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Original Article

UGT1A1 Mutations and Clinical Features in Hereditary Unconjugated Hyperbilirubinemia: A Chinese Cohort Study

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Abstract

Background and Aims: Hereditary unconjugated hyperbilirubinemia is most often caused by *UGT1A1* mutations and includes Gilbert syndrome, Crigler-Najjar syndrome types I and II, and prolonged neonatal unconjugated hyperbilirubinemia. In Chinese patients, however, the variant spectrum and its clinical relevance remain incompletely characterized. We therefore aimed to define the *UGT1A1* variant profile and assess genotype-phenotype correlations in a Chinese cohort.

Methods: We retrospectively analyzed 163 patients from the Affiliated Hospital of Hangzhou Normal University (2016–2025). Sanger sequencing of *UGT1A1* was performed, covering the enhancer, promoter, and all coding regions. The association between variant types and total serum bilirubin levels was evaluated.

Results: *UGT1A1* variants were detected in 156 patients (95.7%), covering 19 distinct variants, including two previously unreported candidate variants (c.272C>G and c.556delinsAATGG). The most common alleles were c.-3279T>G (allele frequency: 0.68), (TA)6>(TA)7 (0.49), and p.G71R (0.23). Coding-region variants were observed more frequently in the Crigler-Najjar syndrome type II group than in the Gilbert syndrome group ($P < 0.05$), while total bilirubin levels were higher with both coding and non-coding variants than with non-coding variants alone (adjusted $P < 0.05$ by Dunn's test), although median-regression confidence intervals included zero.

Conclusions: *UGT1A1* genotyping yields a variant detection rate of 95.7% and identifies two previously unreported candidate variants in this Chinese cohort. Exploratory analyses suggest higher bilirubin levels in patients carrying both coding and non-coding variants than in those carrying non-coding variants alone, warranting confirmation in larger cohorts.

Introduction

Uridine 5′-diphospho-glucuronosyltransferases are enzymes that glucuronidate endogenous and exogenous compounds. UGT1A1, encoded by the *UGT1A1* gene (NM_000463.3) on chromosome 2q37.1, is central to bilirubin metabolism.[1,2] In hepatocytes, UGT1A1 conjugates unconjugated bilirubin with glucuronic acid to generate water-soluble conjugated bilirubin for biliary excretion. Variants in the phenobarbital-responsive enhancer module (PBREM), promoter, or coding region can reduce UGT1A1 activity and cause hereditary unconjugated hyperbilirubinemia, including Gilbert syndrome (GS), Crigler-Najjar syndrome type I, Crigler-Najjar syndrome type II (CNS-II), and prolonged neonatal unconjugated hyperbilirubinemia.[3-5]

Keywords: Hereditary unconjugated hyperbilirubinemia; Gilbert syndrome; Crigler-Najjar syndrome type II; Uridine diphosphate glucuronosyltransferase 1A1; Genetic variation; Genotype-phenotype correlation.
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GS was first reported in 1901 and usually presents as intermittent mild unconjugated hyperbilirubinemia without hemolysis or intrinsic liver disease.[6,7] It is seen most often in adolescents and young adults, with reported prevalence ranging from 3% to 8.6% and a male predominance (male-to-female ratio approximately 2.7:1).[8] Patients typically retain about 30% of normal UGT1A1 activity, and serum bilirubin is usually mildly elevated, mainly in the unconjugated fraction (17.1–85.5 μmol/L). Jaundice is often subtle, but may become more apparent during infection, fasting, physical stress, pregnancy, or surgery.[9,10]

Crigler-Najjar syndrome, first reported in 1952, represents the severe end of hereditary unconjugated hyperbilirubinemia.[11] Arias *et al.* separated Crigler-Najjar syndrome into types I and II according to bilirubin levels and response to phenobarbital.[12,13] Crigler-Najjar syndrome type I reflects near-complete loss of UGT1A1 activity, with total bilirubin (TB) levels of 342–684 μmol/L and a high risk of kernicterus; liver transplantation is the only definitive treatment.[14] In CNS-II, residual UGT1A1 activity is usually about 10%, bilirubin levels are typically 102.6–342 μmol/L, and phenobarbital response is often favorable.[15,16] However, the biochemical boundary between GS and CNS-II is not absolute. Published genotype–phenotype studies suggest that serum bilirubin concentrations form a continuous spectrum and have described patients with intermediate biochemical presentations.[10,13,15] Accordingly, in the present study, a study-defined intermediate bilirubin stratum was operationally defined as a serum total bilirubin concentration of 85.6–102.5 μmol/L. This category was used solely for descriptive and exploratory analyses and was not considered an independent or universally recognized diagnostic entity. Because bilirubin concentration alone may not reliably distinguish GS from CNS-II, *UGT1A1* genotyping may provide complementary diagnostic information. Genotype–phenotype data in Chinese patients remain relatively limited, and many variant databases are weighted toward non-East Asian populations. Cohort-level data from this population may therefore help refine population-specific variant profiles and genotype–phenotype correlations.

Here, we examined the *UGT1A1* variant spectrum in Chinese patients with hereditary unconjugated hyperbilirubinemia and assessed how variant features related to clinical phenotype. We also evaluated the role of *UGT1A1* genotyping in distinguishing GS, intermediate phenotypes, and CNS-II.

Methods

Study design and setting

We performed a retrospective observational cohort study at the Affiliated Hospital of Hangzhou Normal University. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and the completed checklist is provided as supplementary material.

We retrospectively reviewed 163 patients who were evaluated for unconjugated hyperbilirubinemia between 2016 and 2025. Enrollment followed predefined inclusion and exclusion criteria. All participants had complete clinical data and provided written informed consent. Exclusion criteria were active hepatitis, documented hemolytic disorders, bilirubin elevation attributable to alcohol- or drug-induced liver injury, and incomplete or ambiguous data. *UGT1A1* variants were detected in 156 patients, who constituted the analytic cohort for the variant-distribution and genotype–bilirubin analyses. The seven patients without detected *UGT1A1* variants were excluded from these analyses.

For phenotypic stratification, baseline serum total bilirubin was defined as the value measured at the first visit to our hospital, before any treatment specifically directed at hyperbilirubinemia. The 156 patients were categorized into a GS-range stratum (17.1–85.5 μmol/L), a study-defined intermediate bilirubin stratum (85.6–102.5 μmol/L), and a CNS-II-range stratum (102.6–342 μmol/L). These cutoffs were informed by published clinical ranges: most patients with GS have TB concentrations below 85.5 μmol/L, whereas concentrations of 102.6–342 μmol/L are commonly reported for CNS-II.[13,17,18] The intervening range was retained as an operational category for descriptive and exploratory analyses, rather than as an independent diagnostic entity. These biochemical strata were not intended to establish a diagnosis of GS or CNS-II on the basis of a single TB measurement. The study was approved by the Institutional Review Board of the Affiliated Hospital of Hangzhou Normal University (No. 2024(E2)-KS-051).

Blood sample collection and testing

Venous blood samples were collected from all participants after an overnight fast. For complete blood count analysis, including white blood cells, red blood cells, hemoglobin, platelets, and reticulocytes, 2 mL of peripheral blood was drawn into ethylenediaminetetraacetic acid (EDTA)-containing tubes. An additional 2–4 mL of blood was collected in a clot activator-containing tube, and serum was separated for liver function tests. These tests measured total bilirubin (TB), direct bilirubin, indirect bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase. All analyses were performed using a Hitachi 7180 fully automated biochemical analyzer (Tokyo, Japan) following standard protocols in the Department of Laboratory Medicine at the Affiliated Hospital of Hangzhou Normal University.

Genetic mutation analysis

Peripheral blood samples (2–4 mL) were collected from all participants in EDTA-containing tubes and stored at −80°C. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood using the Blood Genome DNA Extraction Kit (TIANGEN Biotech, Beijing, China) according to the manufacturer's instructions. Primers were designed using Primer Premier 5.0 (PREMIER Biosoft, Palo Alto, CA, USA). The PBREM, promoter, all five coding exons, and primer-covered flanking splice-junction regions of *UGT1A1* were amplified by polymerase chain reaction and subjected to Sanger sequencing. The target regions and sequencing approach were based on the method described by Mi *et al.*[19] Primer sequences are provided in Supplementary Table 1. Amplification and sequencing were performed by Sangon Biotech (Shanghai, China). Sequence chromatograms were inspected using Chromas v2.6.4 (Technelysium Pty Ltd., South Brisbane, Australia) and aligned to the *UGT1A1* RefSeq transcript NM_000463.3.

In silico prediction and database annotation

The potential functional effects of the two previously unreported candidate variants were evaluated *in silico*. Both variants were

assessed using MutationTaster2 (GRCh37; https://www.mutationtaster.org)[20] and the Rare Disease Data Center (RDDC) Pathogenicity Predictor (https://rddc.tsinghua-gd.org/tool/pathogenicity).[21] The missense variant c.272C>G (p.Ser91Cys) was additionally evaluated using the SIFT web server (https://sift.bii.a-star.edu.sg),[22] PolyPhen-2 version 2 (HumVar model; http://genetics.bwh.harvard.edu/pph2),[23] and precomputed REVEL scores (https://sites.google.com/site/revelgenomics).[24] SIFT scores ≤0.05 were considered deleterious and scores >0.05 tolerated. PolyPhen-2 HumVar scores were categorized as benign (0–0.446), possibly damaging (0.447–0.908), or probably damaging (0.909–1.000). REVEL scores range from 0 to 1, with higher scores indicating greater predicted pathogenicity. MutationTaster2 and RDDC scores and categorical outputs were recorded as returned by the web servers. *In silico* predictions were considered supportive evidence only and not functional validation.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 (IBM), and statistical charts were generated using GraphPad Prism 9.5. The normality of continuous variables was tested. Normally distributed data are expressed as mean ± standard deviation, while non-normally distributed data are reported as medians and interquartile ranges (IQRs). When comparing two sets of normally distributed variables, an independent-samples t-test was used; one-way analysis of variance was applied to comparisons among three or more groups. For unequal variances, Tamhane's T2 test was used; for equal variances, the least significant difference test was used. Non-normally distributed data were compared using the Mann–Whitney U test (two groups) or the Kruskal–Wallis H test (three or more groups). When the Kruskal–Wallis test indicated an overall difference, pairwise comparisons were performed using Dunn's multiple-comparisons test, with adjusted *P* values reported. Categorical variables were analyzed using chi-square tests. To estimate effect sizes for differences in total bilirubin among the three variant-location groups, univariable median regression ($\tau = 0.50$) was performed, with β coefficients reported as unadjusted, unstandardized differences in conditional median total bilirubin (μmol/L), together with 95% confidence intervals and *P* values. A *P* value <0.05 was considered statistically significant.

Results

Patients and clinical characteristics

This study included 163 patients with unconjugated hyperbilirubinemia. *UGT1A1* variants were identified in 156 patients (95.7%). The cohort comprised 120 males (76.9%) with a median age of 34 years (IQR: 24–40 years) and 36 females (23.1%) with a median age of 39 years (IQR: 28–51 years), yielding a male-to-female ratio of 3.3:1. Chi-square analysis indicated a significant difference in sex distribution ($P < 0.05$), while the age difference between sexes was not statistically significant ($P = 0.057$; Fig. 1A). TB levels across the cohort ranged from 20.2 to 301.2 μmol/L, with a median of 47.95 μmol/L. The median TB was 48.7 μmol/L (IQR: 39.7–64.9 μmol/L) in males and 45.4 μmol/L (IQR: 35.1–59.0 μmol/L) in females, with no significant difference between sexes ($P = 0.202$; Fig. 1B). Based on TB levels, patients were stratified into three clinical phenotype groups: GS group (17.1–85.5 μmol/L, $n = 140$), intermediate group (85.6–102.5 μmol/L, $n = 5$), and CNS-II group (102.6–342 μmol/L, $n = 11$). The progressive increase in median TB levels from the GS to CNS-II groups was statistically significant (Fig. 1C). However, no significant differences were observed in age ($P = 0.775$) or sex distribution ($P = 0.414$) among the three groups (Table 1).

Characterization of the UGT1A1 variant profile

Analysis revealed 19 distinct *UGT1A1* variants (comprising 520 variant sites) in 156 patients (Fig. 2). Variants with allele frequencies >0.01 included c.-3279T>G (0.6795), (TA)6>(TA)7 (0.4904), p.G71R (0.2308), c.-64G>C (0.0801), p.P364L (0.0609), p.P229Q (0.0481), and p.Y486D (0.0288) (Table 2).

Allele frequencies of the seven common *UGT1A1* variants with frequencies >1% were compared between males and females. In the unadjusted analyses, c.-64G>C was more frequent in males than in females (0.0958 *vs.* 0.0278; unadjusted $P = 0.045$), whereas p.G71R was numerically more frequent in females than in males (0.3194 *vs.* 0.2042; unadjusted $P = 0.053$). After Bonferroni correction for seven comparisons, the corresponding adjusted *P* values were 0.315 and 0.371, respectively. No common variant differed significantly between sexes after correction; therefore, these unadjusted patterns were considered exploratory. The other five common variants—c.-3279T>G, (TA)6>(TA)7, p.P364L, p.P229Q, and p.Y486D—also showed no significant sex differences.

Some rare variants were observed in only one sex within this cohort: c.625C>T, c.777C>G, and c.1471G>A were found only in females, whereas c.556delinsAATGG, c.610A>G, and c.1084+1G>T were found only in males.

Previously unreported candidate variants

Two variants identified in this cohort have not been previously reported: c.272C>G (p.Ser91Cys) and c.556delinsAATGG (p.Cys186AsnfsTer73). Sanger sequencing chromatograms are presented in Fig. 3A–B, and predicted protein models are shown in Fig. 3C–D. Searches of ClinVar and the Human Gene Mutation Database did not identify either variant, and we found no prior published descriptions.

The c.272C>G (p.Ser91Cys) change is a missense variant in exon 1 and replaces serine with cysteine at position 91. Prediction tools gave discordant results: MutationTaster suggested a probably harmless effect, SIFT yielded a score of 0.18 and classified the variant as tolerated, PolyPhen-2 yielded a score of 0.965 and classified it as probably damaging, REVEL yielded a score of 0.195, and RDDC classified it as likely pathogenic. Its clinical significance therefore remains uncertain pending functional validation.

The frameshift variant c.556delinsAATGG (p.Cys186AsnfsTer73) alters the reading frame at codon 186 and introduces a premature stop codon 72 residues downstream. This change may markedly disrupt UGT1A1 structure and function. MutationTaster and RDDC classified the variant as disease-causing and pathogenic, respectively.

Differences in serum TB levels between genotypes

Among 140 patients with GS, 50 distinct genotypes were

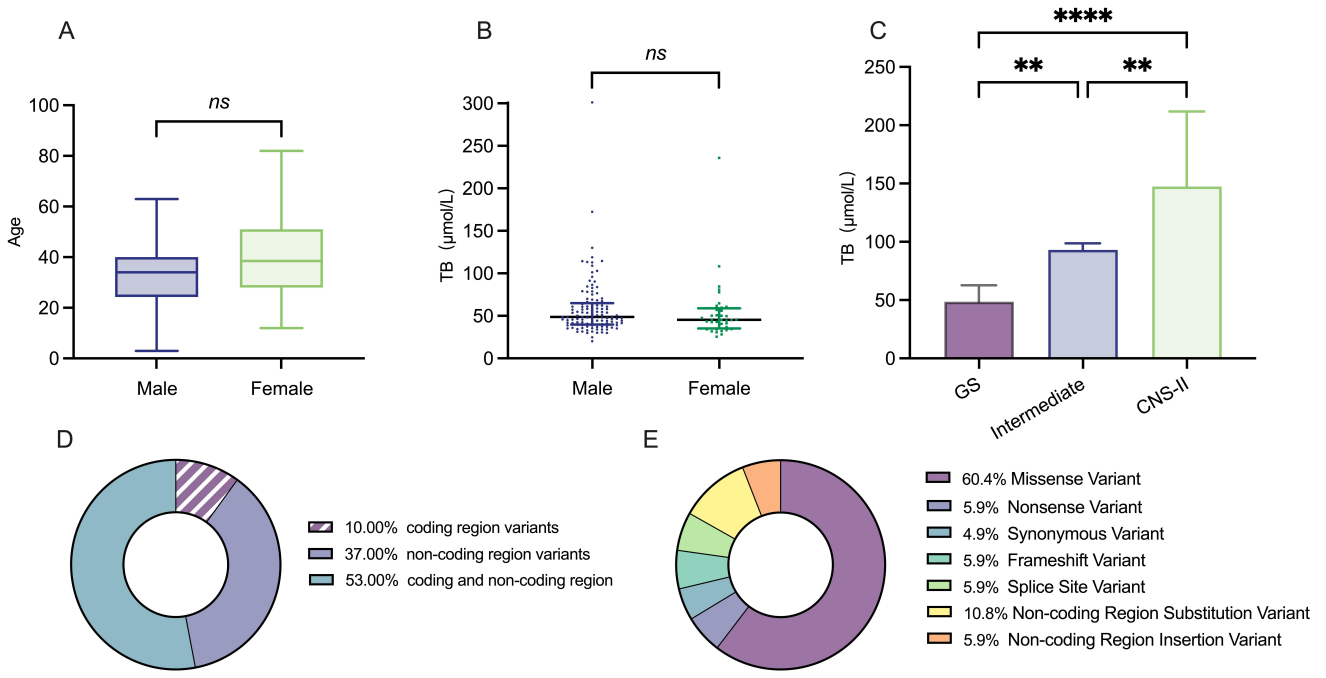


Fig. 1. Demographic characteristics, bilirubin levels, and *UGT1A1* variant spectrum in patients with hereditary unconjugated hyperbilirubinemia. (A) Comparison of age between male and female patients (n = 156). No significant difference was observed in age distribution between sexes (P > 0.05; Mann–Whitney U test). (B) Comparison of serum TB levels between male and female patients (n = 156). No significant difference was observed (P > 0.05). (C) Serum TB levels among patients with Gilbert syndrome (GS), intermediate type, and CNS-II. TB levels increased progressively from GS to CNS-II (P < 0.01; P < 0.0001, Kruskal–Wallis test with Dunn's multiple comparisons). (D) Distribution of *UGT1A1* variants by structural location. Patients were classified into three groups: "coding-only" (variants exclusively in exonic regions), "non-coding-only" (variants located solely in PBREM and promoter regions, with no exonic involvement), and "both" (patients carrying variants in both coding and non-coding regions). (E) Proportion of 19 different *UGT1A1* variant categories identified in the cohort. Missense variants accounted for the majority (60.4%), followed by nonsense (5.9%), synonymous (4.9%), frameshift (5.9%), splice site (5.9%), non-coding region substitution (10.8%), and insertion variants (5.9%). "ns" indicates no statistically significant difference; ** P < 0.01; **** P < 0.0001. PBREM, phenobarbital-responsive enhancer module; TB, total bilirubin; CNS- II, Crigler-Najjar syndrome type II.

Table 1. Clinical and biochemical characteristics in GS, intermediate, and CNS-II groups

	GS	Intermediate	CNS-II	All patients	*P value*
N	140 (89.74%)	5 (3.21%)	11 (7.05%)	156	/
Sex (M/F)	106 M/34 F	5 M/0 F	9 M/2 F	120 M/36 F	0.414
Age, y	35.90 ± 13.31	36.6 ± 22.07	32.91 ± 15.79	35.71 ± 13.72	0.775
Range	3–82	16–61	12–63	3–82	/
TB (μmol/L)	45.75 (37.6–57.8)	91.3 (88.5–98.6)	114.6 (109.0–172.3)	47.95 (39.3–62.5)	<0.001
DB (μmol/L)	10.66 ± 3.99	15.76 ± 7.02	17.72 ± 9.74	11.32 ± 5.06	<0.001
IB (μmol/L)	35.6 (27.1–45.8)	78.6 (70.4–83.5)	104.3 (89.1–154.6)	37.6 (27.9–49.1)	<0.001

Data are presented as mean ± SD or median (IQRs), as appropriate. Bilirubin concentrations are expressed in μmol/L. *P* values were calculated using chi-square tests for categorical variables and one-way ANOVA or Kruskal–Wallis tests for continuous variables. P < 0.05 was considered statistically significant. ANOVA, analysis of variance; CNS-II, Crigler–Najjar syndrome type II; DB, direct bilirubin; F, female; GS, Gilbert syndrome; IB, indirect bilirubin; IQRs, interquartile ranges; M, male; *N*, number of patients; SD, standard deviation; TB, total bilirubin.

identified, 34 of which were unique to single patients. Only genotypes observed in more than six patients were included in the statistical analysis. Ranked by mean serum total bilirubin concentration, the genotypes were: (1) c.-3279T>G Hom+(TA)6>(TA)7 Hom+p.P229Q Het (55.4 μmol/L); (2) c.-3279T>G Het+(TA)6>(TA)7 Het+p.G71R Het (50.7 μmol/L); (3) p.G71R Hom (49.4 μmol/L); (4) c.-3279T>G Hom+(TA)6>(TA)7 Hom (48.5 μmol/L); (5) c.-3279T>G Hom+(TA)6>(TA)7 Het

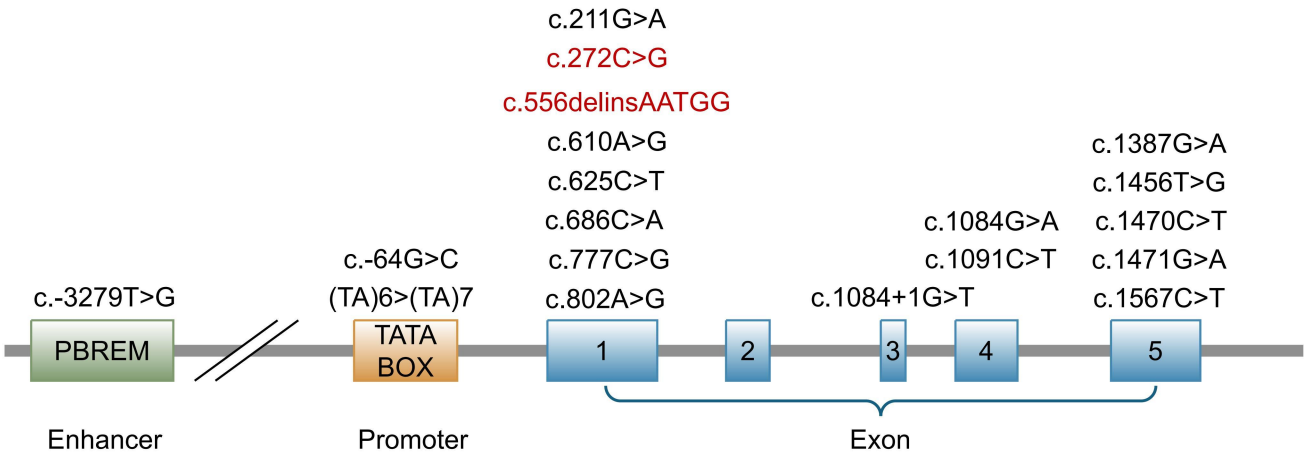


Fig. 2. Distribution of *UGT1A1* variants in 156 patients with unconjugated hyperbilirubinemia. Schematic of *UGT1A1* structure showing all detected variants across the enhancer, promoter, and exonic regions. Previously unreported candidate variants discovered in this study (c.272C>G and c.556delinsAATGG) are highlighted in red. PBREM, phenobarbital-responsive enhancer module.

Table 2. Distribution of *UGT1A1* variants identified in 156 patients

Sequencing region	Nucleotide variant	Amino acid variation	Hom, *n*	Het, *n*	Wild type, *n*	Allele frequency
PBREM	c.-3279T>G		73	66	17	0.6795
Promoter	c.-64G>C		2	21	133	0.0801
	(TA)6>(TA)7		47	59	50	0.4904
Exon 1	c.211G>A	p.G71R	13	46	97	0.2308
	c.272C>G	p.S91C	0	1	155	0.0032
	c.556delinsAATGG	p.Cys186AsnfsTer73	0	1	155	0.0032
	c.610A>G	p.M204V	0	1	155	0.0032
	c.625C>T	p.R209W	1	0	155	0.0064
	c.686C>A	p.P229Q	1	13	142	0.0481
	c.777C>G	p.D259E	0	2	154	0.0064
	c.802A>G	p.I268V	0	1	155	0.0032
Exon 3	c.1084+1G>T		0	1	155	0.0032
Exon 4	c.1084G>A	p.G362S	0	1	155	0.0032
	c.1091C>T	p.P364L	1	17	138	0.0609
Exon 5	c.1387G>A	p.E463K	0	1	155	0.0032
	c.1456T>G	p.Y486D	1	7	148	0.0288
	c.1470C>T	p.D490D	0	1	155	0.0032
	c.1471G>A	p.V491M	0	1	155	0.0032
	c.1567C>T	p.R522X	1	0	155	0.0064

Variants are described relative to *the UGT1A1* transcript NM_000463.3. Allele frequency was calculated as (2 × Hom + Het)/(2 × total number of tested patients). Het, heterozygous variant; Hom, homozygous variant; *n*, number of patients; PBREM, phenobarbital-responsive enhancer module.

(40.4 μmol/L); and (6) c.-3279T>G Het+(TA)6>(TA)7 Het (38.0 μmol/L). One-way analysis of variance with pairwise comparisons indicated that TB levels in patients with genotype 1 were significantly higher than in those with genotypes 5 and 6. No other significant differences were observed ($P > 0.05$, Fig. 4D).

Patients with CNS-II and intermediate phenotypes exhibited distinct genotypes (Table 3), including one nonsense and one frameshift variant, both associated with markedly reduced

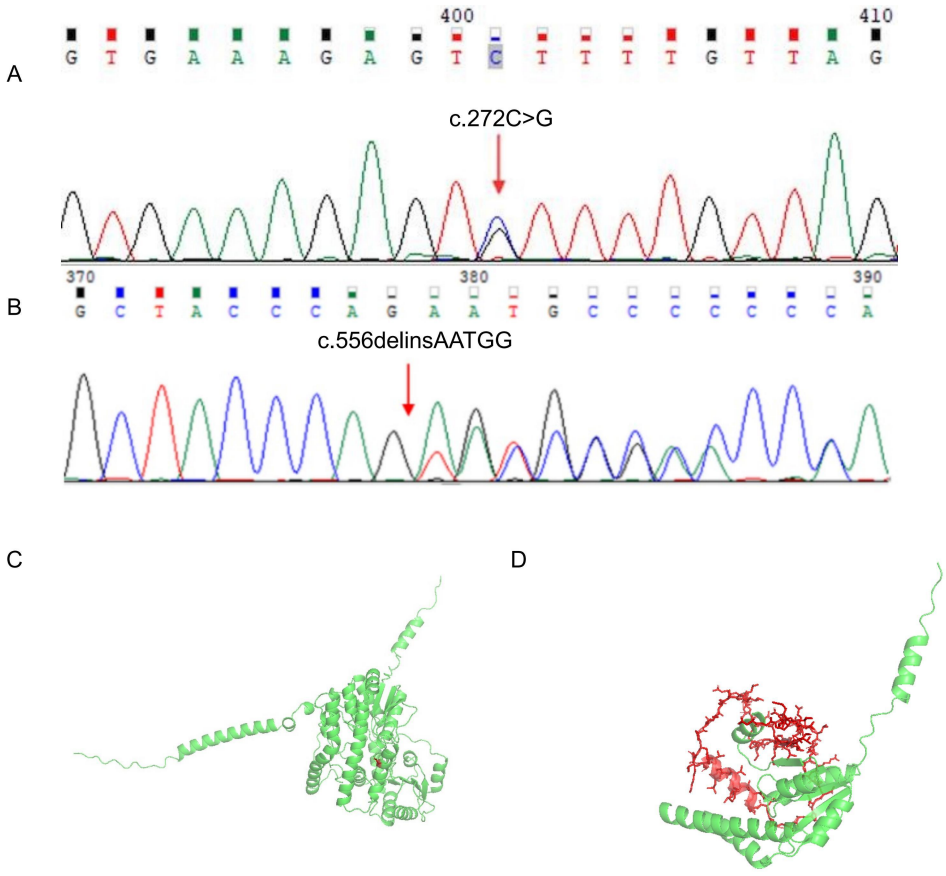


Fig. 3. Previously unreported candidate *UGT1A1* variants identified in patients with hereditary unconjugated hyperbilirubinemia. (A) Sanger sequencing chromatogram showing the heterozygous missense mutation c.272C>G (p.Ser91Cys) located in exon 1. (B) Sanger sequencing chromatogram showing the heterozygous frameshift mutation c.556delinsAATGG (p.Cys186AsnfsTer73), located in exon 1. (C) Predicted tertiary structure of the UGT1A1 protein with the c.272C>G (p.Ser91Cys) variant. (D) Predicted structure of the UGT1A1 protein with the c.556delinsAATGG (p.Cys186AsnfsTer73) frameshift variant, showing major alterations in overall conformation. Putative active sites are highlighted in red.

UGT1A1 activity.

Relationship between variant location and serum TB level

Non-coding alterations predominated in the cohort. Of the 156 patients, 140 (89.7%) carried non-coding variants (58 patients, 37.2%, had only non-coding variants), while 98 (62.8%) carried coding-region alterations (16 patients, 10.3%, carried coding variants alone).

To assess the effect of coding region variants on TB levels, patients were divided into three groups based on variant location: Group I (non-coding variants only, n = 58), median TB 42.30 μmol/L (IQR 35.45–58.23 μmol/L); Group II (both non-coding and coding variants, n = 82), median TB 49.25 μmol/L (IQR 42.35–64.83 μmol/L); and Group III (coding variants only, n = 16), median TB 53.70 μmol/L (IQR 41.70–102.3 μmol/L). TB levels differed significantly among the three groups by the Kruskal–Wallis test (H = 8.696, P = 0.013). In Dunn's multiple-comparisons test following the Kruskal–Wallis test, TB levels differed significantly between Group I and Group II (adjusted P = 0.029), whereas the differences between Group I and Group III (adjusted P = 0.074) and between Group II and Group III (adjusted P = 1.000) were not statistically significant (Fig. 4B). To further quantify between-group differences in serum total bilirubin (TB) levels, median regression analysis was performed to estimate differences in conditional medians. Compared with Group I, Group II had an estimated 6.95 μmol/L higher conditional median TB level (β = 6.95, 95% CI −0.73 to 14.63; P = 0.076), whereas Group III had an estimated 11.40 μmol/L higher conditional median TB level (β = 11.40, 95% CI −10.87 to 33.67; P = 0.313). The estimated conditional median difference between Group III and Group II was 4.45 μmol/L (β = 4.45, 95% CI −17.56 to 26.46; P = 0.690).

The distribution of variants across the enhancer, promoter, and coding regions also differed among the GS, intermediate, and CNS-II groups. The proportion of enhancer and promoter variants showed a non-significant decreasing trend with increasing bilirubin levels, whereas the proportion of coding variants increased. A significant difference in the percentage of coding variants was observed between the GS and CNS-II groups (P < 0.05), but not between the GS and intermediate or the intermediate and CNS-II groups (P > 0.05, Fig. 4A).

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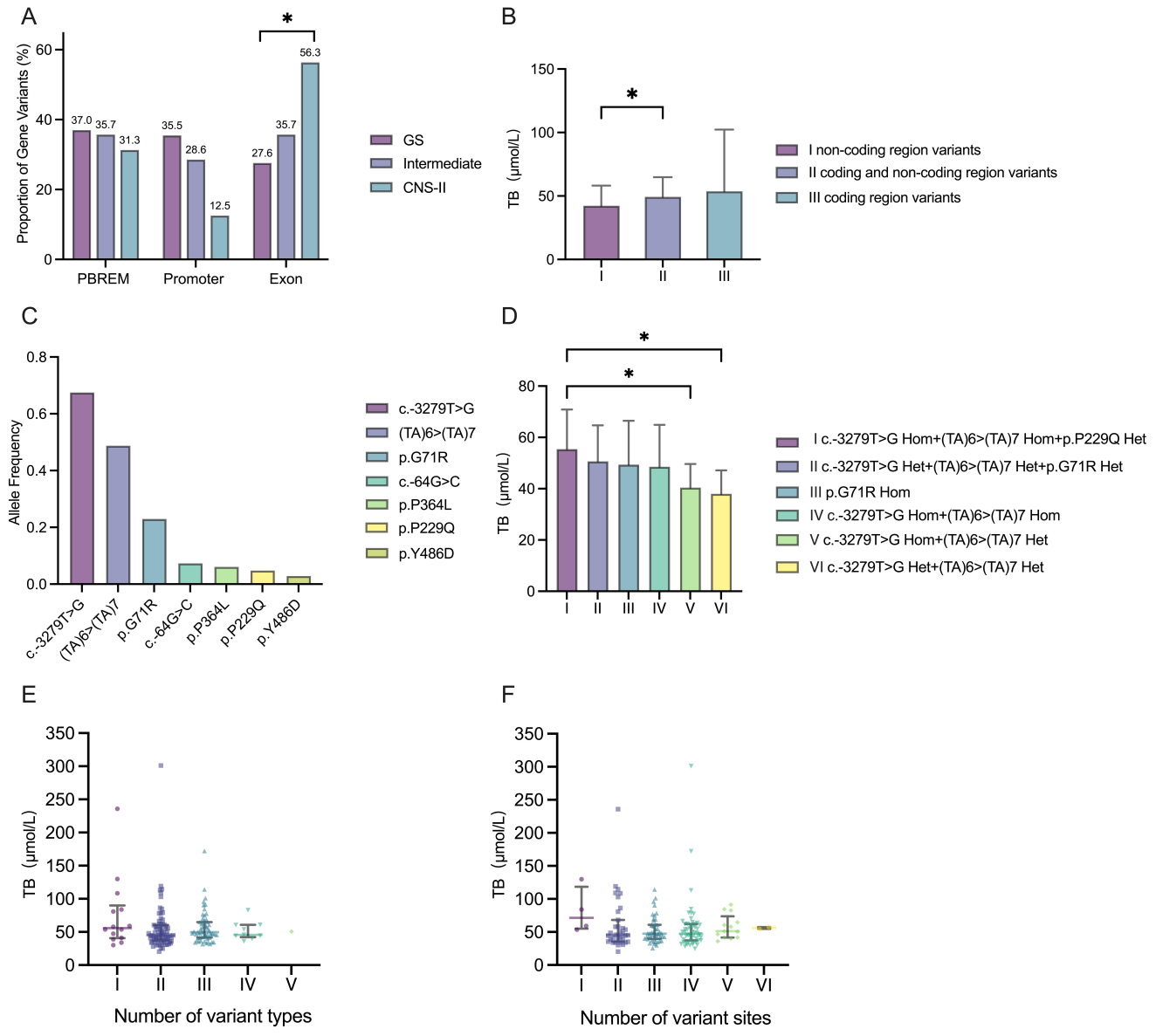


Fig. 4. Proportion of *UGT1A1* variants in different genomic regions across clinical phenotypes. (A) Distribution of *UGT1A1* variant carriers across structural regions (PBREM, promoter, and exon) among patients with Gilbert syndrome (GS), intermediate type, and CNS-II. (B) Comparison of serum TB levels among three groups: patients carrying only non-coding variants (Group I), both coding and non-coding variants (Group II), and only coding variants (Group III). (C) Allele frequencies of the top seven *UGT1A1* variants identified in 156 patients. (D) Serum TB levels stratified by six common genotypes in GS patients. Only genotypes observed in more than six individuals were included. (E) Serum TB levels stratified by the number of distinct *UGT1A1* variant types: one type (Group I; n = 14), two types (Group II; n = 71), three types (Group III; n = 61), four types (Group IV; n = 9), and five types (Group V; n = 1). Group V was excluded from inferential testing because it contained only one patient. (F) Serum TB levels stratified by the number of *UGT1A1* variant sites: one site (Group I; n = 4), two sites (Group II; n = 31), three sites (Group III; n = 47), four sites (Group IV; n = 59), five sites (Group V; n = 13), and six sites (Group VI; n = 2). Only Groups II–V were included in inferential testing because Groups I and VI had small sample sizes; Groups I and VI are presented descriptively. An asterisk indicates a statistically significant difference (P < 0.05). Het, heterozygous; Hom, homozygous; PBREM, phenobarbital-responsive enhancer module; TB, total bilirubin; CNS-II, Crigler-Najjar syndrome type II.

Effect of variant types and number of variant sites on serum TB levels

Patients carried 1–5 *UGT1A1* variant types. Most (142/156, 91.0%) had ≥2 variant types, with 2 being the most common and 5 the least. Grouped by variant type count: 1 variant (n = 14), median TB 75.39 μmol/L (IQR 40.7–90.0 μmol/L); 2 variants (n = 71), 54.51 μmol/L (37.2–60.6 μmol/L); 3 variants (n = 61), 56.75

Table 3. Genotypic and clinical characteristics of patients with CNS-II and intermediate phenotypes

No.	Age, y	Sex	TB (μmol/L)	IB (μmol/L)	Allele	Phenotype
1	61	Male	86.4	64.2	c.-3279T>G Het/(TA)6>(TA)7 Het	Intermediate
2	16	Male	90.5	78.6	c.-3279T>G Het/ (TA)6>(TA)7 Het/ p.G71R Het	Intermediate
3	30	Male	91.3	81.6	c.-3279T>G Hom/ (TA)6>(TA)7 Hom /p.P229Q Het	Intermediate
4	17	Male	95.9	85.4	c.-3279T>G Het/ (TA)6>(TA)7 Het/ p.Cys186AsnfsTer73	Intermediate
5	59	Male	101.2	76.7	c.-3279T>G Het/ p.Y486D Het/ p.G362S Het	Intermediate
6	18	Male	103	89.1	c.-3279T>G Het/p.G71R Het	CNS-II
7	52	Female	108.4	88.7	p.Y486D Hom	CNS-II
8	40	Male	109	89.2	c.-3279T>G Het/p.G71R Het	CNS-II
9	37	Male	113	100.9	c.-3279T>G Hom/(TA)6>(TA)7 Hom	CNS-II
10	21	Male	114.3	109.3	c.-3279T>G Het/ (TA)6>(TA)7 Het/ c.1084+1G>T Het	CNS-II
11	26	Male	114.6	104.3	c.-3279T>G Het/ c.1091C>T Het	CNS-II
12	63	Male	119	78.9	c.-3279T>G Het/p.G71R Het	CNS-II
13	17	Male	130	114.6	p.G71R Het	CNS-II
14	39	Male	172.3	154.6	c.-3279T>G Hom/ (TA)6>(TA)7 Het/p.P364L Het	CNS-II
15	12	Female	235.9	225.5	p.R209W Hom	CNS-II
16	37	Male	301.2	284.1	p.G71R Hom/p.R522X Hom	CNS-II

Bilirubin concentrations are expressed in μmol/L. CNS-II, Crigler–Najjar syndrome type II; Het, heterozygous variant; Hom, homozygous variant; IB, indirect bilirubin; TB, total bilirubin.

μmol/L (41.6–64.9 μmol/L); 4 variants (n = 9), 52.04 μmol/L (42.0–60.6 μmol/L); and 5 variants (n = 1), 50.6 μmol/L. The Kruskal–Wallis test (excluding the n = 1 group) showed no significant differences in TB levels across groups (P = 0.213; Fig. 4E).

Patients were also categorized by the number of variant sites detected: Group I (1 site, n = 4, TB: 53.7, 130, 59.1, 83.9 μmol/L); Group II (2 sites, n = 31, median TB 60.3 μmol/L [IQR 35.5–68.3 μmol/L]); Group III (3 sites, n = 47, 52.8 μmol/L [39.7–62.1 μmol/L]); Group IV (4 sites, n = 59, 56.9 μmol/L [37.3–60.8 μmol/L]); Group V (5 sites, n = 13, 57.7 μmol/L [41.6–73.9 μmol/L]); and Group VI (6 sites, n = 2, TB: 54.9, 57.5 μmol/L). Comparison among groups with sufficient sample sizes (Groups II–V) revealed no significant differences in TB levels (P = 0.243; Fig. 4F).

Discussion

We characterized the *UGT1A1* variant spectrum in 163 Chinese patients with hereditary unconjugated hyperbilirubinemia and detected variants in 156 (95.7%). The predominance of c.-3279T>G, (TA)6>(TA)7, and p.G71R in our cohort is broadly consistent with previous Chinese cohorts.[14] Our findings complement these reports by documenting two previously unreported candidate variants and exploring associations between variant location and bilirubin levels. However, differences in recruitment and phenotype definitions limit direct comparisons across studies. The small phenotype subgroups and absence of functional validation also warrant cautious interpretation of these exploratory findings.

The allele frequency of c.-3279T>G in our cohort was higher than that reported in most other populations, including European (0.39–0.57), Asian (0.24–0.42), and African (0.15) populations, but lower than that in African Americans (0.85), suggesting potential ethnic specificity.[25,26] Functionally, the homozygous c.-3279T>G variant has been shown to reduce *UGT1A1* transcriptional activity by approximately 60%.[27] Consistent with previous studies, it frequently co-occurs with other variants in patients with GS, and its contribution to hyperbilirubinemia may be more pronounced when combined with additional *UGT1A1* variants.[28] The (TA)6>(TA)7 promoter variant, the second most frequent allele in our cohort, exhibited strong linkage disequilibrium with c.-3279T>G, suggesting a possible combined effect on gene expression.[29,30] Heterozygosity for (TA)6>(TA)7 reduces UGT1A1 activity by 10%–35%, while homozygosity reduces it by up to 70%.[31] Notably, no patient carried this variant in isolation, further suggesting that additional genetic modifiers

are typically required for clinical manifestation.

In this cohort, p.G71R appeared in patients with GS, intermediate phenotype, and CNS-II, which is consistent with its recognized enrichment in East Asian populations. Published functional data suggest that p.G71R has little effect on mRNA abundance but reduces protein expression to about 40% of wild-type levels and enzyme activity to about 47%.[32] This points to a post-transcriptional mechanism, such as altered folding, less efficient translation, or faster proteasomal degradation. Nine patients carried p.G71R as the sole detected variant, including eight with GS and one with CNS-II. These findings suggest that p.G71R alone may contribute to hereditary unconjugated hyperbilirubinemia, although its phenotypic expression varies considerably. Likewise, when combined with additional *UGT1A1* variants, p.G71R may further aggravate bilirubin elevation. However, the considerable phenotypic variability observed among patients carrying p.G71R indicates that the functional consequences of DNA variants alone may not fully account for clinical severity. Recent liver transcriptome sequencing studies have shown that RNA sequencing can complement DNA-based diagnosis by identifying aberrant splicing and allele-specific expression, providing additional insight into genotype–phenotype heterogeneity.[33] Although transcriptomic analyses were not performed in our cohort, transcript-level mechanisms could partly explain why patients carrying similar *UGT1A1* genotypes, including p.G71R, exhibit different bilirubin levels. Future studies integrating genomic and hepatic transcriptomic data may improve our understanding of genotype–phenotype correlations in hereditary unconjugated hyperbilirubinemia.

Coding-region variants were more frequent in the CNS-II-range stratum than in the GS-range stratum, although the small number of patients in the former limits interpretation. In a separate analysis grouping patients by *UGT1A1* variant location, TB levels differed significantly across the three groups in the overall Kruskal–Wallis test. In subsequent Dunn's pairwise comparisons with Bonferroni correction, patients carrying both coding and non-coding variants (Group II) had higher TB levels than those carrying non-coding variants alone (Group I), whereas neither comparison involving the coding-only group (Group III) reached statistical significance. Median regression showed a similar numerical pattern, but the corresponding 95% confidence intervals included zero, indicating substantial uncertainty in the estimated between-group differences. These findings suggest an exploratory difference in TB distributions between patients carrying both coding and non-coding variants and those carrying non-coding variants alone, while the magnitude of the median difference remains uncertain.

Notably, Group III, which comprised patients carrying coding variants only, showed a numerically higher median TB level than Group II, which included patients carrying both coding and non-coding variants. This apparent pattern should not be interpreted as evidence that coding-only genotypes confer a greater functional burden. Group III included only 16 patients and showed a wide TB distribution, resulting in imprecise estimates. In addition, the three location-based groups contained heterogeneous variants with different functional consequences and zygosity states. Therefore, variant location alone is unlikely to represent a simple gradient of *UGT1A1* dysfunction. Regulatory variants in the PBREM and promoter primarily affect transcription, whereas coding substitutions or truncating variants may alter protein stability, folding, catalytic activity, or degradation. Taken together, the present results are best regarded as exploratory and require confirmation in larger cohorts with a broader range of genotype patterns.

Beyond variant location, we also examined TB levels across groups defined by the number of detected variants. No statistically significant differences were detected in these comparisons. Although Abuduxikuer *et al.* reported that a greater number of *UGT1A1* variant alleles was associated with an increased risk of Gilbert syndrome and Crigler–Najjar syndrome type II, their study evaluated disease susceptibility relative to healthy controls, whereas our analysis compared serum bilirubin levels among patients with hereditary unconjugated hyperbilirubinemia.[34] In addition, our unweighted variant-count approach assigned equal importance to regulatory and coding variants despite their markedly different functional consequences. These findings suggest that variant count alone may not adequately capture the functional heterogeneity underlying the observed phenotypes.[35]

Males accounted for 76.9% of this cohort (male-to-female ratio, 3.3:1), a distribution similar to previous epidemiological observations. Sex hormones may contribute in part: estrogen has been reported to increase *UGT1A1* mRNA and protein expression, whereas testosterone has not shown a comparable effect.[36,37] In the unadjusted analyses, c.-64G>C was more frequent in males, whereas p.G71R was numerically more frequent in females. However, neither difference remained statistically significant after Bonferroni correction for seven comparisons (adjusted $P = 0.315$ and 0.371, respectively). These exploratory observations should not be interpreted as evidence of sex-specific genetic effects and require confirmation in larger, sex-balanced cohorts.

The two previously unreported candidate variants warrant different levels of caution. The discordant *in silico* predictions for c.272C>G (p.Ser91Cys) support its classification as a variant of uncertain significance pending functional evidence. In contrast, c.556delinsAATGG (p.Cys186AsnfsTer73) is more plausibly associated with loss of function because the frameshift introduces a premature termination codon; however, its effects on transcript stability, protein expression, and enzymatic activity were not experimentally assessed. Thus, these findings expand the candidate *UGT1A1* variant spectrum but do not establish pathogenicity. Segregation analysis and functional assays are required to clarify their clinical significance.

Patients with variants limited to non-coding regions tended to have lower bilirubin levels than those whose genotypes also contained coding changes. This was most evident for the c.-3279T>G + (TA)6>(TA)7 variant combination. In the GS group, patients with c.-3279T>G Hom+(TA)6>(TA)7 Hom had a mean bilirubin level of 48.5 μmol/L; whereas higher levels were observed in patients who also carried p.G71R or p.P229Q. The pattern is compatible with a modifying effect of coding variants, but the small subgroup sizes limit how precisely this effect can be estimated.

One patient carrying the c.-3279T>G Het + (TA)6>(TA)7 Het genotype had a transient increase in bilirubin that coincided with e-cigarette use and normalized after cessation. As this was a single retrospective observation, it should be viewed as a clinical clue

rather than evidence of causality. Larger prospective studies with predefined exposure assessment are needed to determine whether environmental exposures modify bilirubin levels in genetically susceptible individuals.

Several limitations should be considered when interpreting these findings. This was a retrospective, single-center study, and potential referral and selection biases may limit the generalizability of the findings. The study-defined intermediate and CNS-II-range strata included only five and eleven patients, respectively, limiting statistical precision and the reliability of subgroup-specific analyses. The small number of patients with the intermediate phenotype may partly reflect the narrow bilirubin range defining this transition zone. We retained this study-defined intermediate stratum to describe patients with bilirubin concentrations between the selected GS-range and CNS-II-range thresholds, without assigning them to a definitive diagnostic category. Analyses involving this small subgroup should therefore be considered descriptive and hypothesis-generating. In addition, many *UGT1A1* genotypes occurred in only one patient, limiting estimation of the independent associations of individual variants or genotypes with bilirubin levels. Comparisons by sex, age, and variant location should therefore be regarded as exploratory and require confirmation in larger multicenter cohorts with adequate representation across age, sex, and genotype groups.

Conclusions

In this nine-year, single-center Chinese cohort, *UGT1A1* variants occur in 156 of 163 patients (95.7%). The profile of 19 distinct variants is broadly consistent with previous Chinese reports and includes two previously unreported candidate variants requiring further validation. In exploratory analyses, patients carrying both coding and non-coding variants have higher bilirubin levels than those carrying non-coding variants alone, whereas comparisons involving the coding-only group remain inconclusive. These findings add complementary evidence on *UGT1A1* variation and its possible relationship with biochemical phenotype in Chinese patients.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2026.00479.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

XT was responsible for investigation, methodology development, data curation, validation, formal analysis, and writing the original draft. XM conceived the study, acquired funding, provided resources, supervised the project, and reviewed and edited the manuscript. CL participated in the investigation, methodology development, and data curation. RL participated in methodology development, validation, and investigation. ZZ participated in the investigation, data curation, and review of the manuscript. WY participated in the investigation, data curation, and resource provision. GC participated in the investigation, resource provision, and data curation. JS supervised the study, administered the project, contributed to the conceptualization, and reviewed and edited the manuscript. LG reviewed and edited the manuscript and contributed to project administration.

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board of the Affiliated Hospital of Hangzhou Normal University (Approval No. 2024(E2)-KS-051). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from all participants.

Data sharing statement

De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request.

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