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META-ANALYSIS

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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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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 physiologic [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 icterogenic 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 hyperbilirubinemias known as Gilbert's syndrome (GS) and Crigler-Najjar syndrome (GNS) [12,13]. 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	Tukey	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
Travan 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.

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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
		GG	GA	AA	GG	GA	AA	
Akaba et al. 1998	Japan	76	23	2	18	21	3	0.134
Maruo et al. 1999	Japan	35	14	1	11	11	3	0.16
Yamamoto et al. 2002	Japan	33	15	1	8	12	3	0.173
Huang et al. 2002	Taiwan, China	153	62	3	63	46	14	0.156
Takeuchi et al. 2004	Japan	48	20	3	41	17	10	0.183
Huang et al. 2004	Taiwan, China	80	18	2	35	30	7	0.11
Sutomo et al. 2004	Malaysia	35	1	0	28	4	0	0.014
Kanai et al. 2005	Japan	80	31	5	14	14	1	0.177
Yusoff et al. 2005	Malaysia	47	3	0	52	3	0	0.03
Ferraris et al. 2006	Italy	81	2	0	53	0	0	0.012
Farheen et al. 2006	India	90	5	0	85	9	1	0.026
Wong et al. 2007	Malaysia	93	31	1	45	18	11	0.132
Watchko et al. 2009	America	295	4	0	148	4	1	0.007
Chang et al. 2009	Taiwan, China	68	20	2	11	17	7	0.133
Prachukthum et al. 2009	Thailand	80	6	0	68	19	4	0.035
Kilic et al. 2010	Turkey	22	1	0	40	7	0	0.022
Chou et al. 2011	Taiwan, China	367	135	6	111	61	8	0.145
Long et al. 2011	China	81	22	2	62	39	11	0.124
Sato et al. 2012	Japan	236	103	6	31	24	1	0.167
Silva et al. 2012	India	141	39	0	100	26	0	0.108
Tiwari et al. 2013	India	99	1	0	92	8	0	0.005
Wong et al. 2013	Malaysia	226	22	15	47	4	1	0.099
Tiwari et al. 2014	India	217	1	0	107	5	1	0.002
Narter et al. 2011	Turkey	47	19	4	23	13	3	0.24
Total		2730	598	53	1293	412	90	0.104

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	/	Random
Heterogeneity (I^2)	/	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	/	Figure 1A	Figure 1B	/	Figure 1C	/	Figure 1D

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

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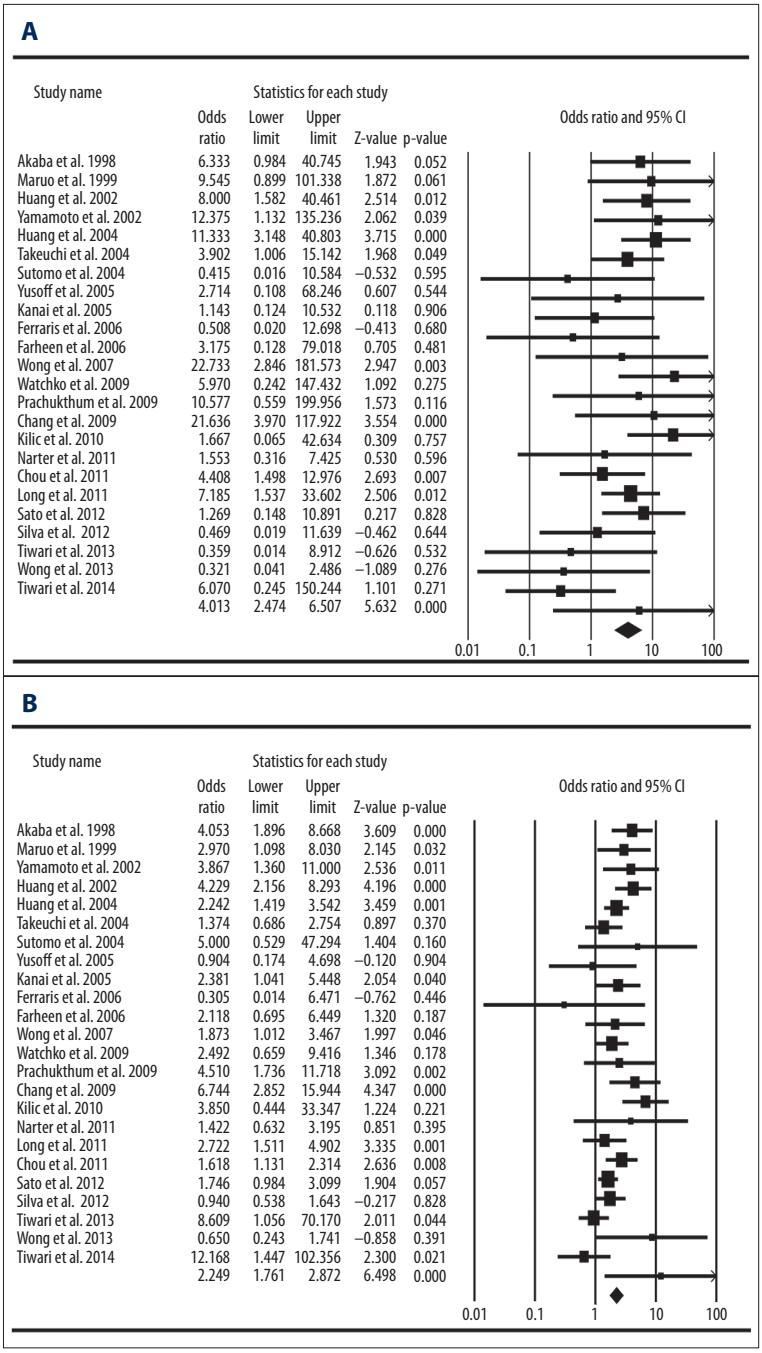

Statistical analysis

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

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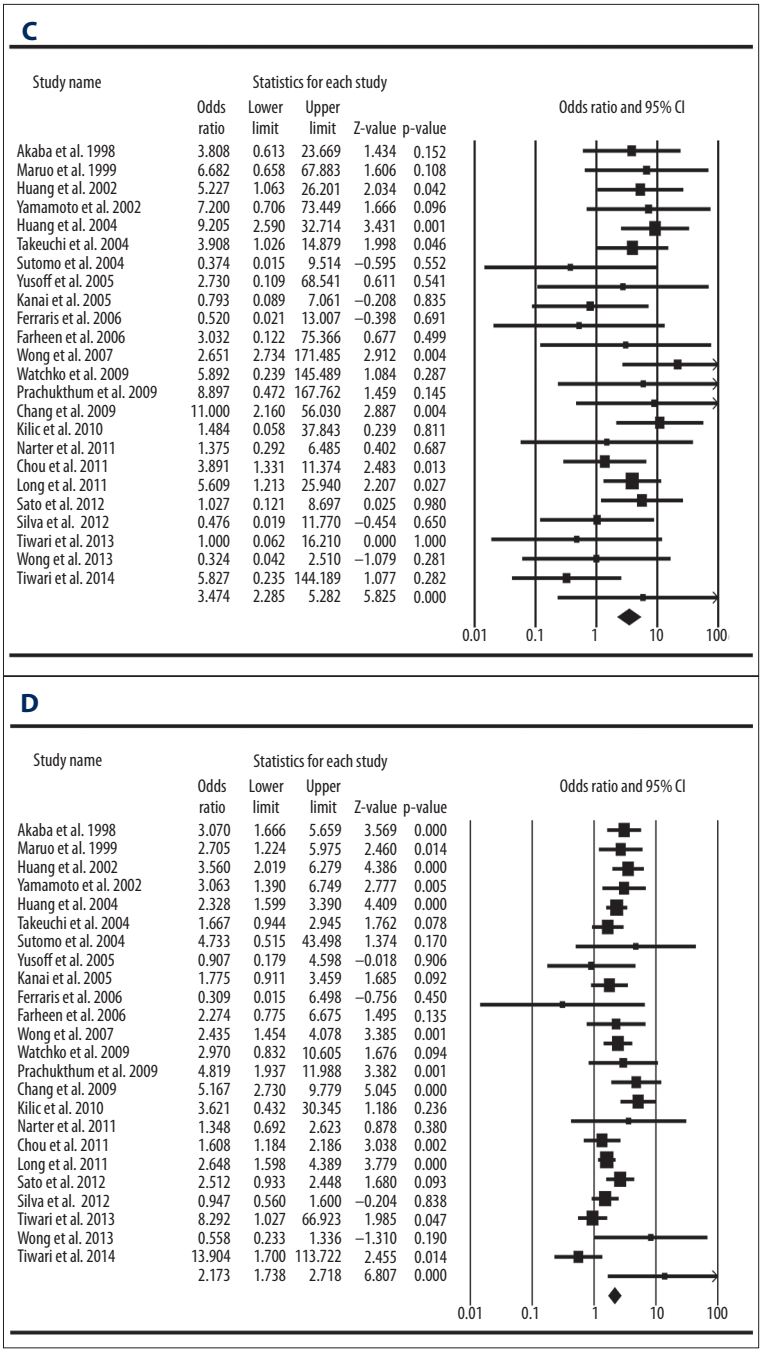

Figure 1. Meta-analysis of UGT1A1 Gly71Arg polymorphism and neonatal hyperbilirubinemia. (**A**) Comparison of A/A *vs.* G/G; (**B**) comparison of A/A+G/A *vs.* G/G; (**C**) comparison of A/A *vs.* G/G+G/A; (**D**) comparison of A allele *vs.* G allele.

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.

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Table 4. Allele frequencies of TATA promoter UGT1A1 polymorphisms in cases of neonatal hyperbilirubinemia and controls.

Author	Country	Control (n)			Case (n)			(TA) 7 allele frequencies in control group
		6/6	6/7	7/7	6/6	6/7	7/7	
Maruo et al. 1999	Japan	37	11	2	23	2	0	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	32	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
Yusoff et al. 2005	Malaysia	43	6	1	41	10	4	0.08
Babaoglu et al. 2006	Tukey	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	6	0.056
Chou et al. 2011	Taiwan, China	392	107	9	147	27	6	0.123
Sato et al. 2012	Japan	254	81	10	49	7	0	0.146
Tiwari et al. 2013	India	37	53	10	31	50	19	0.365
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	89	63	19	36	63	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.

	(TA) 6/6	(TA) 7/7	(TA) 6/7 + (TA) 7/7	(TA) 6/6 + (TA) 6/7	(TA) 7/7	(TA) 6	(TA) 7
Model	/	Random	Random	/	Random	/	Random
Heterogeneity (I^2)	/	70.8%	85.1%	/	73.4%	/	89.2%
OR (95%CI)	/	2.71 (1.52 to 4.82)	1.56 (1.02 to 2.40)	/	2.24 (1.29 to 3.92)	/	1.51 (1.03 to 2.20)
P	/	0.001	0.042	/	0.004	/	0.035
Figure	/	Figure 2A	Figure 2B	/	Figure 2C	/	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

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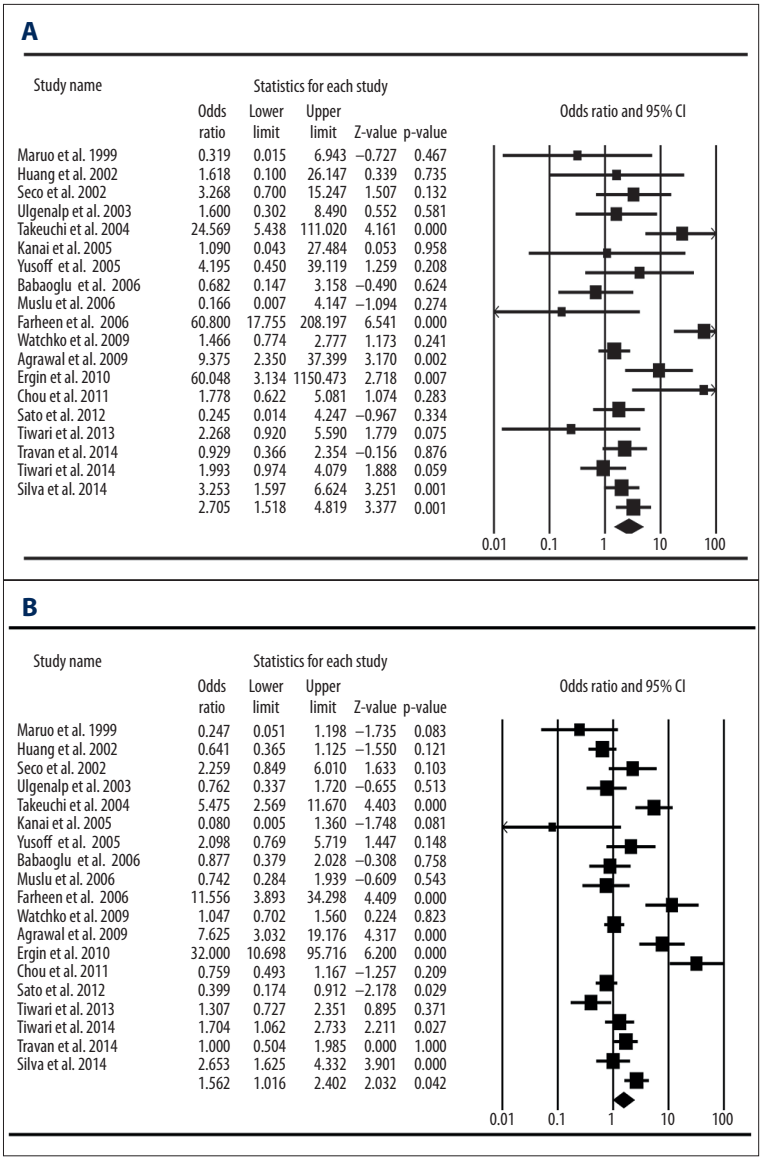

genotypes were associated with the risk for hyperbilirubinemia (AG + AA *vs.* GG, OR=2.25, 95% CI=1.76–2.87, P<0.0001). For a recessive model of the A allele, the AA homozygote genotype was associated with susceptibility to hyperbilirubinemia (AA *vs.* AG+GG, OR=3.47, 95% CI =2.29–5.28, P <0.0001, Heterogeneity=0.058) (Figure 1C). For the extreme genotype, the AA genotype was associated with the risk for hyperbilirubinemia (AA *vs.* GG, OR=4.01, 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=89.2%) (Figure 2D). For a dominant model of the 6/6 allele, the 6/7+7/7 genotypes were associated with the risk for hyperbilirubinemia (6/7+7/7 *vs.* 6/6, OR=1.56, 95%CI=1.02–2.40, P=0.042, Heterogeneity=85.1%) (Figure 2B). For the 7/7

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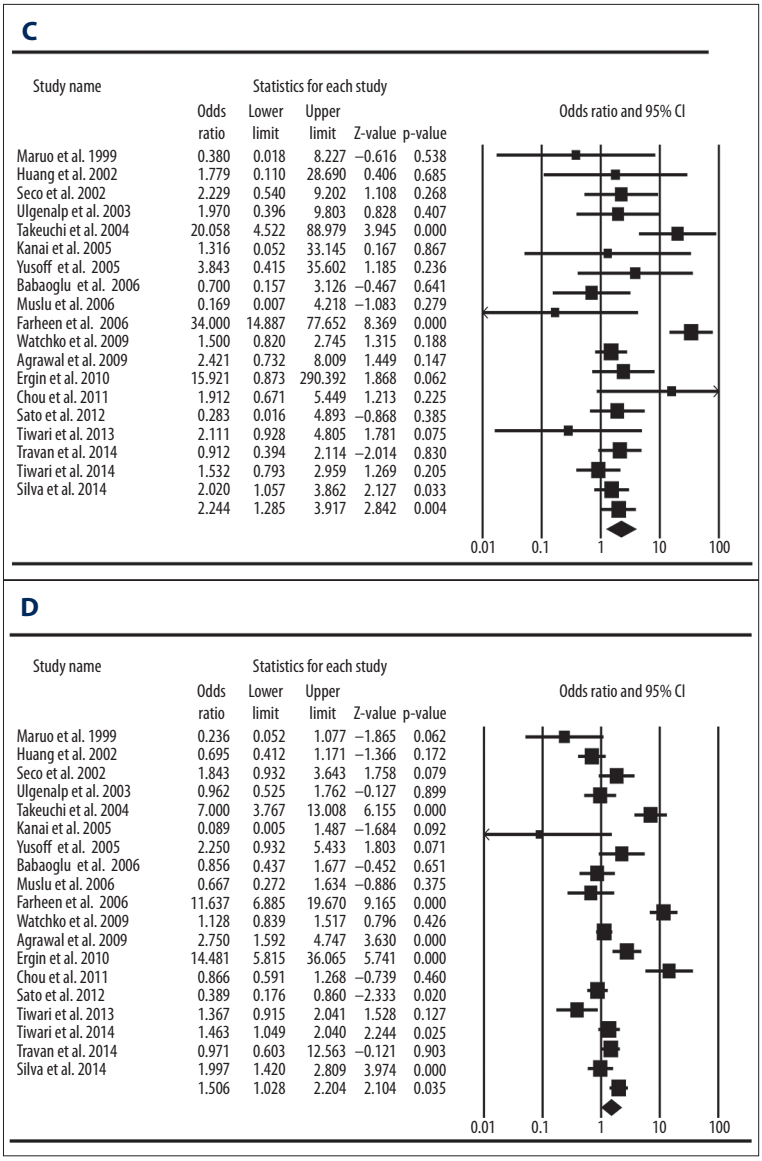

Figure 2. Meta-analysis of TATA promoter UGT1A1 polymorphism and neonatal hyperbilirubinemia. (**A**) Comparison of 7/7 *vs.* 6/6; (**B**) comparison of 7/7+6/7 *vs.* 6/6; (**C**) comparison of 7/7 *vs.* 6/6+/7; (**D**) comparison of 7 allele *vs.* 6 allele.

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.* 6/6, OR=2.71, 95% CI=1.52–4.82, 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

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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 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 (TA)7 polymorphism influences serum total bilirubin values by increasing heme catabolism as well as decreasing bilirubin conjugation [23]. In analogous studies, the (TA)7 variant was associated with modestly higher total serum bilirubin levels and (TA)7 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 (TA)7 promoter polymorphism of UGT1A1 had no association with hyperbilirubinemia [50]. Ultimately, our research showed that (TA)7 promoter polymorphism was associated with increased risk of neonatal hyperbilirubinemia. Some studies have found a synergic effect with the (TA)7TAA 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 (TA)7TAA 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 (TA)7 promoter polymorphisms in the UGT1A1 gene significantly increase risk of neonatal hyperbilirubinemia.

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