Association of Idiopathic Infant Jaundice with Genetic Variation in Northern Guangdong

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Abstract

Abstract Objective To investigate the genetic factors of unexplained infant jaundice in the Northern Guangdong region and evaluate the importance of jaundice-related genetic testing. Methods Infants with unexplained jaundice who presented to the Neonatology and Pediatrics Departments of Yuebei People's Hospital from January 2022 to July 2024 were selected as study subjects. Using high-throughput sequencing technology based on target gene capture, the exon regions of 161 jaundice-related genes were detected, and statistical analysis was performed on the results. Results A total of 56 pediatric patients with unexplained infant jaundice were included in the study, among whom 28 cases (50%) showed positive results, involving 6 diseases: 7 cases (12.5%) of Gilbert syndrome, 8 cases (14.2%) of sodium taurocholate cotransporting polypeptide deficiency, 4 cases (7.1%) of glucose-6-phosphate dehydrogenase deficiency, 4 cases (7.1%) of Gilbert syndrome combined with glucose-6-phosphate dehydrogenase deficiency, 1 case (1.8%) of Citrin deficiency combined with glucose-6-phosphate dehydrogenase deficiency, 1 case (1.8%) of Dubin-Johnson syndrome combined with Rotor type hyperbilirubinemia, 2 cases (3.6%) of sodium taurocholate cotransporting polypeptide deficiency combined with glucose-6-phosphate dehydrogenase deficiency, and 1 case (1.8%) of sodium taurocholate cotransporting polypeptide deficiency combined with Gilbert syndrome. Among the 56 pediatric patients, 55 cases (98.2%) carried one or more gene variant loci, and only 1 case (1.8%) had no variants detected. The five high-frequency variant loci were UGT1A1 gene c.211G>A and c.-53-52TA[81 locus, G6PD gene c.1376G>T, c.871G>A, and c.1388G>A loci, and SLC10A1 gene c.800C>T locus. Conclusion Genetic factors are important contributors to the pathogenesis of unexplained infant jaundice in the Northern Guangdong region. The common pathogenic genes are the UGTIAI gene, G6PD gene, and SLC10A1 gene, with high-frequency carrier loci present in the population. Genetic testing for infants with unexplained jaundice has important clinical significance.

Full Text

Study on the Correlation Between Unexplained Infant Jaundice and Genetic Variants in Northern Guangdong Province

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Abstract

Objective: To explore the genetic profile of unexplained infant jaundice in northern Guangdong Province and assess the importance of jaundice-related gene screening.

Methods: Infants with unexplained jaundice attending the neonatology and pediatrics departments of Yuebei People's Hospital from January 2022 to July 2024 were selected as study subjects. The exon regions of 161 jaundice-related genes were detected using targeted capture and high-throughput sequencing technology, and the results were statistically analyzed.

Results: A total of 56 infants with unexplained jaundice were included in the study. Positive results were identified in 28 cases (50%), involving six diseases: Gilbert syndrome in 7 cases (12.5%), sodium taurocholate co-transporting polypeptide (NTCP) deficiency in 8 cases (14.2%), glucose-6-phosphate dehydrogenase (G6PD) deficiency in 4 cases (7.1%), combined Gilbert syndrome and G6PD deficiency in 4 cases (7.1%), citrin deficiency combined with G6PD deficiency in 1 case (1.8%), Dubin-Johnson syndrome combined with Rotor syndrome in 1 case (1.8%), NTCP deficiency combined with G6PD deficiency in 2 cases (3.6%), and NTCP deficiency combined with Gilbert syndrome in 1 case (1.8%). Among the 56 infants, 55 cases (98.2%) carried one or more gene mutation sites, with only 1 case (1.8%) showing no mutation sites. Five high-frequency mutation sites were identified: UGT1A1 gene c.211G>A and c.-53-52TA[8] sites, G6PD gene c.1376G>T, c.871G>A, and c.1388G>A sites, and SLC10A1 gene c.800C>T site.

Conclusion: Genetic factors are significant contributors to the development of unexplained infant jaundice in northern Guangdong. Common pathogenic

genes include UGT1A1, G6PD, and SLC10A1, with high-frequency mutation sites present in the population. Conducting genetic screening for infants with unexplained jaundice has important clinical significance.

Keywords: Neonate; Infant; Jaundice; Hyperbilirubinemia; Gene

Introduction

Jaundice is a common clinical problem in the neonatal period, manifested by abnormal elevation of serum bilirubin levels. It is estimated that over 80% of newborns develop visible jaundice within the first week after birth, with approximately 10% requiring medical intervention [1]. Hyperbilirubinemia not only affects short-term neonatal health but may also impact long-term neurodevelopment, particularly when serum bilirubin levels exceed certain thresholds, potentially leading to serious complications such as bilirubin encephalopathy. Persistent hyperbilirubinemia can affect various aspects of systemic immunity [2]. The pathogenesis of hyperbilirubinemia involves multiple factors, including genetic factors [3]. While previous literature has primarily focused on single genetic jaundice diseases, few studies have simultaneously investigated over 100 jaundice-related genes.

This study employed next-generation sequencing technology to detect 161 jaundice-related genes in infants with unexplained jaundice in northern Guangdong, aiming to understand the genetic factors and variant sites of related genes in this region, thereby providing a theoretical basis for genetic screening in jaundice patients.

Methods

1.1 Study Subjects We selected infants with unexplained jaundice who visited the neonatology and pediatrics departments of Yuebei People's Hospital from January 2022 to July 2024. Inclusion criteria were: (1) infant age 0-1 year; (2) meeting diagnostic criteria for infant jaundice based on the hour-specific serum bilirubin nomogram for newborns in the United States [1]; prolonged jaundice (persisting beyond 2 weeks in term infants or 4 weeks in preterm infants) or recurrent jaundice with poor treatment response, accompanied by persistent hyperbilirubinemia; and family history of adverse jaundice outcomes, such as exchange transfusion or bilirubin encephalopathy. (3) parental consent for jaundice-related genetic testing. Exclusion criteria included infectious diseases, maternal-fetal blood group incompatibility hemolytic disease, or other jaundice with clear etiology. This study was approved by the Ethics Committee of Yuebei People's Hospital (approval number: KY-2022-018), and informed consent was obtained from all parents.

1.2.1 Gene Selection Through literature review and expert consultation, we included 161 genes associated with over 200 types of jaundice-related hereditary diseases. The diseases encompassed all conditions where jaundice was either a primary or secondary manifestation. The tested genes mainly included SLC10A1, UGT1A1, G6PD, SPTA1, PIEZO1, ATP7B, MYO5B, SMPD1, ABCC2, CFTR, SLC25A13, SLCO1B1, AGL, EPB41, HBB, NEK8, NOTCH2, SPTB, among others.

1.2.2 Gene Sequencing High-throughput sequencing was performed with a sequencing depth of over 200×. Peripheral blood (2 ml each) was collected from infants and their parents using EDTA anticoagulant tubes. Genomic DNA was extracted, fragmented, followed by library construction, capture sequencing, and result analysis. Positive variants, short fragment deletions, or insertions identified by high-throughput sequencing were further analyzed through family verification using Sanger sequencing. Results were interpreted and pathogenicity of variants was determined according to the ACMG guidelines [4].

1.3 Statistical Analysis Data were analyzed using SPSS 22.0 software. Measurement data were expressed as mean ± standard deviation; normally distributed measurement data were analyzed using t-tests, while non-normally distributed data were analyzed using rank-sum tests. Count data were expressed as case numbers and percentages.

Results

2.1 General Findings A total of 56 infants with unexplained jaundice were included in this study, including 36 males (64.2%) and 20 females (35.7%). The oldest infant was 236 days old, the youngest was 2 days old, with a median age of 40.50 (23.75, 60.75) days.

Among the 56 infants, 28 cases (50%) were diagnosed with genetic diseases, including 18 males (64.2%) and 10 females (35.7%). The positive rate was significantly higher in males than in females, with statistical significance ($P<0.01$). Positive cases involved six diseases: Gilbert syndrome (GS) in 7 cases (12.5%), glucose-6-phosphate dehydrogenase (G6PD) deficiency in 4 cases (7.1%), sodium-taurocholate cotransporting polypeptide (NTCP) deficiency in 8 cases (14.2%), combined Gilbert syndrome and G6PD deficiency in 4 cases (7.1%), citrin deficiency combined with G6PD deficiency in 1 case (1.8%), Dubin-Johnson syndrome combined with Rotor syndrome in 1 case (1.8%), NTCP deficiency combined with G6PD deficiency in 2 cases (3.6%), and NTCP deficiency combined with Gilbert syndrome in 1 case (1.8%). The age of positive cases was 40.5 (16.25, 65.5) days, while negative cases was 40.5 (27.75, 59.25) days. There was no statistically significant difference between the two groups ($z=0.802$, $p=0.541$).

Among the 161 tested genes, variants were found in 96 genes. The UGT1A1 gene detected five variants: c.211G>A, c.-53_-52TA[8], c.1046C>T, c.1091C>T, and c.686C>A (overall carrier rate 40.2%). The SLC10A1 gene detected three variants: c.800C>T, c.263T>C, and c.682_{683del} (overall carrier rate 25.0%). The G6PD gene detected five variants: c.1376G>T, c.871G>A, c.1388G>A, c.1478G>A, and c.95A>G (overall carrier rate 10.7%). High-frequency variant sites (carrier rate >1%) included six sites: UGT1A1 gene c.211G>A and c.-53-52TA[8] sites, SLC10A1 gene c.800C>T site, and G6PD gene c.1376G>T, c.871G>A, and c.1388G>A sites, as shown in Table 1 .

Table 1 High-frequency variant sites and carrier rates in 56 infants

Gene	Variant	Amino Acid Change	Carrier Rate (%)
UGT1A1	c.211G>A	p.Gly71Arg	
UGT1A1	c.-53_-52TA[8]		
SLC10A1	c.800C>T	p.Ser267Phe	
G6PD	c.1376G>T	p.Arg45Leu	
G6PD	c.871G>A	p.Val291Met	
G6PD	c.1388G>A	p.Arg463His	

Discussion

The primary harm of jaundice is the neurotoxic effect of bilirubin, an extremely complex and serious problem that can lead to bilirubin encephalopathy and bilirubin-induced neurologic dysfunction (BIND) [5]. The etiology of infant jaundice and factors contributing to its persistence are complex and diverse, involving physiological, genetic, environmental, and feeding factors, and may also be related to climatic factors such as temperature, rainfall, atmospheric pressure, cloud cover, and sunshine duration [6]. Both hereditary diseases and variants in bilirubin metabolism-related genes [7] can cause increased bilirubin levels and jaundice. Genetic factors are important contributors to jaundice pathogenesis. For infants with unexplained jaundice, the possibility of genetic factors should be considered, and early genetic testing can help clinicians further clarify the etiology [8]. In this study, a genetic cause of jaundice was identified in half of the infants with unexplained jaundice, which is higher than the average positive rate in Guangdong Province (42%) [8].

This study identified six jaundice-related genetic diseases, with the most common being Gilbert syndrome, G6PD deficiency, and NTCP deficiency. Gilbert syndrome is caused by reduced activity of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), leading to decreased hepatic clearance of bilirubin and elevated serum bilirubin levels [9]. Variants in the UGT1A1 gene can induce quantitative reductions in UGT1A1 enzyme activity to varying degrees. The c.211G>A (p.Gly71Arg) variant is a common hypofunctional vari-

ant in Asian populations, with homozygous mutations reducing enzyme activity to (32.2$±1.6)±$2.5)% of normal [10]. The carrier rate of the UGT1A1 gene c.211G>A variant in the jaundice patient population in northern Guangdong was 31.25%, comparable to rates in Guangdong Province [8] (32.3%) and Japanese patients [10] (32.0%). The TATA box insertion variant (c.-53_-52TA[8]) is another common hypofunctional variant located in the promoter region upstream of the first exon of the UGT1A1 gene. The repeated base pairs reduce the binding affinity of binding proteins to the TATA box, decreasing gene expression and thereby reducing UGT1A1 enzyme activity. Homozygous c.-53_-52TA[8] variants can reduce UGT1A1 enzyme activity in liver tissue homogenates by 52%, while heterozygous variants can reduce activity by 37% [11]. The carrier rate of the c.-53_-52TA[8] variant in northern Guangdong jaundice patients was 6.25%, lower than other reported rates of 9.0%-16.0% [12]. Due to reduced enzyme activity, bilirubin clearance is impaired, causing delayed resolution of jaundice, and some infants with heterozygous variants also exhibit slow jaundice resolution clinically. BIND may also result from reduced UGT1A1 enzyme activity, which impedes bilirubin metabolism, leading to accumulation of unconjugated bilirubin in blood, ultimately crossing the blood-brain barrier and depositing in the basal ganglia, thereby causing neurological injury [13].

NTCP deficiency is a novel inherited bile acid metabolism disorder caused by biallelic variants in the solute carrier family 10 member 1 (SLC10A1) gene. In 2015, Vaz et al. [14] reported the first NTCP deficiency patient, describing the clinical manifestations of such patients. Our research group [15] reported the youngest NTCP deficiency patient in 2017 and proposed that NTCP deficiency causes neonatal indirect hyperbilirubinemia. Subsequent studies have confirmed that 92.31% of NTCP deficiency patients develop neonatal indirect hyperbilirubinemia, with longer jaundice resolution times, and indirect hyperbilirubinemia resolves by 2.5 months after birth [16]. The SLC10A1 gene c.800C>T variant is a high-frequency variant site in northern Guangdong, with a carrier rate of 23.21% in jaundice patients, slightly lower than the carrier rate in Guangdong Province [8] of 29.6%.

G6PD deficiency is an X-linked incompletely dominant inherited red blood cell enzyme defect and an important cause of pathological jaundice in newborns. Our study found that G6PD gene c.1376G>T, c.871G>A, and c.1388G>A were high-frequency sites, which differ from the high-frequency sites in Guangdong Province [8]. This may be due to the relatively large Hakka population in northern Guangdong, as c.1376G>T and c.1388G>A are high-frequency variants in the Hakka population [17].

This study identified nine infants with two concurrent hereditary jaundice diseases, and such multiple combinations may make jaundice resolution more difficult. This study also found significantly more male than female infants, and some studies have shown that male newborns have a higher probability of developing jaundice than female newborns, which may be related to sex-related physiological differences, though the specific mechanisms remain unclear [18].

In summary, this project utilized next-generation sequencing technology to detect jaundice-related genes in infants with unexplained jaundice in northern Guangdong. The results reveal that genetic factors play a key role in the pathogenesis of unexplained infant jaundice in this region. Common pathogenic genes include UGT1A1, G6PD, and SLC10A1, and these genes have high-frequency carrier sites in the population. Therefore, implementing genetic testing for infants with unexplained jaundice has significant clinical importance.

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Note: Figure translations are in progress. See original paper for figures.