/6 allele, the 6/7+/77 genotypes were associated with the risk for hyperbilirubinemia (6/7+/77 vs. 6/6, OR=1.56, 95% CI=1.02–2.40, P=0.042, Heterogeneity=0.851) (Figure 2B). For the 7/7
Our meta-analysis showed that both UGT1A1 G71R and TATA promoter polymorphisms are risk factors for developing hyperbilirubinemia in white, black and Asian neonates, which was consistent with some previous studies but conflicted with others. Homozygous or heterozygous G71R and (TA)7 polymorphism were frequent not only in hyperbilirubinemia patients but also in healthy subjects [27,28]. It has been reported that the high frequency of G71R and (TA) insertion of the UGT1A1 gene are associated with a high incidence of neonatal hyperbilirubinemia [29–31]. Sato et al. found that the influence of G71R polymorphism might be overcome by adequate breastfeeding [32]. However, contrary to these findings, Mezzacappa et al. did not find any significant effect of the variants on bilirubin levels among the newborns [20,33–37].

An in vitro study verified that the UGT1A1 G71R mutant could decrease UGT1A1 enzymatic activity, which could cause moderately delayed bilirubin elimination [38]. Therefore, neonates carrying the G71R UGT1A1 variant may be at risk for hyperbilirubinemia [18]. However, some studies found no effect of the allele, the homozygote genotype was also associated with hyperbilirubinemia (6/7 + 6/6 vs. 7/7, OR=2.24, 95% CI=1.29–3.92, P=0.004, Heterogeneity=73.4%) (Figure 2C). For the extreme genotype, the 7/7 genotype was associated with the risk for hyperbilirubinemia (7/7 vs. 6/7, OR=2.76, 95% CI=1.55–4.95, P=0.001, heterogeneity=70.8%) (Figure 2A, Table 5). Analysis of these studies indicated that the TATA promoter polymorphism also increased the risk of neonatal hyperbilirubinemia.

Discussion

Our meta-analysis showed that both UGT1A1 G71R and TATA promoter polymorphisms are risk factors for developing hyperbilirubinemia in white, black and Asian neonates, which was consistent with some previous studies but conflicted with others. Homozygous or heterozygous G71R and (TA)7 polymorphism were frequent not only in hyperbilirubinemia patients but also in healthy subjects [27,28]. It has been reported that the high frequency of G71R and (TA) insertion of the UGT1A1 gene are associated with a high incidence of neonatal hyperbilirubinemia [29–31]. Sato et al. found that the influence of G71R polymorphism might be overcome by adequate breastfeeding [32]. However, contrary to these findings, Mezzacappa et al. did not find any significant effect of the variants on bilirubin levels among the newborns [20,33–37].

An in vitro study verified that the UGT1A1 G71R mutant could decrease UGT1A1 enzymatic activity, which could cause moderately delayed bilirubin elimination [38]. Therefore, neonates carrying the G71R UGT1A1 variant may be at risk for hyperbilirubinemia [18]. However, some studies found no effect of the
polymorphism [36,39]. Therefore, the mechanism of the G71R polymorphism requires further research [40,41].

The (TA) insertion in the promoter also has been considered to be associated with hyperbilirubinemia [42]. The A (TA7) TAA allele was reported to be frequently present in GS [43]. The extra TA reduced expression of the enzyme, resulting in decreased bilirubin glucuronidation activity [44]. The SNP could reduce the promoter activity, which leads to unconjugated nonhemolytic hyperbilirubinemia [45,46].

The data strongly suggest that UGT1A1 promoter (TA7) polymorphism influences serum total bilirubin values by increasing heme catabolism as well as decreasing bilirubin conjugation [23]. In analogous studies, the (TA7) variant was associated with modestly higher total serum bilirubin levels and (TA7) polymorphism in the promoter developed prolonged indirect hyperbilirubinemia [7,47,48]. However, some other studies have failed to demonstrate a clinically significant effect of UGT1A1 TATA promoter variations on hyperbilirubinemia risk [23,49], such as a southern Brazil study that found the (TA7) promoter polymorphism of UGT1A1 had no association with hyperbilirubinemia [50]. Ultimately, our research showed that (TA7) promoter polymorphism was associated with increased risk of neonatal hyperbilirubinemia. Some studies have found a synergic effect with the (TA7)TAA promoter and G71R variants on the level of plasma bilirubin [51]. By the pathway of influence of the metabolism of heme oxygenase, we can speculate that neonates carrying the Gly71Arg or (TA7)TAA polymorphisms have decreased UGT1A1 activity, which may directly or indirectly increase COHbc and decrease serum conjugated bilirubin fractions [52].

The most important limitation of this meta-analysis is the inconsistency of the baseline characteristics (e.g., age, sex, and concomitant disease) between the case and control groups, which might increase the selection bias.

Conclusions

Our meta-analysis suggests that Gly71Arg and (TA7) polymorphisms in the UGT1A1 gene significantly increase risk of neonatal hyperbilirubinemia.

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