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Review

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Roles of UGT1A1 Gly71Arg and TATA promoter polymorphisms in neonatal hyperbilirubinemia: A meta-analysis

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Running title: UGT1A1 polymorphisms in neonatal hyperbilirubinemia

Abstract

Objective

To identify the association between UGT1A1 Gly71Arg and TATA promoter polymorphisms and neonatal hyperbilirubinemia.

Methods

The studies related to the correlation between UGT1A1 Gly71Arg and TATA promoter polymorphisms and neonatal hyperbilirubinemia were searched systematically in various databases. According to the presence or absence of significant heterogeneity, a random-effect or fixed-effect model was chosen to estimate the overall odds rations (ORs) and 95% confidence intervals (CIs).

Results

Totally 21 studies on Gly71Arg polymorphism including 4738 neonates and 13 studies

on TATA promoter polymorphism involving 2841 neonates were identified. Significant associations were presented between Gly71Arg polymorphism and neonatal hyperbilirubinemia in Asia [A *vs.* G, OR(95%CI): 2.327(1.904-2.845), *P*<0.001; AA+GA *vs.* GG, OR(95%CI): 2.253(1.954-2.598), *P*<0.001; AA *vs.* GG+GA, OR(95%CI): 5.166(3.520-7.564), *P*<0.001; AA *vs.* GG, OR(95%CI): 6.458(4.376-9.531), *P*<0.001; GA *vs.* GG, OR(95%CI): 1.920(1.654-2.228), *P*<0.001] and Africa [A *vs.* G, OR(95% CI): 9.750(1.214-78.301), *P*=0.032; AA+GA *vs.* GG, OR(95% CI): 11.000(1.290-93.832), *P*=0.028; GA *vs.* GG, OR(95% CI): 10.000(1.163-85.998), *P*=0.036]. TATA promoter polymorphism was associated with an increased risk of neonatal hyperbilirubinemia in Asia [TA7/7 *vs.* TA6/6+TA6/7, OR(95%CI): 1.670(1.034-2.696), *P*=0.036] and Europe [TA7/7 *vs.* TA6/6+TA6/7, OR(95%CI): 2.627(1.722-4.008), *P*<0.001].

Conclusion

The risk of neonatal hyperbilirubinemia may be increased by the variation of UGT1A1 Gly71Arg in Asia and Africa, as well as the variation of UGT1A1 TATA promoter in Asia and Europe.

Abbreviations

ORs, overall odds rations; Cis, confidence intervals; UGT, Uridine diphosphate glucuronosyl transferase; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale;

Keywords: Neonatal hyperbilirubinemia; Gly71Arg; TATA promoter; Single nucleotide polymorphism

Roles of UGT1A1 Gly71Arg and TATA promoter polymorphisms in neonatal hyperbilirubinemia: A meta-analysis

1. Introduction

Hyperbilirubinemia, a common disorder in neonates, is one of the most co mmon causes for neonatal readmission to hospital [1]. It is caused by increase d blood bilirubin levels, with the yellowing of skin, sclera or other organs as major clinical manifestations [2]. At present, the prevalence of neonatal hyperbi lirubinemia remains completely unclear. Approximately 80% preterm and 50% f ull-term neonates are estimated to have hyperbilirubinemia [3], and 8%-9% of neonates within the first week after birth suffer from high-risk hyperbilirubinem ia [4, 5]. Although hyperbilirubinemia in most neonates can disappear spontane ously, some can be subjected to severe hyperbilirubinemia even bilirubin encep halopathy and kernicterus due to the metabolic difference of bilirubin in differe nt individuals or pathological factors, which can lead to the neurological impair ment, such as hearing disorder, mental retardation and cerebral palsy [6, 7].

Uridine diphosphate glucuronosyl transferase (UGT), a key enzyme regulating bilirubin metabolism, can generate water-soluble conjugated bilirubin by mediating the glucuronic acid conjugation of unconjugated bilirubin, thus favoring the bilirubin elimination from the body [8]. UGT1A1 gene mutations, including the mutation in the coding region and mutation in the promoter region, can result in the decreased enzymatic activity or functional deficiency, consequently leading to the bilirubin metabolic disorder and occurrence of hyperbilirubinemia [9-11]. 211G>A (Gly71Arg), one of the most common UGT1A1 gene polymorphisms in the coding region, was reported to be a risk factor for neonatal hyperbilirubinemia, which might cause unconjugated hyperbilirubinemia through a reduction of enzymatic activity [12-14].

Additionally, UGT1A1 promoter polymorphisms were also found to be associated with neonatal hyperbilirubinemia [15]. UGT1A1 can precisely regulate DNA sequences of transcriptional initiation, while TATA mutation can cause the aberrant frequency and accuracy of transcriptional initiation [16, 17]. Although the nucleotide polymorphism of promoter sequence can generate the enzyme molecule with the normal structure, but its decreased expression can reduce the enzymatic activity [18].

For the past few years, a lot of studies have indicated that UGT1A1 gene polymorphisms may vary with ethnicities [19-21]. Herein, a meta-analysis was conducted to evaluate the association between UGT1A1 gene polymorphisms (Gly71Arg and TATA promoter polymorphisms) and neonatal hyperbilirubinemia based on the currently-available evidence.

2. Materials and methods

2.1 Literature search

A systematic search related to the association between UGT1A1 Gly71Arg and TATA promoter polymorphisms and neonatal hyperbilirubinemia was performed in various databases updated on July 23, 2019, involving Web of Science, Embase, PubMed and Cochrane Library (Cochrane Center Register of Controlled Trials). The search terms included “Infants, Newborn” OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates” OR “Infant, Newborn”[Mesh] AND “Hyperbilirubinemias” OR “Bilirubinemia” OR “Bilirubinemias” OR “Hyperbilirubinemia”[Mesh] OR “Jaundice”[Mesh] OR “Icterus” OR “Jaundice, Hemolytic” OR “Hemolytic Jaundice” OR “Hemolytic Jaundices” OR “Jaundices, Hemolytic” AND “uridine diphosphate-glucuronosyl transferase 1A1” OR “UDP-glucuronosyl transferase 1A1” OR “UDP-glucuronosyl transferase” OR “UGT1A1” AND “Polymorphisms, Genetic” OR “Genetic Polymorphisms” OR “Genetic Polymorphism” OR “Polymorphism (Genetics)” OR “Polymorphisms (Genetics)” OR “Polymorphism” OR “Mutation” OR “Variant” OR “Polymorphism, Genetic”[Mesh].

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) case-control studies; (2) the case group involving the

neonates diagnosed as neonatal hyperbilirubinemia and the control group including those without neonatal hyperbilirubinemia; (3) select the latest one for the studies of the same author; (4) studies published in English; (5) no significant difference regarding the *p* value of Hardy-Weinberg equilibrium (HWE) in control group.

Exclusion criteria: (1) studies with undefined genotypes; (2) reviews, meta-analyses or animal experiments; (3) studies unable to extract the effective data.

2.3 Data extraction and quality assessment

Based on the inclusion and exclusion criteria, two authors (J. Wang and J.S. Yin) were responsible for extracting the data of the published articles. The third author (M. Xue) would participate in the data extraction if a consensus was not reached. The extracted information included: the first author, year of publication, ethnicity, country, genotyping method, genotype distribution and frequency, quality assessment and its score, as well as the value of HWE (*p*).

The quality of studies was assessed independently by two authors (J. Wang and J.S. Yin) using modified Newcastle-Ottawa Scale (NOS) which was applied to evaluate the quality mainly based on the comparability of study groups, patient selection and outcome assessment [22]. The total score of this scale was 10. The studies with scores ≥ 5 and scores <5 were respectively considered as high-quality and low- or moderate-quality.

2.4 Statistical analysis

In this meta-analysis, STATA 14.0 software (Stata Corporation, College Station, TX, USA) was adopted. Heterogeneity test was used for each model. Random-effect model was performed at the time of heterogeneous statistics $I^2 \geq 50\%$, on the contrary, fixed-effect model was conducted. The effects of UGT1A1 Gly71Arg and TATA promoter polymorphisms on neonatal hyperbilirubinemia were evaluated by pooled odds rations (ORs) and 95% confidence intervals (CIs). The sensitivity was analyzed among all the models, and the publication bias was assessed by Harboard test. $P<0.05$ was considered statistically significant.

3. Results

3.1 Literature search and study selection

Totally, 311 studies were identified by searching the databases. After removing the duplicates, irrelevant studies, reviews or meta-analyses, as well as those with the *p* value of HWE less than 0.05, 27 studies were finally included in this meta-analysis. It was worth noting that there were 9 studies associated with Gly71Arg & TATA promoter polymorphisms. The flow chart describing the study selection was presented in Figure 1.

Totally 21 studies on Gly71Arg polymorphism including 4738 neonates (case group: n=1977, control group: n=2761) and 13 studies on TATA promoter polymorphism involving 2841 neonates (case group: n=1477, control group: n=1364) were enrolled in this meta-analysis for quantitative analysis. The basic characteristics of included studies were shown in Tables 1-2.

3.2 Overall and subgroup meta-analysis of Gly71Arg polymorphism

The overall meta-analysis of Gly71Arg polymorphism was indicated in Table 3 and Figure 2. It was found that Gly71Arg polymorphism had a close association with neonatal hyperbilirubinemia among all the models, including the allele contrast [A *vs.* G, OR(95%CI): 2.360(1.972-2.890), *P*<0.001], dominant model [AA+GA *vs.* GG, OR(95%CI): 2.253(1.954-2.598), *P*<0.001], recessive model [AA *vs.* GG+GA, OR(95%CI): 5.103(3. 495-7.452), *P*<0.001], and codominant model [AA *vs.* GG, OR(95%CI): 6.388(4.341-9.402), *P*<0.001; GA *vs.* GG, OR(95%CI): 1.945(1.677-2.256), *P*<0.001].

Based on the ethnicity, genotyping method and quality assessment, the subgroup analyses were performed. As shown in Table 3 and Figure 3. There were significant correlations between Gly71Arg polymorphism and neonatal hyperbilirubinemia in Asia [A *vs.* G, OR(95%CI): 2.327(1.904-2.845), *P*<0.001; AA+GA *vs.* GG, OR(95%CI): 2.253(1.954-2.598), *P*<0.001; AA *vs.* GG+GA, OR(95%CI): 5.166(3.520-7.564), *P*<0.001; AA *vs.* GG, OR(95% CI): 6.458(4.376-9.531), *P*<0.001; GA *vs.* GG, OR(95%CI): 1.920(1.654-2.228), *P*<0.001] and Africa [A *vs.* G, OR(95%CI): 9.750(1.214-78.301), *P*=0.032; AA+GA *vs.* GG, OR(95%CI): 11.000(1.290-93.832), *P*=0.028; GA *vs.* GG, OR(95%CI): 10.000(1.163-85.998), *P*=0.036]. In terms of

genotyping method, Gly71Arg polymorphism was obviously associated with neonatal hyperbilirubinemia in the five genetic models of PCR assay [A *vs.* G, OR(95%CI): 2.395(2.004-2.862), *P*<0.001; AA+GA *vs.* GG, OR(95%CI): 2.343(2.012-2.728), *P*<0.001; AA *vs*. GG+GA, OR(95%CI): 5.221(3.525-7.732), *P*<0.001; AA *vs*. GG, OR(95%CI): 6.583(4.406-9.836), *P*<0.001; GA *vs.* GG, OR(95%CI): 2.004(1.710-2.349), *P*<0.001]. Additionally, the differences were all pronounced between Gly71Arg polymorphism and neonatal hyperbilirubinemia in all the genetic models of low- and moderate-quality and high-quality studies (all *P*<0.001; Table 3).

3.3 Overall and subgroup meta-analysis of TATA promoter polymorphism

The overall meta-analysis of TATA promoter polymorphism revealed that TATA promoter polymorphism was related to an increased risk of neonatal hyperbilirubinemia in the allele contrast [(TA)7 *vs.* (TA)6, OR(95%CI): 1.044(0.678-1.608), *P*<0.001] and recessive model [TA7/7 *vs*. TA6/6+TA6/7, OR(95%CI): 2.164(1.579-2.966), *P*<0.001] instead of the dominant model [TA7/7+TA6/7 *vs.* TA6/6, OR(95%CI): 1.049(0.625-1.761), *P*=0.856] and codominant model [TA7/7 *vs*. TA6/6, OR(95%CI): 1.962(0.951-4.047), *P*=0.068; TA6/7 *vs.* TA6/6, OR(95%CI): 0.991(0.611-1.607), *P*=0.971] (Table 4).

As presented in Table 4, TATA promoter polymorphism was associated with an increased risk of neonatal hyperbilirubinemia in Asia [TA7/7 *vs*. TA6/6+TA6/7, OR(95%CI): 1.670(1.034-2.696), *P*=0.036] and Europe [TA7/7 *vs*. TA6/6+TA6/7, OR(95%CI): 2.627(1.722-4.008), *P*<0.001]. With regard to the genotyping methods, significant differences were exhibited between TATA promoter polymorphism and neonatal hyperbilirubinemia in PCR-RFLP [(TA)7 *vs.* TA(6), OR(95%CI): 1.463(1.049-2.040), *P*=0.025; TA7/7+TA6/7 *vs.* TA6/6, OR(95%CI): 1.704(1.062-2.733), *P*=0.027] and in PCR [TA7/7 *vs.* TA6/6+TA6/7, OR(95%CI): 2.380(1.656-3.421), *P*<0.001]. Additionally, a significant association of TATA promoter polymorphism with neonatal hyperbilirubinemia was also demonstrated in low- and moderate-quality studies [TA7/7 *vs*. TA6/6+TA6/7, OR(95%CI): 2.396(1.627-3.528), *P*<0.001].

3.4 Publication bias

No apparent publication bias was shown in Gly71Arg polymorphism, with the *P* values of 0.110 in allele contras, 0.100 in dominant model, 0.405 in recessive model, 0.326 (AA *vs*. GG) and 0.079 (GA *vs.* GG) in co-dominant model, respectively. Meanwhile, there was also no publication bias in all the genetic models of TATA promoter polymorphism, and the *P* values were 0.173, 0.618, 0.192, 0.337 (TA7/7 *vs*. TA6/6) and 0.945 (TA6/7 *vs.* TA6/6) in turn.

4. Discussion

In the present meta-analysis, a total of 27 studies were included, in which 9 studies were relevant to both Gly71Arg and TATA promoter polymorphisms. Finally, 21 studies on Gly71Arg polymorphism including 4738 neonates and 13 studies on TATA promoter polymorphism involving 2841 neonates were identified. Our results indicated that the variation of UGT1A1 Gly71Arg could augment the risk of neonatal hyperbilirubinemia in Asia and Africa, while that of UGT1A1 TATA promoter was associated with an increased risk of neonatal hyperbilirubinemia in Asia and Europe.

It was reported that the missense mutation in the coding region, especially the UGT1A1 Gly71Arg, is most common in the yellow race [11]. The homozygous and heterozygous mutations of Gly71Arg polymorphic sites could decease the transferase activity to 30% and 60% of the normal levels, respectively, and had been confirmed to be related to hyperbilirubinemia in Asian populations [46, 47]. The frequency of Gly71Arg mutation in neonates with hyperbilirubinemia was 2-3 times of those without hyperbilirubinemia in Asia [48]. To the best of our knowledge, UGT1A1 gene polymorphisms may change depending on the ethnicities. Therefore, in the present meta-analysis, the subgroup meta-analysis was performed based on the ethnicities. The results demonstrated that Gly71Arg polymorphism could increase the risk of neonatal hyperbilirubinemia in Asia and Africa, but almost all the included studies were from Asia, and only 1 from Africa, thereby more studies from a variety of ethnicities are required to be carried out to further verify the role of Gly71Arg polymorphism in different populations. In terms of genotyping method, PCR assay was suggested to be a useful tool in detecting Gly71Arg polymorphism of neonates at a high risk of

developing hyperbilirubinemia. Moreover, there were also significant differences regarding all the genetic models of low- and moderate-quality and high-quality studies.

UGT1A1 activity declines with the increased length of TA repeats [49, 50]. The most prevalent UGT1A1 gene polymorphism is the insertion mutation in Caucasians, which refers to the insertion of an additional TA into the normal sequence A(TA)6TAA of the promoter's TATA box, namely A(TA)7TAA. The study indicated that UGT1A1 promoter (TA)7 polymorphism may depend on lowering bilirubin conjugation and increasing heme catabolism to affect the level of serum total bilirubin [20]. When compared with the (TA)6 carriers, the (TA)7 homozygote could result in a reduction of 70% in UGT1A1 gene expression [41], and the frequency of (TA)7 mutant genotype was diverse in the neonates from different regions, such as 8.2% in Turkey [41], 2.0% in Malaysia [51] and 8.9% in China [52]. In the present meta-analysis, the subgroup results based on different ethnicities revealed that TATA promoter polymorphism was a potential risk factor for developing hyperbilirubinemia in Asian and European neonates, which needed more multi-ethnic studies to confirm due to inclusion of only two European studies.

The present meta-analysis had some advantages. For example, the studies related to the association between UGT1A1 Gly71Arg and TATA promoter polymorphisms and neonatal hyperbilirubinemia were systematically searched in a variety of databases, which ensured the completeness of retrieval. The distribution of genotypes in all included studies was in HWE and no pronounced publication bias was indicated, which led to the results more reliable and convincible. Whereas in the present meta-analysis, the relevant suspected factors were unadjusted before analysis of the research results, and the quality of included studies was common.

5. Conclusions

The risk of neonatal hyperbilirubinemia may be increased by the variation of UGT1A1 Gly71Arg in Asia and Africa, as well as the variation of UGT1A1 TATA promoter in Asia and Europe. However, more multi-ethnic studies need to be performed in the future to further verify the effects of UGT1A1 Gly71Arg and TATA promoter

polymorphisms on the development of neonatal hyperbilirubinemia.

Conflict of interest:

The authors declare they have no conflict of interest.

Authors' contribution

Jing Wang was responsible for the study concept and design; Jiansong Yin, Mei Xue and Jun Lv were involved in data collection, data screening and statistical analysis; Jing Wang wrote the manuscript, and Yu Wan took charge of supervising the manuscript. The final manuscript was approved by all the authors above.

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Table 1. The basic characteristics of included studies (Gly71Arg)

First author	Year	Ethnicity	Country	Genotyping method	Score	Quality	Genoty		
							NH_GG	NH_GA	NH
Maruo [12]	1999	Asian	Japan	PCR	5	HQ	11	11	
Yamamoto [23]	2002	Asian	Japan	PCR	4	LMQ	8	12	
Sutomo [24]	2004	Asian	Malaysia	PCR	4	LMQ	28	4	
Yusoff [25]	2006	Asian	Malaysia	PCR	5	HQ	52	3	
Wong [26]	2007	Asian	Malaysia	PCR	5	HQ	45	18	
Prachukthum [27]	2009	Asian	Thailand	PCR–RFLP	5	HQ	68	19	
Boo [28]	2009	Asian	Malaysia	PCR	6	HQ	45	18	
Kilic [29]	2010	Asian	Turkey	PCR	5	HQ	40	7	
Narter [30]	2011	Asian	Turkey	PCR	5	HQ	23	13	
D'Silva [31]	2012	Asian	India	PCR-RFLP	3	LMQ	100	26	
Dastgerdy [32]	2012	Asian	Iran	PCR-RFLP	5	HQ	16	6	
Tiwari [33]	2013	Asian	India	PCR	3	LMQ	92	8	
Zhou [34]	2014	Asian	China	PCR	4	LMQ	85	73	
Yang [35]	2015	Asian	China	PCR	5	HQ	67	50	
Wu [14]	2015	Asian	China	PCR	3	LMQ	144	59	
Yang [36]	2016	Asian	China	PCR	4	LMQ	24	25	
Guo [37]	2016	Asian	China	PCR	5	HQ	104	44	
Mohammed [8]	2016	African	Egypt	PCR	4	LMQ	19	10	
Halis [38]	2017	Asian	Turkey	PCR	3	LMQ	85	14	
Liu [11]	2017	Asian	China	PCR	4	LMQ	42	56	
Zhou [39]	2018	Asian	China	PCR	4	LMQ	147	110	

Notes: PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restricted fragment length polymorphisms; LMQ: low and moderate quality; HQ: high quality; NH: neonatal hyperbilirubinemia; C: control group; HWE: Hardy-Weinberg equilibrium

Table 2. The basic characteristics of included studies (TATA promoter)

Year	Ethnicity	Country	Genotyping method	Score	Quality	Genotype distribution (n)				
						NH_TA6/6	NH_TA6/7	NH_TA7/7	C_ TA6/6	C_ TA6/7
1999	Asian	Japan	PCR	5	HQ	23	2	0	37	11
2003	Asian	Turkey	PCR	4	LMQ	35	32	8	14	19
2006	Asian	Malaysia	PCR	5	HQ	41	10	4	43	6
2006	Asian	Turkey	PCR	4	LMQ	44	25	5	18	11
2007	Asian	Turkey	PCR	5	HQ	95	12	0	47	7
2010	Asian	Turkey	PCR	5	HQ	10	34	6	48	6
2014	European	Croatia	PCR	4	LMQ	52	87	78	83	80
2014	European	Italy	PCR	4	LMQ	26	31	13	26	30
2014	Asian	India	PCR-RFLP	5	HQ	38	57	18	101	93
2015	Asian	China	PCR	5	HQ	115	14	0	74	34
2015	Asian	China	PCR	3	LMQ	176	38	4	141	48
2016	Asian	China	PCR	4	LMQ	50	8	0	45	20
2018	Asian	China	PCR	4	LMQ	241	45	0	200	50

Notes: PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restricted fragment length polymorphisms; LMQ: low and moderate quality; HQ: high quality; NH: neonatal hyperbilirubinemia; C: control group; HWE: Hardy-Weinberg equilibrium

Table 3 Overall and subgroup analysis of Gly71Arg polymorphism and neonatal hyperbilirubinemia

Characteristics	OR (95%CI)	*P*	I^2 (%)
Allele contrast (A *vs.* G)			
Overall	2.360(1.972-2.890)	<0.001	50.5
Ethnicity			
Asian	2.327(1.904-2.845)	<0.001	50.5
African	9.750(1.214-78.301)	0.032	NA
Genotyping method			
PCR	2.395(2.004-2.862)	<0.001	32.9
PCR-RFLP	2.420(0.862-6.792)	0.093	78.3
Quality assessment			

Low and moderate quality	2.268(1.674-3.072)	<0.001	63.7
High quality	2.537(1.994-3.228)	<0.001	16.9
Dominant model (AA+GA *vs.* GG)			
Overall	2.253(1.954-2.598)	<0.001	38.3
Ethnicity			
Asian	2.226(1.932-2.569)	<0.001	37.1
African	11.000(1.290-93.832)	0.028	NA
Genotyping method			
PCR	2.343(2.012-2.728)	<0.001	12.0
PCR-RFLP	1.699(1.131-2.554)	0.011	74.2
Quality assessment			
Low and moderate quality	2.146(1.796-2.564)	<0.001	58.1
High quality	2.453(1.934-3.112)	<0.001	2.3
Recessive model (AA *vs.* GG+GA)			
Overall	5.103(3. 495-7.452)	<0.001	19.2
Ethnicity			
Asian	5.166(3.520-7.564)	<0.001	23.7
African	2.085(0.081-53.758)	0.658	NA
Genotyping method			
PCR	5.221(3.525-7.732)	<0.001	28.9
PCR-RFLP	3.649(0.861-15.471)	0.079	0.0
Quality assessment			
Low and moderate quality	3.850(2.410-6.153)	<0.001	0.0
High quality	8.194(4.219-15.915)	<0.001	22.9
Codominant model (AA *vs.* GG)			
Overall	6.388(4.341-9.402)	<0.001	18.2
Ethnicity			
Asian	6.458(4.376-9.531)	<0.001	23.0
African	3.000(0.115-78.272)	0.509	NA
Genotyping method			
PCR	6.583(4.406-9.836)	<0.001	27.5
PCR-RFLP	4.186(0.982-17.843)	0.053	0.0
Quality assessment			
Low and moderate quality	4.997(3.095-8.068)	<0.001	2.5
High quality	9.568(4.894-18.706)	<0.001	22.1
Codominant model (GA *vs.* GG)			
Overall	1.945(1.677-2.256)	<0.001	30.5
Ethnicity			

Asian	1.920(1.654-2.228)	<0.001	28.2
African	10.000(1.163-85.998)	0.036	NA
Genotyping method			
PCR	2.004(1.710-2.349)	<0.001	12.3
PCR-RFLP	1.578(1.039-2.399)	0.033	67.3
Quality assessment			
Low and moderate quality	1.933(1.608-2.324)	<0.001	48.7
High quality	1.967(1.532-2.526)	<0.001	10.8

Notes: NA: no answer.

Table 4 Overall and subgroup analysis of TATA promoter polymorphism and neonatal hyperbilirubinemia

Characteristics	OR (95%CI)	*P*	I^2 (%)
Allele contrast [(TA)7 *vs.* TA(6)]			
Overall	1.044(0.678-1.608)	<0.001	87.4
Ethnicity			
Asian	0.956(0.591-1.547)	0.854	84.7
European	1.573(0.637-3.884)	0.326	90.6
Genotyping method			
PCR	1.006 (0.613-1.652)	0.980	88.3
PCR-RFLP	1.463(1.049-2.040)	0.025	NA
Quality assessment			
Low and moderate quality	0.941(0.585-1.511)	0.800	85.1
High quality	1.198(0.442-3.247)	0.722	90.9
Dominant model (TA7/7+TA6/7 *vs.* TA6/6)			
Overall	1.049(0.625-1.761)	0.856	86.7
Ethnicity			
Asian	0.960(0.534-1.723)	0.890	86.1
European	1.657(0.669-4.105)	0.275	80.4
Genotyping method			
PCR	1.002(0.565-1.776)	0.995	87.3
PCR-RFLP	1.704(1.062-2.733)	0.027	NA
Quality assessment			
Low and moderate quality	0.885(0.542-1.447)	0.626	78.5
High quality	1.351 (0.400-4.559)	0.628	91.8
Recessive model (TA7/7 *vs.* TA6/6+TA6/7)			
Overall	2.164(1.579-2.966)	<0.001	49.8
Ethnicity			

Asian	1.670(1.034-2.696)	0.036	7.2
European	2.627(1.722-4.008)	<0.001	87.7
Genotyping method			
PCR	2.380(1.656-3.421)	<0.001	52.4
PCR-RFLP	1.532(0.793-2.959)	0.205	NA
Quality assessment			
Low and moderate quality	2.396(1.627-3.528)	<0.001	63.7
High quality	1.729(0.995-3.002)	0.052	31.1
Codominant model (TA7/7 *vs*. TA6/6)			
Overall	1.962(0.951- 4.047)	0.068	61.1
Ethnicity			
Asian	1.776(0.765-4.123)	0.181	38.1
European	2.286(0.424-12.314)	0.336	89.5
Genotyping method			
PCR	1.925(0.776-4.779)	0.158	64.7
PCR-RFLP	1.993(0.974-4.079)	0.059	NA
Quality assessment			
Low and moderate quality	1.829(0.681 -4.913)	0.231	70.4
High quality	2.130(0.475- 9.555)	0.323	56.8
Codominant model (TA6/7 *vs*. TA6/6)			
Overall	0.991(0.611 -1.607)	0.971	83.4
Ethnicity			
Asian	0.932(0.526-1.651)	0.808	84.5
European	1.457(0.901-2.356)	0.125	26.5
Genotyping method			
PCR	0.945 (0.558-1.601)	0.834	83.7
PCR-RFLP	1.629 (0.990-2.680)	0.055	NA
Quality assessment			
Low and moderate quality	0.829(0.569-1.209)	0.330	59.8
High quality	1.325(0.403-4.361)	0.643	90.9

Notes: NA: no answer.

Highlights:

1. Multiple databases are searched to ensure the completeness of retrieval.
2. Included studies are all in Hardy-Weinberg equilibrium.
3. No pronounced publication bias makes the results more convincible.