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ORIGINAL ARTICLE

Retrospective Cohort Study

Genetic variation features of neonatal hyperbilirubinemia caused by inherited diseases

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Abstract

BACKGROUND

Genetic factors play an important role in neonatal hyperbilirubinemia (NH) caused by genetic diseases.

AIM

To explore the characteristics of genetic mutations associated with NH and analyze the correlation with genetic diseases.

METHODS

This was a retrospective cohort study. One hundred and five newborn patients diagnosed with NH caused by genetic diseases were enrolled in this study between September 2020 and June 2023 at the Second Affiliated Hospital of Xiamen Medical College. A 24-gene panel was used for gene sequencing to analyze gene mutations in patients. The data were analyzed *via* Statistical Package for the Social Sciences 20.0 software.

RESULTS

Seventeen frequently mutated genes were found in the 105 patients. *Uridine 5'-diphospho-glucuronosyltransferase 1A1* (*UGT1A1*) variants were identified among the 68 cases of neonatal Gilbert syndrome. In patients with sodium taurocholate cotransporting polypeptide deficiency, the primary mutation identified was *Na+/taurocholate cotransporting polypeptide Ntcp* (*SLC10A1*). *Adenosine triphosphatase 7B* (*ATP7B*) mutations primarily occur in patients with hepatolenticular degeneration (Wilson's disease). In addition, we found that *UGT1A1* and *glucose-6-phosphate dehydrogenase* mutations were more common in the high-risk group than in the low-risk group, whereas mutations in *SLC10A1*, *ATP7B*, and *heterozygous 851del4 mutation* were more common in the low-risk group.

CONCLUSION
Genetic mutations are associated with NH and significantly increase the risk of disease in affected newborns.

Key Words: Hyperbilirubinemia; Gene mutation; Neonates; Genetic polymorphisms; Inherited diseases

Core Tip: Variations in the frequency and distribution of gene mutations are observed in neonatal hyperbilirubinemia (NH) caused by inherited diseases, with *uridine 5'-diphospho-glucuronosyltransferase 1A1* mutations prevalent in neonatal Gilbert syndrome cases, *Na+/taurocholate cotransporting polypeptide Ntcp* mutations in sodium taurocholate cotransporting polypeptide deficiency patients, and *Adenosine triphosphatase* mutations in Wilson's disease. The distinct genetic profiles between the high-risk and low-risk groups suggest the potential utility of genetic screening for risk stratification and early intervention in NH.

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INTRODUCTION

Neonatal hyperbilirubinemia (NH) is one of the most common clinical issues in newborns, with an incidence as high as 60% in healthy full-term infants[1,2]. Most cases are physiological and mild and often do not require treatment. However, it can also be associated with certain underlying conditions. Severe cases can lead to bilirubin encephalopathy without timely treatment, resulting in intellectual impairment, damage to the nervous and auditory systems, and even death[3].

The aetiology of NH is complex, and different cases of hyperbilirubinemia can have single or mixed causes. Known pathogenic factors include ABO blood group or Rh blood group incompatibility, infections, and delayed meconium passage[4-6]. However, there are also cases where the cause of jaundice is unclear. For patients with NH of unknown cause, identifying the underlying etiology is crucial for timely diagnosis and effective treatment. In some instances, abnormally elevated bilirubin levels may indicate underlying genetic factors, where genetic mutations may play a pivotal role[7,8].

With the rapid advancement of gene mutation detection technologies, the significance of genetic factors in NH has attracted increasing attention. Long *et al*[9] detected *Uridine 5'-diphospho-glucuronosyltransferase 1A1* (*UGT1A1*) gene mutations in infants with hyperbilirubinemia *via* methods such as polymerase chain reaction (PCR). They reported that the *UGT1A1* 211G>A mutation is associated with NH in Asians. In another study, *UGT1A1* variants were recognized as potential risk factors for prolonged jaundice and hyperbilirubinemia, particularly among full-term, exclusively breastfed infants of Chinese descent, *via glucose-6-phosphate dehydrogenase* (*G6PD*) enzyme quantification assays[10]. However, previous studies have focused primarily on detecting single genes *via* traditional methods such as PCR. However, comprehensive studies exploring the broader genetic landscape of NH in which multiple genes are targeted remain scarce. This highlights the need for further investigations and more extensive genomic analyses. In clinical practice, high-throughput sequencing for neonatal genetic screening could facilitate the identification of genetic variants associated with hyperbilirubinemia, offering valuable guidance for clinical diagnosis and treatment.

Some studies have shown that several genetic disorders can lead to hyperbilirubinemia, including Dubin-Johnson syndrome (DJS), Crigler–Najjar syndrome, Gilbert syndrome (GS), and Lucey–Driscoll syndrome[11]. With the advancement of genetic testing technologies, the crucial role of genetic mutations in the occurrence of NH is increasingly recognized. GS is a common genetic disorder characterized by elevated levels of bilirubin in the blood[12]. Its main feature is mutations in the *UGT1A1* gene, which is involved in bilirubin metabolism. Research has indicated that mutations in the *UGT1A1* gene lead to decreased bilirubin metabolism capacity, thereby increasing the risk of NH[13]. Crigler–Najjar syndrome is a rare but severe genetic disorder characterized by high levels of bilirubin in the blood. Its aetiology is also associated with mutations in the *UGT1A1* gene[14]. In addition, other genetic mutations related to bilirubin metabolism, such as *OATP transporters* (*SLCO1B1*), *heterozygous 851del4 mutation* (*SLC25A13*), and *biliverdin reductase A* (*BLVRA*)[15-17], are associated with NH. These findings indicate that genetic mutations play a significant role in the pathogenesis of NH, providing important clues for a deeper understanding of the genetic basis and pathological mechanisms of this disease. However, previous studies have focused mainly on exploring the correlation between specific gene variants and patients with hyperbilirubinemia, and a systematic exploration of the association between more unknown genes and NH in large-scale populations is lacking.

Given the potential complexity and clinical significance of NH, a thorough understanding of the associated genetic mutations is crucial for elucidating the genetic basis of this condition, guiding clinical diagnosis, and formulating individualized treatment. Therefore, this study aims to explore genetic mutations associated with NH comprehensively and investigate the correlation between these mutations and the pathogenesis of the disease. These results provide a

foundation for future clinical practice and genetic counseling, offering a deeper understanding and guidance for the prevention and treatment of NH.

MATERIALS AND METHODS

Study population and data collection

We prospectively collected data from 105 newborn patients who were diagnosed with NH caused by genetic diseases between September 2020 and June 2023 at the Second Affiliated Hospital of Xiamen Medical College. The inclusion criteria were as follows: (1) They were diagnosed with NH caused by genetic diseases; and (2) They had undergone genetic testing. The exclusion criteria were as follows: Individuals with hyperbilirubinemia who did not undergo 24-gene panel testing. Whole blood samples were collected from all patients and stored at -20 °C for genetic sequencing. The study was conducted in accordance with the Helsinki Declaration and approved by the Clinical Research Ethics Committee of the Second Affiliated Hospital of Xiamen Medical College (No. 2020039). Informed consent was obtained from all the legal guardians of the study participants.

Targeted panel sequencing and genetic analysis

Targeted panel sequencing of 23 genes, including: (1) *Adenosine triphosphatase* (*ATP*)*-binding cassette transporters* (*ABCB11*); (2) *ATP-binding cassette subfamily C member 2* (*ABCC2*); (3) *ATP-binding cassette sub-family D member 3* (*ABCD3*); (4) *Trihydroxycoprostanoyl-CoA oxidase* (*ACOX2*); (5) *ATP7B*; (6) *UGT1A1*; (7) *Cytochrome P450, Family 7, Subfamily B, Polypeptide 1* (*CYP7B1*); (8) *G6PD*; (9) *Beta-globin gene* (*HBB*); (10) *3β-hydroxy-Δ5-C27-steroid oxidoreductase* (*HSD3B7*); (11) *Jagged 1* (*JAG1*); (12) *Niemann-Pick type C 1* (*NPC1*); (13) *NPC2*; (14) *NOTCH2*; (15) *SMase gene* (*SMPD1*); (16) *Glucocerebrosidase*; (17) *ABCB4*; (18) *Farnesoid X receptor* (*NR1H4*); (19) *Monoclonal antibody P504S*; (20) *Aldo-keto reductase family 1 member D1*; (21) *ATP8B1*; (22) *Na+/taurocholate cotransporting polypeptide Ntcp* (*SLC10A1*); and (23) *SLC25A13,* was performed for each patient. Genomic DNA was extracted from whole-blood samples *via* a QIAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer's protocol. Genomic DNA fragments were enriched for targeted panel sequencing (Agilent ClearSeq Inherited Disease Kit; Agilent). After enrichment, the DNA libraries underwent next-generation sequencing (Illumina HiSeq 2000/2500 platform). The sequencing data were first processed to remove low-quality reads and adapter sequences. Burrows-Wheeler Aligner software was then used to align the sequencing reads to the human reference genome (version hg19). Genome analysis toolkit software was subsequently employed to identify single nucleotide variants and insertions/deletions within the aligned reads. Annotation analysis was conducted *via* databases including the 1000 Genomes Project, ExAC, gnomAD, ClinVar, Human Gene Mutation Database (HGMD) Professional, and local databases.

Statistical analysis

Statistical Package for the Social Sciences 20.0 was used for data analysis. The continuous variables in the data group are expressed as the means ± SD. Count data are presented as frequencies and percentages. The Pearson χ^2 test was used, and $P < 0.05$ was considered statistically significant.

RESULTS

General clinical characteristics

A total of 105 newborns with hyperbilirubinemia caused by genetic diseases (54 males and 43 females) were included in this study (Table 1). Among these patients, the birth weight was 2.01-4.10 kg, with an average of 3.25 kg ± 0.82 kg, and the gestational age was 36-41 weeks, with an average of 38 weeks ± 2 weeks. The occurrence of hyperbilirubinemia ranged from 1 day to 60 days, with an average of 16.5 days. There were 87 full-term infants, 9 preterm infants, and 9 unknown. Seventy-three infants were fully breastfed, 24 were mixed fed, and 8 were unknown. The peak value of total serum bilirubin (TSB) was 291-722.39 μmol/L, with an average of 398.07 μmol/L ± 55.09 μmol/L. Among them, 68 patients (64.7%) had GS, 14 patients (13.3%) had sodium taurocholate cotransporting polypeptide deficiency (NTCP) deficiency, and 9 patients (8.6%) had Citrin deficiency. There were five cases each of *G6PD* deficiency, Niemann-Pick disease (NPD), Wilson's disease, and congenital bile acid synthesis disorders (4.8%). There were four cases (3.8%) of progressive familial intrahepatic cholestasis and four cases (3.8%) of Alagille syndrome. Three patients (2.9%) had DJS, and two patients (1.9%) had thalassemia.

Genetic spectrum of the study participants

We tested the samples through a 24-gene panel, and variants defined as pathogenic or likely pathogenic (LP) were selected for analysis. Among the 105 patients, 75 (71.4%) were pathogenic or LP variant carriers. In a study of 82 patients, a total of 17 pathogenic mutated genes were detected, including: (1) *ABCB11*; (2) *ABCC2*; (3) *ABCD3*; (4) *ACOX2*; (5) *ATP7B*; (6) *UGT1A1*; (7) *CYP7B1*; (8) *G6PD*; (9) *HBB*; (10) *HSD3B7*; (11) *JAG1*; (12) *NPC1*; (13) *NR1H4*; (14) *ATP8B1*; (15) *SLC10A1*; (16) *SLC25A13*; and *SMPD1* (Figure 1). Among these genes, *UGT1A1* (77.3%) had the highest mutation frequency, accounting for 67.2% (39/58) of the heterozygous mutations and 32.7% (19/58) of the homozygous mutations. The gene with the highest frequency was *SLC10A1* (18.7%), which included 92.9% (13/14) of the genes with heterozygous mutations and 7.1% (1/14) with homozygous mutations. This was followed by genes that were entirely heterozygous

Table 1 Demographic and clinical characteristics of the study population, *n* (%)

Variable	Patient cohorts (*n* = 105)
Sex	
Female	43
Male	54
Gestational age (weeks)	38 ± 2
birth weight (kg)	3.25 ± 0.82 (2.01-4.10)
Age of onset (days)	
1-3 days	59
4-7 days	11
≥ 8 days	6
Feeding pattern	
Full breastfeeding	73
Mix feeding	24
Premature birth	
Yes	9
No	87

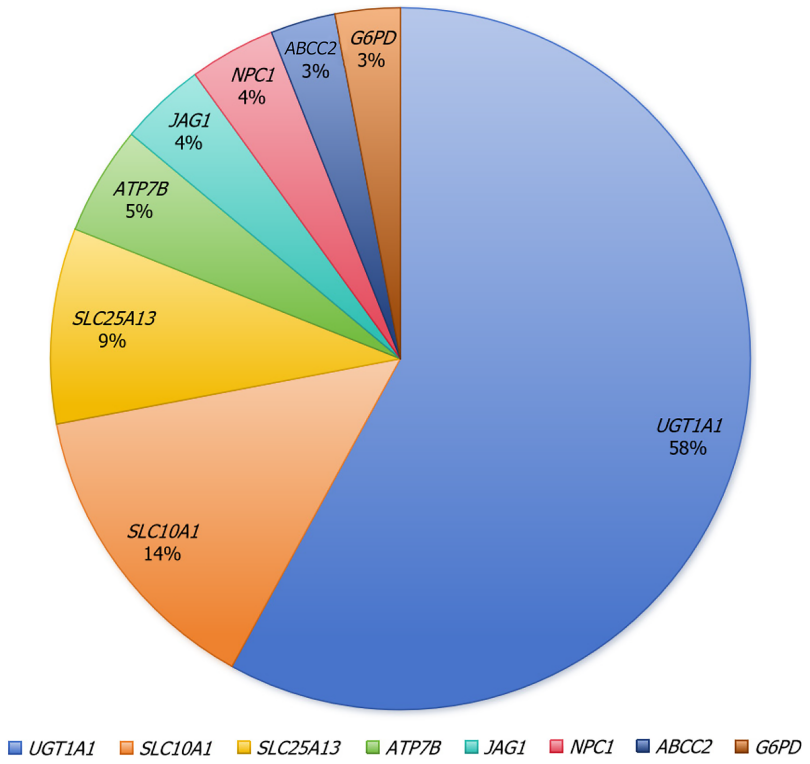

Figure 1 Results for the percentage of mutated genes in 105 patients. *UGT1A1*: *Uridine 5'-diphospho-glucuronosyltransferase 1A1*; *SLC10A1*: *Na+/taurocholate cotransporting polypeptide Ntcp*; *SLC25A13*: *Heterozygous 851del4 mutation*; *ATP7B*: *Adenosine triphosphatase 7B*; *JAG1*: *Jagged 1*; *NPC1*: *Niemann-Pick type C 1*; *ABCC2*: *Adenosine triphosphatase-binding cassette subfamily C member 2*; *G6PD*: *Glucose-6-phosphate dehydrogenase*.

mutations: (1)*SLC25A13* (12%); and (2) *ATP7B* (6.7%). The remaining genes were low-frequency pathogenic genes, including: (1) *JAG1* (5.3%); (2) *NPC1* (5.3%); (3) *ABCC2* (4.0%); and (4) G6PD (4.0%). These gene mutations are associated with the onset of NH caused by genetic diseases.

Analysis of genetic factors in NHs

We analyzed the molecular genetic factors of hyperbilirubinemia caused by genetic diseases, and the list of gene

mutations is shown in Table 2. Among the 17 detected genetic diseases, GS is the most common, and through diagnostic analysis, 4 different *UGT1A1* variants were identified among the 71 cases of neonatal GS. The most common variant was p.Gly71Arg (84.5%), followed by p.Pro364Leu (9.9%) and p.Tyr486Asp (2.8%). The three known mutations were classified as pathogenic according to the HGMD standards/guidelines. The p.Pro451Leu mutation is a variant of uncertain significance identified for the first time. The primary mutation identified in patients with NTCP deficiency is *SLC10A1* (p.Ser267Phe). *ATP7B* mutations primarily occur in patients with hepatolenticular degeneration (Wilson's disease), among which there are four variants of uncertain clinical significance: (1) P.Asp1164Asn; (2) P.Arg827Gln; (3) P.Thr935Met; and (4) P.Cys157Phe. Mutations in *G6PD* are associated with hemolytic anemia due to G6PD deficiency. When considering NPD, the *HSD3B7* (p.Ser738Ter and p.Gln81His), *SMPD1* (p.Leu124Arg), and *ABCD3* (p.Ala321Val) gene mutation rates were 12.2% (28/230) and 9.6% (22/230), respectively. In patients with DJS, mutations occur in the *ABCC2* gene. Among these mutations, p.Gln93Ter is classified as LP, and the other two novel variants (p.Arg1310Gly and p.Glu881del) are classified as variants of uncertain significance. Additionally, we identified several rare mutations, including *HBB* mutations in patients with thalassemia, *ACOX2* mutations in patients with type 1 congenital bile acid synthesis disorder, and *SMPD1* mutations in patients with neonatal DJS.

Gene mutations and their distribution in high-risk patients

Patients were classified into high-risk and low-risk groups based on a total bilirubin level of 342 μmol/L. First, we analyzed the correlation between clinical characteristics and TSB levels. Our bivariate analysis results of the clinical characteristics are shown in Table 3. Exclusive breastfeeding was shown to be associated with severe TSB ($P < 0.05$). Sex, feeding method, birth weight, and gestational age were unrelated to TSB. An analysis of the frequency of genetic mutations in the high-risk and low-risk groups was conducted. The results revealed that the proportions of *UGT1A1* and *G6PD* mutations were greater in the high-risk group, whereas mutations in *SLC10A1*, *ATP7B*, and *SLC25A13* were more common in the low-risk group (Figure 2). The results of the bivariate analysis of gene mutation and the TSB are shown in Table 4. None of the genes were associated with severe TSB.

DISCUSSION

NH is a common condition in newborns, and its pathogenesis involves abnormalities in the bilirubin metabolism pathway[18]. In recent years, more studies have shown a close association between hyperbilirubinemia and genetic mutations[19]. These mutations affect the function of related genes, leading to abnormalities in bilirubin metabolism. In this study, we explored the relationships between hyperbilirubinemia caused by inherited diseases and genetic mutations and analyzed their potential clinical significance.

UGT1A1 is an enzyme responsible for conjugating bilirubin with glucuronic acid. Genetic variants of *UGT1A1* that result in reduced enzyme activity and expression are associated with nonhemolytic hyperbilirubinemia syndromes, such as GS and Crigler-Najjar (CN) syndrome type I and type II (referred to as CN I and CN II, respectively)[20-22]. Previous studies confirmed that the prevalence of *UGT1A1* gene mutations in patients with hyperbilirubinemia is significantly greater than that in healthy controls, suggesting that *UGT1A1* gene mutations play an important role in the pathogenesis of hyperbilirubinemia[23]. Additionally, research by Mazur-Kominek *et al*[24] has shown that *UGT1A1* mutations are among the key causes of NH. These mutations decrease the expression level of the *UGT1A1* gene, thereby reducing the rate of bilirubin metabolism and increasing the concentration of bilirubin in the blood, ultimately leading to hyperbilirubinemia. The present study revealed that *UGT1A1* has the highest mutation frequency in patients with hyperbilirubinemia, which is consistent with previous research results. Furthermore, our study revealed that the mutation frequency of *UGT1A1* in high-risk bilirubin patients was greater than that in low-risk patients. The *ATP7B* gene is one of the genes that encode copper-transporting proteins in the human genome. The protein encoded by this gene is an ATPase that plays a critical role in maintaining the body's balance and metabolism of copper ions. Previous studies have suggested that mutations in the *ATP7B* gene may affect the structure or function of the ATP7B protein, leading to abnormal copper accumulation in the liver and resulting in Wilson's disease[25,26]. Wilson's disease may cause liver diseases such as liver fibrosis and cirrhosis, which may interfere with the metabolism and excretion of bilirubin, ultimately leading to hyperbilirubinemia[27]. Our research revealed that the mutation frequency of the *ATP7B* gene was greater in the high-risk bilirubin patient group. These findings suggest that *ATP7B* plays an important role in hyperbilirubinemia. Our study also revealed common mutations in *G6PD* among patients with high bilirubin levels. Functional loss mutations in the *G6PD* gene cause G6PD deficiency. G6PD deficiency is a significant risk factor for NH[28]. Several studies have indicated that infants with G6PD deficiency are prone to severe neonatal jaundice[29-31]. Elevated levels of bilirubin in the blood and ineffective bilirubin clearance in the liver can also lead to the accumulation of serum bilirubin, resulting in NH. This condition is more common and severe in infants with G6PD deficiency[32]. Furthermore, studies have indicated that variations in the *UGT1A1* gene are risk factors for NH in infants with G6PD deficiency[33]. The *ABCC2* gene is located on chromosome 10q24 and encodes multidrug resistance-associated protein 2 (MRP2). Studies have confirmed that conjugate hyperbilirubinemia is the most obvious consequence of mutations in ABCC2 that lead to DJS[34].

We identified several rare mutations, including *HBB* mutations in patients with beta-thalassemia, *ACOX2* mutations in patients with type 1 congenital bile acid synthesis disorder, and *SMPD1* mutations in patients with DJS. The *HBB* gene encodes the beta-globin chain of hemoglobin. Beta-thalassemia is an inherited blood disorder caused by mutations in the *HBB* gene, resulting in impaired synthesis of beta-globin, leading to hemolytic anemia and chronic anemia, and hemolysis may lead to hyperbilirubinemia[35]. The *ACOX2* gene encodes acyl-coenzyme an oxidase 2, which is key in the bile acid synthesis pathway. Defects in *ACOX2* can block bile acid synthesis, leading to bile stasis and hyperbilirubinemia[36]. The

Table 2 List of pathogenic/likely pathogenic variants in patients

Gene	Cytogenetic location	Mutation variant	Amino acid variant	Type of gene	Allele frequency
Uridine 5'-diphospho-glucuronosyltransferase 1A1	Chr2: 234669144	C.211G>A	P.Gly71Arg	Het/hom	0.152
	Chr2: 234676872	C.1091C>T	P.Pro364 Leu	Het	0.012
	Chr2: 234681059	C.1456T>G	P.Tyr486Asp	PAT	0.001
	Chr2: 234680955	C.1352C>T	P.Pro451 Leu	Het	0.005
Na+/taurocholate cotransporting polypeptide Ntcp	Chr14: 70245193	C.800C>T	P.Ser267Phe	Het/hom	0.078
heterozygous 851del4 mutation	Chr7: 95818684	C.852_855delTATG	P.Met285ProfsTer2	Het	0.004
	Chr7: 95813702	C.1064G>A	P.Arg355Gln	Het	3.48^{E-04}
	Chr7: 95775896	C.1424G>A	P.Arg475Gln	Het	-
	Chr7: 95751240	C.1638_1660dup	P.Ala554GlyfsTer17	Het	0.0013
ATP 7B	Chr13: 52515283	C.3490G>A	P.Asp1164Asn	Het	-
	Chr13: 52524503	C.2480G>A	P.Arg827Gln	Het	5.80^{E-4}
	Chr13: 52523859	C.2804C>T	P.Thr935Met	Het	0.002
	Chr13: 52548886	C.470G>T	P.Cys157Phe	Het	-
	Chr13: 52524515	C.2468A>G	P.Glu823Gly	Het	1.16^{E-4}
	Chr13: 52534313	C.2092A>C	P.Ile698 Leu	Het	-
Glucose-6-phosphate dehydrogenase	ChrX: 153774276	C.185A>G	P.His62Arg	Hemi	0.002
	ChrX: 153763476	C.482G>T	P.Gly161Val	Het	6.03^{E-4}
	ChrX: 153760484	C.1466G>T	P.Arg489 Leu	Het	0.008
	ChrX: 153760472	C.1478G>A	P.Arg493His	Hemi	0.005
Beta-globin gene	Chr11: 5246931	C.341T>A	P.Val114Glu	Het	2.32^{E-4}
Cytochrome P450, Family 7, Subfamily B, Polypeptide 1	Chr8: 65536958	C.259+2T>C		Het	1.16^{E-4}
ATP-binding cassette subfamily C member 2	Chr10: 101552060	C.277C>T	P.Gln93Ter	Het	1.16^{E-4}
Jagged 1	Chr20: 10622442	C.2671G>A	P.Ala891Thr	Het	-
Niemann-Pick type C 1	Chr18: 21116653	C.3229C>T	P.Arg1077Ter	Het	-
Farnesoid X receptor	Chr12: 100926359	C.569T>A	P.Met190 Lys	Het	-
3β-hydroxy-Δ5-C27-steroid oxidoreductase	Chr16: 30998260	C.631C>T	P.Arg211Cys	Het	-
	Chr18: 21123451	C.2213C>A	P.Ser738Ter	Het	1.16^{E-4}
	Chr18: 21152082	C.243G>C	P.Gln81His	Het	-
ATP 8B1	Chr18: 55351421	C.1477G>A	P.Val493Ile	Het	7.11^{E-4}
	Chr20: 10629285	C.1481A>G	P.Asn494Ser	Het	-
Trihydroxycoprostanoyl-CoA oxidase	Chr3: 58512313	C.1226G>A	P.Arg409His	Het	0.002
	Chr3: 58508322	C.1533A>G	P.Ile511Met	Het	5.78^{E-4}
SMase gene	Chr11: 6412666	C.371T>G	P.Leu124Arg	Het	3.47^{E-4}
	Chr10: 101604163	C.3928C>G	P.Arg1310Gly	Het	-
	Chr12: 100904723	C.247C>G	P.Pro83Ala	Het	5.78^{E-04}
	Chr10: 101590078	C.2643_2645delAGA	P.Glu881del	Het	-
ATP-binding cassette transporters	Chr2: 169830310	C.1349T>C	P.Met450Thr	Het	4.65^{E-4}
	Chr11: 5247153	C.316-197C>T		Het	-
ATP-binding cassette sub-family D member 3	Chr1: 94933490	C.262C>T	P.Leu88Phe	Het	0.001

	Chr18: 21136571	C.962C>T	P.Ala321Val	Het	3.67^{E-4}
	Chr20: 10623197	C.2511T>G	P.Asp837Glu	Het	-

ATP: Adenosine triphosphatase.

Table 3 The correlation between clinical characteristics and total serum bilirubin levels

	Hyperbilirubinemia		
Factors	**Total serum bilirubin ≥ 342 μmol/L**	**Total serum bilirubin < 342 μmol/L**	***P* value**
Gender			
Female	17	26	0.67
Male	18	36	
Exclusive breastfeeding			
Yes	31	42	0.027
No	4	20	
Gestational age (week)	38.9 ± 1.26	38.6 ± 1.43	0.170
Birth weight (kg)	3.19 ± 0.41	3.16 ± 0.41	0.38
P			
Yes	2	7	0.48
No	33	54	

Table 4 Gene mutation analysis between high and low total serum bilirubin groups

	Hyperbilirubinemia		
Mutation	**Total serum bilirubin ≥ 342 μmol/L**	**Total serum bilirubin < 342 μmol/L**	***P* value**
Uridine 5'-diphospho-glucuronosyltransferase 1A1			
G/A	32	11	0.32
C/T	4	3	
T/G	1	1	
Na+/taurocholate cotransporting polypeptide Ntcp			
C/T	6	7	NA
Heterozygous 851del4 mutation			
C.852_855delTATG	2	3	0.57
C.1638_1660dup	0	1	
G/A	0	1	
Adenosine triphosphatase 7B			
G/T	1	0	0.26
A/C	1	0	
G/A	0	1	
C/T	0	1	
Glucose-6-phosphate dehydrogenase			
G/T	1	2	0.32
G/A	1	0	
A/G	0	1	

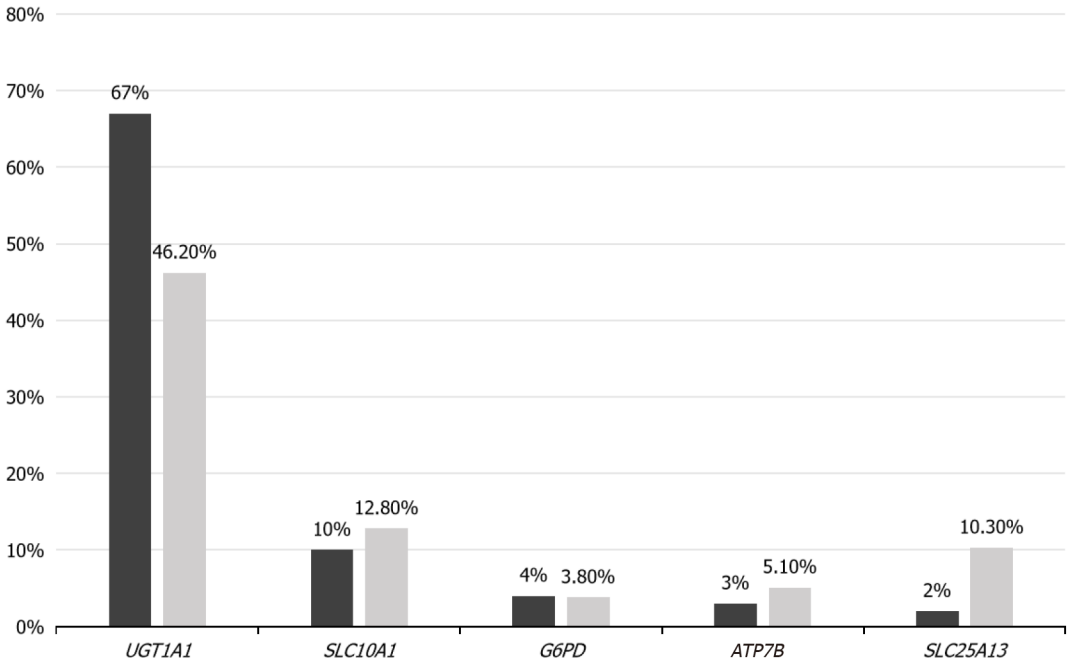

Figure 2 Analysis of the percentage of genes between the high and low total serum bilirubin groups. The blue bars represent the high-risk group with a total bilirubin level greater than 342 μmol/L. The orange bars correspond to the high-risk group with a total bilirubin level of less than 342 μmol/L. *UGT1A1*: *Uridine 5'-diphospho-glucuronosyltransferase 1A1*; *SLC10A1*: *Na+/taurocholate cotransporting polypeptide Ntcp*; *SLC25A13*: *Heterozygous 851del4 mutation*; *ATP7B* : *Adenosine triphosphatase 7B*; *G6PD*: *Glucose-6-phosphate dehydrogenase*.

SMPD1 gene encodes acid sphingomyelinase, which maintains lysosomal function by degrading lysosomal membranes in the lysosome. DJS is a rare genetic disorder caused by mutations in the *SMPD1* gene, resulting in impaired acid sphingomyelinase activity, obstruction of bilirubin excretion, and hyperbilirubinemia[37]. Identifying these rare mutations emphasizes the genetic variations of hyperbilirubinemia, where different gene mutations may lead to varying types of hyperbilirubinemia. Further investigation of these rare mutations will help us better understand the patho-genesis of hyperbilirubinemia and provide new clues and methods for diagnosing and treating related diseases[38].

Genetic screening is a valuable tool for identifying neonates who may be at increased risk for hyperbilirubinemia because of mutations or polymorphisms in genes involved in bilirubin metabolism, such as the *UGT1A1* gene and *SLCO1B1* gene[17]. Early identification of these genetic risk factors allows for the stratification of neonates into high-risk and low-risk categories. This stratified approach enables more tailored monitoring and intervention strategies[39,40]. High-risk infants can be prioritized for more frequent bilirubin level checks and earlier therapeutic interventions, such as phototherapy, thereby reducing the risk of severe complications such as phototherapy[41]. Moreover, low-risk infants may avoid unnecessary interventions, contributing to more efficient use of healthcare resources. Based on genetic screening, clinicians can develop more personalized treatment plans. By identifying susceptibility genes for hyperbilirubinemia, high-risk individuals who may develop severe hyperbilirubinemia can be identified early, allowing for more aggressive preventive and intervention measures[42]. This precision medicine strategy enhances the effectiveness of early interventions and reduces the incidence of severe complications.

This study has certain limitations. First, the limited number of cases may restrict the reliability and generalizability of the study results. Second, there are challenges in collecting clinical data on NH, including issues related to the quality and completeness of case data, which may affect the reliability of the study results. Additionally, differences in the number of samples available for analysis between different groups may also lead to experimental biases. Therefore, in the future, larger sample sizes and more comprehensive studies are needed to determine the correlation between genomic variations and the severity of hyperbilirubinemia.

CONCLUSION

There is a close association between hyperbilirubinemia and genetic mutations, where genetic mutations affect the normal functioning of bilirubin metabolism pathways, leading to hyperbilirubinemia. Research on genetic mutations related to hyperbilirubinemia not only helps us understand the pathogenesis of hyperbilirubinemia in depth but also provides new insights for its prevention, diagnosis, and treatment. Future studies should continue to explore the relationship between hyperbilirubinemia and genetic mutations to promote advancements in clinical practice, ultimately improving the prognosis of infants with hyperbilirubinemia.

FOOTNOTES

Author contributions: You JY conceived and designed the study; Xiong LY wrote the manuscript; Wu MF, Fan JS, Fu QH, and Qiu MH collected data and performed bioinformatics analysis; You JY and Xiong LY edited and revised the manuscript; all of the authors read and approved the final version of the manuscript to be published.

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REFERENCES

1 **Sarici SU**. Incidence and etiology of neonatal hyperbilirubinemia. *J Trop Pediatr* 2010; **56**: 128-129 [PMID: 19502601 DOI: 10.1093/tropej/fmp041]
2 **Mitra S**, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. *Br J Hosp Med (Lond)* 2017; **78**: 699-704 [PMID: 29240507 DOI: 10.12968/hmed.2017.78.12.699]
3 **Lee HY**, Ithnin A, Azma RZ, Othman A, Salvador A, Cheah FC. Glucose-6-Phosphate Dehydrogenase Deficiency and Neonatal Hyperbilirubinemia: Insights on Pathophysiology, Diagnosis, and Gene Variants in Disease Heterogeneity. *Front Pediatr* 2022; **10**: 875877 [PMID: 35685917 DOI: 10.3389/fped.2022.875877]
4 **Dennery PA**, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001; **344**: 581-590 [PMID: 11207355 DOI: 10.1056/NEJM200102223440807]
5 **Ip S**, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, Maisels MJ, Lau J; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. *Pediatrics* 2004; **114**: e130-e153 [PMID: 15231986 DOI: 10.1542/peds.114.1.e130]
6 **Huang MJ**, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res* 2004; **56**: 682-689 [PMID: 15319464 DOI: 10.1203/01.PDR.0000141846.37253.AF]
7 **Kaplan M**. Genetic interactions in the pathogenesis of neonatal hyperbilirubinemia: Gilbert's Syndrome and glucose-6-phosphate dehydrogenase deficiency. *J Perinatol* 2001; **21** Suppl 1: S30-34; discussion S35 [PMID: 11803413 DOI: 10.1038/sj.jp.7210630]
8 **Lin R**, Wang X, Wang Y, Zhang F, Wang Y, Fu W, Yu T, Li S, Xiong M, Huang W, Jin L. Association of polymorphisms in four bilirubin metabolism genes with serum bilirubin in three Asian populations. *Hum Mutat* 2009; **30**: 609-615 [PMID: 19243019 DOI: 10.1002/humu.20895]
9 **Long J**, Zhang S, Fang X, Luo Y, Liu J. Neonatal hyperbilirubinemia and Gly71Arg mutation of UGT1A1 gene: a Chinese case-control study followed by systematic review of existing evidence. *Acta Paediatr* 2011; **100**: 966-971 [PMID: 21272068 DOI: 10.1111/j.1651-2227.2011.02176.x]
10 **Yang Z**, Lin F, Xu JX, Yang H, Wu YH, Chen ZK, Xie H, Huang B, Lin WH, Wu JP, Ma YB, Li JD, Yang LY. UGT1A1*6 mutation associated with the occurrence and severity in infants with prolonged jaundice. *Front Pediatr* 2022; **10**: 1080212 [PMID: 36605758 DOI: 10.3389/fped.2022.1080212]
11 **Radlović N**. Hereditary hyperbilirubinemias. *Srp Arh Celok Lek* 2014; **142**: 257-260 [PMID: 24839786 DOI: 10.2298/sarh1404257r]
12 **Arnold JC**, Otto G, Kraus T, Kommerell B, Theilmann L. Gilbert's syndrome--a possible cause of hyperbilirubinemia after orthotopic liver transplantation. *J Hepatol* 1992; **14**: 404 [PMID: 1500702 DOI: 10.1016/0168-8278(92)90191-q]
13 **Tomerak RH**, Helal NF, Shaker OG, Yousef MA. Association between the Specific UGT1A1 Promoter Sequence Variant (c-3279T>G) and Unconjugated Neonatal Hyperbilirubinemia. *J Trop Pediatr* 2016; **62**: 457-463 [PMID: 27318112 DOI: 10.1093/tropej/fmw031]
14 **Abdellaoui N**, Abdelmoula B, Abdelhedi R, Kharrat N, Tabebi M, Rebai A, Bouayed Abdelmoula N. Novel combined UGT1A1 mutations in Crigler Najjar Syndrome type I. *J Clin Lab Anal* 2022; **36**: e24482 [PMID: 35527687 DOI: 10.1002/jcla.24482]
15 **Liu J**, Long J, Zhang S, Fang X, Luo Y. Polymorphic variants of SLCO1B1 in neonatal hyperbilirubinemia in China. *Ital J Pediatr* 2013; **39**: 49 [PMID: 24090270 DOI: 10.1186/1824-7288-39-49]

16 **Wang H**, Shu S, Chen C, Huang Z, Wang D. Novel mutations in the SLC25A13 gene in a patient with NICCD and severe manifestations. *J Pediatr Endocrinol Metab* 2015; **28**: 471-475 [PMID: 25381944 DOI: 10.1515/jpem-2014-0278]

17 **Fan J**, He HY, Li HH, Wu PL, Tang L, Deng BY, Dong WH, Wang JH. Associations between UGT1A1, SLCO1B1, SLCO1B3, BLVRA and HMOX1 polymorphisms and susceptibility to neonatal severe hyperbilirubinemia in Chinese Han population. *BMC Pediatr* 2024; **24**: 82 [PMID: 38279097 DOI: 10.1186/s12887-024-04537-0]

18 **Abbey P**, Kandasamy D, Naranje P. Neonatal Jaundice. *Indian J Pediatr* 2019; **86**: 830-841 [PMID: 30790186 DOI: 10.1007/s12098-019-02856-0]

19 **Zhou J**, Yang C, Zhu W, Chen S, Zeng Y, Wang J, Zhao H, Chen Y, Lin F. Identification of Genetic Risk Factors for Neonatal Hyperbilirubinemia in Fujian Province, Southeastern China: A Case-Control Study. *Biomed Res Int* 2018; **2018**: 7803175 [PMID: 30298137 DOI: 10.1155/2018/7803175]

20 **Cozzi L**, Nuti F, Degrassi I, Civeriati D, Paolella G, Nebbia G. Gilbert or Crigler-Najjar syndrome? Neonatal severe unconjugated hyperbilirubinemia with P364L UGT1A1 homozygosity. *Ital J Pediatr* 2022; **48**: 59 [PMID: 35436954 DOI: 10.1186/s13052-022-01251-4]

21 **Maruo Y**, Nakahara S, Yanagi T, Nomura A, Mimura Y, Matsui K, Sato H, Takeuchi Y. Genotype of UGT1A1 and phenotype correlation between Crigler-Najjar syndrome type II and Gilbert syndrome. *J Gastroenterol Hepatol* 2016; **31**: 403-408 [PMID: 26250421 DOI: 10.1111/jgh.13071]

22 **Kraemer D**, Scheurlen M. [Gilbert disease and type I and II Crigler-Najjar syndrome due to mutations in the same UGT1A1 gene locus]. *Med Klin (Munich)* 2002; **97**: 528-532 [PMID: 12371080 DOI: 10.1007/s00063-002-1180-6]

23 **Kim JJ**, Oh J, Kim Y, Lee KA. Genetic Spectrum of UGT1A1 in Korean Patients with Unconjugated Hyperbilirubinemia. *Ann Lab Med* 2020; **40**: 281-283 [PMID: 31858773 DOI: 10.3343/alm.2020.40.3.281]

24 **Mazur-Kominek K**, Romanowski T, Bielawski K, Kiełbratowska B, Preis K, Domżalska-Popadiuk I, Słomińska-Frączek M, Sznurkowska K, Renke J, Plata-Nazar K, Śledzińska K, Sikorska-Wiśniewska G, Góra-Gębka M, Liberek A. Association between uridin diphosphate glucuronosylotransferase 1A1 (UGT1A1) gene polymorphism and neonatal hyperbilirubinemia. *Acta Biochim Pol* 2017; **64**: 351-356 [PMID: 28399191 DOI: 10.18388/abp.2016_1450]

25 **Wang J**, Tang L, Xu A, Zhang S, Jiang H, Pei P, Li H, Lv T, Yang Y, Qian N, Naidu K, Yang W. Identification of mutations in the ATP7B gene in 14 Wilson disease children: Case series. *Medicine (Baltimore)* 2021; **100**: e25463 [PMID: 33879678 DOI: 10.1097/MD.0000000000025463]

26 **Balashova MS**, Tuluzanovskaya IG, Glotov OS, Glotov AS, Barbitoff YA, Fedyakov MA, Alaverdian DA, Ivashchenko TE, Romanova OV, Sarana AM, Scherbak SG, Baranov VS, Filimonov MI, Skalny AV, Zhuchenko NA, Ignatova TM, Asanov AY. The spectrum of pathogenic variants of the ATP7B gene in Wilson disease in the Russian Federation. *J Trace Elem Med Biol* 2020; **59**: 126420 [PMID: 31708252 DOI: 10.1016/j.jtemb.2019.126420]

27 **Lucena-Valera A**, Ruz-Zafra P, Ampuero J. Wilson's disease: overview. *Med Clin (Barc)* 2023; **160**: 261-267 [PMID: 36697289 DOI: 10.1016/j.medcli.2022.12.016]

28 **Liu H**, Liu W, Tang X, Wang T. Association between G6PD deficiency and hyperbilirubinemia in neonates: a meta-analysis. *Pediatr Hematol Oncol* 2015; **32**: 92-98 [PMID: 24684295 DOI: 10.3109/08880018.2014.887803]

29 **Nannelli C**, Bosman A, Cunningham J, Dugué PA, Luzzatto L. Genetic variants causing G6PD deficiency: Clinical and biochemical data support new WHO classification. *Br J Haematol* 2023; **202**: 1024-1032 [PMID: 37415281 DOI: 10.1111/bjh.18943]

30 **Olusanya BO**, Emokpae AA, Zamora TG, Slusher TM. Addressing the burden of neonatal hyperbilirubinaemia in countries with significant glucose-6-phosphate dehydrogenase deficiency. *Acta Paediatr* 2014; **103**: 1102-1109 [PMID: 24990658 DOI: 10.1111/apa.12735]

31 **Isa HM**, Mohamed MS, Mohamed AM, Abdulla A, Abdulla F. Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency. *Korean J Pediatr* 2017; **60**: 106-111 [PMID: 28461823 DOI: 10.3345/kjp.2017.60.4.106]

32 **Huang CS**, Chang PF, Huang MJ, Chen ES, Chen WC. Glucose-6-phosphate dehydrogenase deficiency, the UDP-glucuronosyl transferase 1A1 gene, and neonatal hyperbilirubinemia. *Gastroenterology* 2002; **123**: 127-133 [PMID: 12105841 DOI: 10.1053/gast.2002.34173]

33 **Wang M**, Chen T, Chen R, Bi Z, Peng J, Shao Q, Li J. Neonatal jaundice caused by compound mutations of SLC10A1 and a novel UGT1A1 gene. *Clin Res Hepatol Gastroenterol* 2024; **48**: 102340 [PMID: 38588793 DOI: 10.1016/j.clinre.2024.102340]

34 **Ottosson A**, Edvinsson L, Sjögren A, Löwenhielm P. Digoxin, magnesium, and potassium levels in a forensic autopsy material of sudden death from ischemic heart disease. *Z Rechtsmed* 1988; **101**: 27-36 [PMID: 3218385 DOI: 10.1186/s13023-020-1346-4]

35 **Jiang H**, Zhou JY, Li J, Li DZ. Unstable Hemoglobin Variants: The Need for Clinical Vigilance in Infants with Congenital Jaundice. *Hemoglobin* 2019; **43**: 60-62 [PMID: 31092072 DOI: 10.1080/03630269.2019.1582429]

36 **Vilarinho S**, Sari S, Mazzacuva F, Bilgüvar K, Esendagli-Yilmaz G, Jain D, Akyol G, Dalgiç B, Günel M, Clayton PT, Lifton RP. ACOX2 deficiency: A disorder of bile acid synthesis with transaminase elevation, liver fibrosis, ataxia, and cognitive impairment. *Proc Natl Acad Sci U S A* 2016; **113**: 11289-11293 [PMID: 27647924 DOI: 10.1073/pnas.1613228113]

37 **Grasko Y**, Hooper AJ, Burnett JR, Watts GF. A novel missense SMPD1 gene mutation, T460P, and clinical findings in a patient with Niemann-Pick disease type B presenting to a lipid disorders clinic. *Ann Clin Biochem* 2014; **51**: 615-618 [PMID: 24643943 DOI: 10.1177/0004563214527067]

38 **Xia H**, Zhang Z, Luo C, Wei K, Li X, Mu X, Duan M, Zhu C, Jin L, He X, Tang L, Hu L, Guan Y, Lam DCC, Yang J. MultiPrime: A reliable and efficient tool for targeted next-generation sequencing. *Imeta* 2023; **2**: e143 [PMID: 38868227 DOI: 10.1002/imt2.143]

39 **Yang H**, Li H, Xia Q, Dai W, Li X, Liu Y, Nie J, Yang F, Sun Y, Feng L, Yang L. UGT1A1 variants in Chinese Uighur and Han newborns and its correlation with neonatal hyperbilirubinemia. *PLoS One* 2022; **17**: e0279059 [PMID: 36520959 DOI: 10.1371/journal.pone.0279059]

40 **Cui Z**, Shen W, Sun X, Li Y, Liu Y, Sun Z. Developing and evaluating a predictive model for neonatal hyperbilirubinemia based on UGT1A1 gene polymorphism and clinical risk factors. *Front Pediatr* 2024; **12**: 1345602 [PMID: 38487473 DOI: 10.3389/fped.2024.1345602]

41 **Bhutani VK**; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2011; **128**: e1046-e1052 [PMID: 21949150 DOI: 10.1542/peds.2011-1494]

42 **Xu JX**, Lin F, Wu YH, Chen ZK, Ma YB, Yang LY. Etiology analysis for term newborns with severe hyperbilirubinemia in eastern Guangdong of China. *World J Clin Cases* 2023; **11**: 2443-2451 [PMID: 37123300 DOI: 10.12998/wjcc.v11.i11.2443]

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