Associations between UGT1A1 and SLCO1B1 polymorphisms and susceptibility to neonatal hyperbilirubinemia in Thai population

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Abstract

Hyperbilirubinemia is the main mechanism that causes neonatal jaundice, and genetics is one of the risk factors of hyperbilirubinemia. Therefore, this study aims to explore the correlation between two genes, UGT1A1 and SLCO1B1, and hyperbilirubinemia in Thai neonates. One hundred thirty seven neonates were recruited from Division of Clinical Chemistry, Ramathibodi Hospital. UGT1A1*28 and *6 were determined by pyrosequencing whereas, SLCO1B1 388A > G and 521 T > C genetic variants were determined by TaqMan® real-time polymerase chain reaction. Neonates carrying with homozygous (AA) and heterozygous (GA) variants in UGT1A1*6 were significantly related to hyperbilirubinemia development compared with wild type (GG; P < 0.001). To the combined of UGT1A1, total bilirubin levels in homozygous variant were higher significantly than heterozygous variant and wild type (P = 0.002, P = 0.003, respectively). Moreover, SLCO1B1 combination was significant differences between the hyperbilirubinemia and the control group (P = 0.041). SLCO1B1 521 T > C variant provide protection for Thai neonatal hyperbilirubinemia (P = 0.041). There are no significant differences in UGT1A1*28 and SLCO1B1 388A > G for the different severity of hyperbilirubinemia. The combined UGT1A1*28 and *6 polymorphism is a strong risk factor for the development of severe hyperbilirubinemia in Thai neonates. Therefore, we suggest neonates with this gene should be closely observed to avoid higher severities of bilirubin.

Keywords: Genetic polymorphisms, UGT1A1, SLCO1B1, Hyperbilirubinemia, Neonates

Introduction

Neonatal hyperbilirubinemia, one of the most common clinical problems in newborns, occurs up to 60% of healthy full-term newborns [1]. In general, elevated levels of total serum bilirubin can develop into severe neonatal jaundice that result in bilirubin-induced neurological damage such as hearing loss, athetosis, and rarely, intellectual deficits. Ultimately, severe cases may lead to seizures, coma, and death. The demographic, environmental, and genetic factors could account for risk of developing neonatal hyperbilirubinemia [2, 3].

The causes of neonatal jaundice can be due to the elevation of bilirubin, which is caused by the increased production or inability to metabolize and excrete it. This can be due to the immature liver of the newborn. Another cause is due to the decreased bilirubin uptake and conjugation due to the deficiency of the process of serum albumin binding to bilirubin, and carrying it to the
liver [4]. However, there is a transient deficiency in new- 
borns of the enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1), which in turns leads to a reduced amount 
of ligandin, a bilirubin binding protein. Lastly, it may be 
caused by increased enterohepatic circulation. As con- 
jugated bilirubin is excreted through the bile into the 
intestine, it is then deconjugated by a mucosal enzyme, 
β-glucuronidase, and reabsorbed into the enterohepatic 
circulation, before excretion via the stool. Newborns 
have slow intestinal motility, due to less gut flora, so this 
can be a cause of concern for major problems regarding 
excretion. Other causes include ABO incompatibility, 
hemolytic anemia and infection [5, 6].

The metabolism of bilirubin plays a huge role in hyper- 
bilirubinemia. Firstly, when the individual component, “haem” is broken down into iron and biliverdin. Biliver- 
din is then reduced to create unconjugated bilirubin. As 
it is in the bloodstream, unconjugated bilirubin binds 
to albumin, facilitating the transport to the liver, and 
glucuronic acid is added by the enzyme UDP-glucuron- 
osyltransferases [5, 7]. The first being UDP Glucuronoso- 
ltransferase Family 1 Member A1 (UGT1A1) which 
provides instructions for making enzymes called UDP- 
glucuronosyltransferases. This form conjugated biliru- 
bin, which is soluble, and in turn can be excreted in the 
duodenum. Once inside, normal gut flora deconjugate 
bilirubin and convert it into urobilinogen. It is mostly 
oxidized by intestinal bacteria, and converted to stercobi- 
lin, which is then excreted through stool. The rest is then 
reabsorbed into the bloodstream as a part of the entero- 
hepatic circulation [8].

The main factors that can be attributed to increased 
bilirubin may include race, acquired defects, and genetic 
polymorphism. Previous studies have been limited to 
only one genetic polymorphism [9, 10]. Therefore, two 
important genes, UGT1A1 and SLCO1B1 will be ana- 
yzed in this study. UGT1A1 helps with the conjugation 
of bilirubin. Two single nucleotide polymorphisms of 
this gene will be studied. The frequency allele UGT1A1*28 is 
distinguished by the insertion of a TA in the TATAA box 
of the gene, consequently decreasing gene transcription 
[11]. There have been studies that shows the relation- 
ship between high bilirubin levels and UGT1A1*28 [12]. 
Another variant is UGT1A1*6, 211G>A at exon 1, has 
been reported as a risk factor for neonatal hyperbiliru- 
bininemia in Asians. Overall, these two single nucleotide 
polymorphism (SNP) have shown correlation in previous 
studies before [13].

Another gene, Solute Carrier Organic Anion Trans- 
porter Family Member 1B1 (SLCO1B1) provides 
instructions for making the protein “OATP1B1”, which 
transports compounds from the blood into the liver, 
so that they can be cleared from the body. Regarding 
bilirubin, SLCO1B1 mediates the uptake of bilirubin, 
where it is conjugated and excreted from the body. 
Deficiencies in this gene can cause hyperbilirubine- 
mia [14]. This includes the two SNPs, 388A>G and 
521 T>C [15, 16].

Specifically, being able to identify the risk factors for 
neonatal jaundice can be crucial in developing treatment 
for this condition and minimize major consequences 
that may follow. The previous studies have been limited 
to only one type of gene in neonates, and there are only 
a few exploring the Thai population. This study aims to 
explore the correlation of the genetic variant of the two 
genes, UGT1A1 and SLCO1B1 causing hyperbilirubine- 
mia in Thai newborns.

Methods
Patients
The subjects of case-control study were obtained 
between November 2019 and November 2020 at Division 
of Clinical Chemistry, Department of Pathology, Faculty 
of Medicine Ramathibodi Hospital, Mahidol University, 
Bangkok, Thailand. Eligible subjects including Thai 
neonates (≥37 weeks of gestation) were enrolled in this 
study. Exclusion criteria were causes of hyperbilirubine- 
mia, such as hemolytic anemia, liver dysfunction, chol- 
estasis, ABO and Rh incompatibilities, positive coombs 
test, glucose-6-phosphate dehydrogenase (G-6-PD) defi- 
ciency, hypothyroidism, cephalhematoma, encephalopa- 
thy and presence of neurological disorders in the brain.

Neonatal hyperbilirubinemia was defined as total serum bilirubin concentration of >15 mg/dL beyond 
14 days of life. The control group consisted of neonates 
who did not show prolonged hyperbilirubinemia beyond 
14 days of life. The criteria was modified from the guide- 
line of 2004 American Academy of Pediatrics [17].

This study was reviewed and approved by the Ethics 
Review Committee on Human Research of the Faculty 
of Medicine Ramathibodi Hospital, Mahidol University, 
Thailand (MURA2020/1514) and conducted in accord- 
ance with the Declaration of Helsinki.

Molecular analysis
All leftover samples from total serum bilirubin deter- 
mination were analyzed genetic polymorphisms. DNA 
extractions from clot blood samples was conducted 
using the Genomic DNA Mini Kit (Geneaid® 
Geneaid Biotech Ltd., Taipei, Taiwan). Genomic DNA 
was quantified using NanoDrop ND-1000 Spectropho- 
tometer (Thermo Fisher Scientific, DE, USA). The two 
single nucleotide polymorphisms (SNPs) at nucleo- 
tide 388A>G (rs2306283; on reference sequence NM_006446.4, assay ID: C_: 1901697_20) and 521 T>C 
(rs4149056; on reference sequence NM_006446.4, assay
Statistical analysis
Hardy–Weinberg equilibrium was assessed using Fisher’s exact and chi-square test for UGT1A1 and SLCO1B1 variants. Allele and genotype frequencies were determined by direct counting. Comparisons between the case group and the control group were performed with chi-square test. Mann-Whitney U test was performed according to difference of case-control groups and nonparametric data [Birth weight (g), Gestational age (week)]. One-way ANOVA was performed according to genetic groups and total bilirubin levels (mg/dl). All statistical analyses were performed by using SPSS version 21.0 (SPSS, Chicago, IL, USA). A P-value < 0.05 was considered to be statistically significant.

Statement of confirmation
All methods aforementioned above were carried out in accordance with relevant guidelines and regulations.

Results
Clinical analysis
A total of 137 neonates were enrolled into the study. Sixty-seven neonates were classified into the hyperbilirubinemia group and 70 neonates were control group. Table 1 summarizes the demographic and clinical data between the hyperbilirubinemia group and control group. The factors listed here were gender, birth weight, gestational age, total bilirubin, and nutrition. The median of birth weight and gestational age were 3015.0 ± 770.0 g and 39.0 ± 1.0 weeks, respectively for case group and 2995.0 ± 695.0 g and 38.0 ± 3.0 weeks, respectively for control group. The average total bilirubin of the case group was 18.8 ± 2.6 mg/dl higher than the control group. The P-value < 0.001 was considered to be statistically significant.

The genotype and allele frequency of SLCO1B1 and UGT1A1 variants
The analysis of the genotype and allele frequency of SLCO1B1 and UGT1A1 variants are shown in Table 2. The allele frequencies of SLCO1B1 388A > G, 521 T > C, UGT1A1*28 and *6 were 0.79, 0.13, 0.17, and 0.13, respectively. Genotyping of SLCO1B1 388A > G was firstly mentioned. Homozygous variant (GG) was the most abundant, showing 84 (61.3%) and followed by 48 (35.0%) in heterozygous variant (AG) and 5 (3.6%) in wild type (AA). For SLCO1B1 521 T > C, TT, TC, and CC were also measured, and the genotype frequencies were 105 (76.6%), 29 (21.2%) and 3 (2.2%), respectively. The next gene explored was UGT1A1*28. The genotypes of TA6/Ta6, Ta6/Ta7, and Ta7/Ta7 were 90 (65.7%), 46 (33.6%) and 1 (0.7%), respectively. The genotyping of UGT1A1*6211G > A, was GG, GA, and AA, the frequencies are 107 (78.1%), 25 (18.2%) and 5 (3.6%) respectively.

Regarding combined SLCO1B1, the frequency values for normal, intermediate and low function were as follows; 105 (76.6%), 29 (21.2%) and 3 (2.2%), respectively. Lastly, combined UGT1A1 frequencies were measured. The wild type, heterozygous, and homozygous variant were genotyped to 66 (48.2%), 59 (43.1%) and 12 (8.8%) respectively.

The correlation between case-control group and genetic factors
Table 3 was showed the distributions for genetic factors for neonatal hyperbilirubinemia. The SLCO1B1 521 T > C variant showed significantly a low risk of neonatal hyperbilirubinemia in neonates (P = 0.041). The combined of SLCO1B1 was significantly related to severe hyperbilirubinemia (P = 0.041). In this study found that all neonates
carrying homozygous variant in UGT1A1*6 had high development of hyperbilirubinemia (5/5; 100%; \(P<0.001\)). Moreover, UGT1A1 combination was significantly increases the risk of hyperbilirubinemia (\(P=0.005\)).

Similar to Fig. 1, this box plot diagram shows that neonate carrying homozygous variant of combined UGT1A1 had a significantly increased of total bilirubin levels when compared with heterozygous variant and wild type (\(P=0.002\), and 0.003, respectively).

As shown in Fig. 2, this box plot diagram shows the results of combined SLC01B1 with low (\(5^*/5^*\), \(5^*/15^*\), \(15^*/15^*\)), intermediate (\(1a^*/5^*\), \(1a^*/15^*\), \(1b^*/15^*\)), and normal (\(1a^*/1a^*\), \(1a^*/1b^*\), \(1b^*/1b^*\)) function and the total bilirubin (mg/dL) measured. There was no significant association between combined SLC01B1 and total bilirubin levels. However, our results shown that neonates with low function had a decreasing trend in total bilirubin levels compared with intermediate and normal function. The average of total bilirubin in low, intermediate and normal function as follow: 11.0 ± 3.0 mg/dL, 12.2 ± 5.0 mg/dL, and 13.7 ± 4.9 mg/dL, respectively.

### Table 2 Genotype and allele frequency of SLC01B1 and UGT1A1 variants

| Genetic polymorphism | Allele frequency | Genotype frequency (%) |
|----------------------|------------------|------------------------|
| SLC01B1 388A > G     | A allele 0.21     | AA 5 (3.6)              |
|                      | G allele 0.79     | AG 48 (35.0)            |
|                      |                  | GG 84 (61.3)            |
| SLC01B1 521 T > C    | T allele 0.87     | TT 105 (76.6)           |
|                      | C allele 0.13     | TC 29 (21.2)            |
|                      |                  | CC 3 (2.2)              |
| Combined SLC01B1a    | Normal function  | 105 (76.6)              |
|                      | Intermediate function 29 (21.2) |
|                      | Low function 3 (2.2) |
| UGT1A1*28            | TA6 allele 0.83   | TA6/TA6 90 (65.7)       |
|                      | TA7 allele 0.17   | TA7/TA7 46 (33.6)       |
|                      |                  | TA7/TA7 1 (0.7)         |
| UGT1A1*6211G > A     | G allele 0.87     | GG 107 (78.1)           |
|                      | A allele 0.13     | GA 25 (18.2)            |
|                      |                  | AA 5 (3.6)              |
| Combined UGT1A1b     | Wild type 66 (48.2) |
|                      | Heterozygous variant 59 (43.1) |
|                      | Homozygous variant 12 (8.8) |

a Normal function consists of *1a/*1a, *1a/*1b, *1b/*1b; Intermediate function consists of *1a/*5, *1a/*15, *1b/*15; Low function consists of *5/*5, *5/*15, *15/*15
b Combined UGT1A1 wild type (*1/*1); heterozygous variant (*1/*28, *1/*6); homozygous variant (*28/*28, *28/*6, *6/*6)

### Table 3 Correlation between case-control group and genetic factors

| Factors | Hyperbilirubinemia group n = 67 (%) | Control group n = 70 (%) | \(P\)-value |
|---------|-------------------------------------|--------------------------|----------------|
| SLC01B1 388A > G | AA 1 (20.0) | 4 (80.0) | 0.173 |
|          | AG 21 (43.8) | 27 (56.3) |
|          | GG 45 (53.6) | 39 (46.4) |
| SLC01B1 521 T > C | TT 57 (54.3) | 48 (45.7) | 0.041*  |
|          | TC 9 (31.0) | 20 (69.0) |
|          | CC 1 (33.3) | 2 (66.7) |
| Combined SLC01B1 | Normal function 57 (54.3) | 48 (45.7) | 0.041*  |
|          | Intermediate function 9 (31.0) | 20 (69.0) |
|          | Low function 1 (33.3) | 2 (66.7) |
| UGT1A1*28 | TA6/TA6 49 (54.4) | 41 (45.6) | 0.097 |
|          | TA6/TA7 18 (39.1) | 28 (60.9) |
|          | TA7/TA7 0 (0) | 1 (100) |
| UGT1A1*6211G > A | GG 44 (41.1) | 63 (58.9) | <0.001* |
|          | GA 18 (72) | 7 (28) |
|          | AA 5 (100) | 0 (0) |
| Combined UGT1A1 | Wild type 31 (47.0) | 35 (53.0) | 0.005* |
|          | Heterozygous variant 26 (44.1) | 33 (55.9) |
|          | Homozygous variant 10 (33.3) | 2 (16.7) |

* \(P\)-value < 0.05 was considered to be statistically significant.
Discussion

In this study, the correlation between hyperbilirubinemia and two genes, \(\text{SLCO1B1}\) and \(\text{UGT1A1}\) variants were investigated in Thai neonates. Our results showed that combined \(\text{UGT1A1}^{*28}\) and \(\text{UGT1A1}^{*6}\) is a high-risk factor for developing neonatal hyperbilirubinemia. We were the first study to conduct on combined \(\text{UGT1A1}\) variants and its effects on Thai neonatal hyperbilirubinemia. Regarding \(\text{SLCO1B1}\), a trend was evident, as the total bilirubin levels were decreasing in low function compared with intermediate and normal function.

\(\text{UGT1A1}^{*28} (\text{A(TA)^{77}TAA})\) is a variant allele that is commonly found in African-Americans (0.42–0.45 allele frequency), and less in Asian populations (0.09–0.16 allele frequency) [19, 20]. It provides instructions for making UDP-glucuronosyltransferase, which is crucial in the overall process of converting unconjugated bilirubin. However, our results showed that \(\text{UGT1A1}^{*28}\) is not a risk factor for developing neonatal hyperbilirubinemia. Similarly, to a meta-analysis by Li H, et al. [21], concluding that the gene polymorphism of \(\text{UGT1A1}^{*28}\) might not be associated with the risk of neonatal hyperbilirubinemia.

\(\text{UGT1A1}^{*6211G>A}\), another SNP variant, was explored. The results from Prachukthum S, et al. [22], reported that \(\text{UGT1A1}^{*6}\) was an important risk factor for developing jaundice in infants. It found that infants who were carrying homozygous (AA) and heterozygous (GA) variants were more susceptible to develop hyperbilirubinemia when compared with wildtype (GG). Yanagi T, et al. [23], showed that \(\text{UGT1A1}^{*6}\) is a risk factor for prolonged unconjugated hyperbilirubinemia in Japanese preterm infants. Moreover, Nguyen TT, et al. [13], revealed that bilirubin levels in the patient carrying homozygous c.211G>A was significantly higher than heterozygous variant and wild type. Our results demonstrated that all Thai neonates carrying the homozygous variant in \(\text{UGT1A1}^{*6}\) were significantly classified into the hyperbilirubinemia group.

For our results regarding combined \(\text{UGT1A1}^{*28}\) and \(\text{UGT1A1}^{*6}\), it showed that these two genes were strongly significantly associated with hyperbilirubinemia \((P=0.005)\). The total bilirubin levels in the homozygous variant were significantly higher compared with heterozygous variant and wildtype.

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**Fig. 1** Correlation between combined \(\text{UGT1A1}^{*28}\) and \(\text{UGT1A1}^{*6}\) and total bilirubin levels in Thai neonates; Combined \(\text{UGT1A1}\) wild type (*1/*1); heterozygous variant (*1/*28, *1/*6); homozygous variant (*28/*28, *28/*6, *6/*6)
The second gene studied was \textit{SLCO1B1}. This gene provides instructions for making a protein, OATP1B1, an influx transporter responsible for the transportation of compounds in the bloodstream to the liver [24]. The allele frequency of \textit{SLCO1B1} 388 A>G in this study was 0.79, similarly to the Han Chinese population having an allele frequency of 0.64 reported by Liu et al. [11]. Moreover, Bai J, et al. [25], found that the 388 G>A variant of the \textit{SLCO1B1} gene was associated with infant hyperbilirubinemia in Chinese. However, the data from our study indicates that there were no statistically significant differences in risk factor of neonatal hyperbilirubinemia and \textit{SLCO1B1} 388 A>G variant. Similar to Amandito R, et al. [26], demonstrated that there was no statistically significant differences between occurrence of \textit{SLCO1B1} 388 A>G and hyperbilirubinemia in newborns. In \textit{SLCO1B1} 521 T>C variant, there was a significant correlation between hyperbilirubinemia and \textit{SLCO1B1} 521 T>C ($P = 0.041$). Similarity to a systematic review with meta-analysis of Liu J et al. [27], reported that the \textit{SLCO1B1} 521 T>C variant protective factor against hyperbilirubinemia in Chinese neonates.

Regarding combined \textit{SLCO1B1}, there was a decreasing trend of total bilirubin levels in normal (*1a/*1a, *1a/*1b, *1b/*1b), intermediate (*1a/*5, *1a/*15, *1b/*15), low (5/*5, 5/*15, *15/*15) function respectively. The relationship between low function neonates, having lower total bilirubin levels than that of intermediate and normal function, was evident.

In the present study, total bilirubin levels were significantly between case and control groups. In case group, mean of total bilirubin levels were 18.8 ± 2.6 mg/dL, which had higher total bilirubin levels than control group (10.7 ± 3.5 mg/dL). The total bilirubin levels in control group showed slightly high levels in Thai neonates. There was a nutrition significance to be noted in this study. The results showed that there was a correlation between nutrition and neonatal hyperbilirubinemia in Thai neonates ($P = 0.013$). The finding was consistent with Bratton S et al. [28], stating that breast milk may cause jaundice in newborns in their first week of life. There is limited research regarding formula and mixed-feeding and its association with neonatal jaundice.

In addition, some limitations of this study were regarding small sample size, which does not represent the whole population. Large sample size could be studied in further study. Our study was also limited to only two genes, \textit{SLCO1B1} and \textit{UGT1A1}, so other genes related with hyperbilirubinemia could be investigated in further

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Fig_2}
\caption{Correlation between combined \textit{SLCO1B1} and total bilirubin levels in Thai neonates; normal function consists of *1a/*1a, *1a/*1b, *1b/*1b; intermediate function consists of *1a/*5, *1a/*15, *1b/*15; low function consists of *5/*5, *5/*15, *15/*15}
\end{figure}
studies. Since this was a retrospective study, some clinical data were also missed, including nutrition.

Conclusion
The combined UGT1A1*28 and *6 polymorphism was a strong risk factor for hyperbilirubinemia in Thai neonates. Therefore, we suggest neonates with this gene should be closely observed to avoid higher severities of bilirubin.

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Authors’ contributions
All authors helped to perform the research; Chalirmporn Atasilp sample collection, manuscript writing, drafting conception and design, performing procedures and data analysis; Janjira Kanjanapipak sample and clinical data collection; Jasatdao Vichayaprasertkul manuscript writing; Pimpon Jinda, Rawiporn Tiaysirichokchai performing procedures; Porppen Sirisawadi, Chatchay Prempunpong, Monpat Chammaphon Apachaya Puangpetch drafting conception and design; Natchaya Vanwong data analysis; Suwiti Klongthelay drafting conception; Thawnee Jantaratongtong performing procedures; Chonlaphat Sukasem drafting conception and design, contribution to writing the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
Full data set and other materials on this study can be obtained from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Review Committee on Human Research of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (MURA2020/1514) and conducted in accordance with the Declaration of Helsinki. Informed Consent was waived due to the research use specimens left over from clinical care at Division of Clinical Chemistry, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The specimens were not collected specifically for the proposed research, and no additional specimen was collected for the purpose of this research. Also, the analysis used anonymous clinical data.

Consent for publication
Not applicable.

Competing interests
Not applicable.

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