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Crigler–Najjar Syndrome Type II Caused by a Homozygous UGT1A1 c.1456T>G (p.Tyr486Asp) Variant Despite a Normal Promoter TA-Repeat Genotype: A Case Report and Diagnostic Approach

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Case Report

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Abstract

Background

Crigler–Najjar syndrome type II (CNS-II; Arias syndrome) is an uncommon recessively inherited condition in which hepatic bilirubin glucuronidation is impaired, but not abolished, owing to reduced uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) activity. Genetic testing restricted to the *UGT1A1* promoter TA-repeat polymorphism, widely used to confirm Gilbert syndrome, does not examine the coding exons and may be falsely reassuring.

Case presentation:

A 21-year-old man had a 5-year history of intermittent jaundice with persistent isolated unconjugated hyperbilirubinemia (total bilirubin 6–10 mg/dL). At presentation (19 September 2026), total bilirubin was 9.8 mg/dL (direct 1.2 mg/dL), with normal aminotransferases, alkaline phosphatase, gamma-glutamyl transferase and hepatic synthetic function. Hemolysis was excluded (normal peripheral smear, glucose-6-phosphate dehydrogenase and lactate dehydrogenase), viral markers were negative, abdominal ultrasonography was normal, and an earlier liver biopsy showed normal histology. A *UGT1A1* promoter assay revealed a wild-type 6/6 TA-repeat genotype (*UGT1A1**1/*1). Comprehensive genetic analysis subsequently identified a homozygous, likely pathogenic missense variant in exon 5, c.1456T > G (p.Tyr486Asp). A graded phenobarbitone challenge (30 mg/day escalated to 120 mg/day) reduced serum total bilirubin from 9.8 to 4.1 mg/dL (a 58% reduction), demonstrating inducible residual UGT1A1 activity and confirming CNS-II.

Conclusions

A normal *UGT1A1* promoter genotype does not exclude a clinically significant UGT1A1 defect. When unconjugated hyperbilirubinemia exceeds the range expected for Gilbert syndrome, full-gene *UGT1A1* analysis combined with a phenobarbitone challenge provides a definitive, non-invasive diagnosis and may obviate liver biopsy.

1. Introduction

Before it can be excreted in bile, the bilirubin formed from heme breakdown must be conjugated with glucuronic acid inside the hepatocyte, and UGT1A1 is essentially the only enzyme able to carry out this step [1, 2] (Fig. 1). Genetic loss of UGT1A1 function therefore results in unconjugated hyperbilirubinemia, and the three recognized clinical entities can be ranked by how much enzyme activity remains: Gilbert syndrome (approximately 30% of normal activity), Crigler–Najjar syndrome type II (CNS-II; usually less than 10%) and Crigler–Najjar syndrome type I (CNS-I; activity absent) [3–5].

CNS-I, first described by Crigler and Najjar in 1952, presents in the neonatal period with severe jaundice and a high risk of bilirubin encephalopathy [6]. CNS-II, characterized by Arias a decade later, is milder: serum bilirubin typically ranges from about 6 to 20 mg/dL, kernicterus is uncommon, and residual UGT1A1 activity can be induced by phenobarbitone — the property that distinguishes it clinically from CNS-I [7, 8]. Both forms are rare, with an estimated combined incidence of the order of one per million live births [9].

Gilbert syndrome is most often associated with homozygosity for an additional TA dinucleotide in the TATA box of the *UGT1A1* promoter [A(TA)$_7$TAA; *UGT1A1**28] [10], and promoter TA-repeat genotyping has therefore become the first-line — and frequently the only — genetic test requested for unconjugated hyperbilirubinemia. CNS-I and CNS-II, by contrast, are caused predominantly by coding-region and splice-site variants distributed across all five exons of the gene [3, 11], which a promoter assay cannot detect.

We report a young man with CNS-II due to a homozygous *UGT1A1* c.1456T > G (p.Tyr486Asp) variant in whom an initial promoter assay was normal, and we propose a stepwise diagnostic approach for persistent unconjugated hyperbilirubinemia. This report was prepared in accordance with the CARE guidelines [12].

2. Case Presentation

2.1 Patient information

A 21-year-old gentleman, resident of Jalandhar, Punjab, India, was referred for evaluation of isolated unconjugated hyperbilirubinemia. He was asymptomatic at presentation but reported intermittent episodes of jaundice over approximately 5 years, during which serum total bilirubin had generally ranged between 6 and 10 mg/dL. There was no history of blood transfusion or overt hemolytic episodes, and no similar illness was documented in family members. No history of neonatal/ childhood jaundice/phototherapy. No history of parental consanguinity. No alcohol or complementary and alternative medication use. No history of precipitating factors such as fasting or intercurrent illness.

2.2 Clinical findings

The patient was conscious, oriented and hemodynamically stable. Scleral icterus was present. There were no stigmata of chronic liver disease, abdominal examination was unremarkable, and no neurological abnormality was detected.

2.3 Diagnostic assessment

Laboratory results are summarized in Table 1. Serum total bilirubin on 19 September 2026 was 9.8 mg/dL with a direct fraction of 1.2 mg/dL, giving a calculated indirect (unconjugated) bilirubin of 8.6 mg/dL (88% of total). Aminotransferases, alkaline phosphatase and gamma-glutamyl transferase were normal, and serum total protein and albumin indicated preserved hepatic synthetic function. The hemogram was normal, the peripheral smear showed no evidence of hemolysis, glucose-6-phosphate

dehydrogenase (G6PD) activity was normal and lactate dehydrogenase (LDH) was 168 U/L. Renal function was preserved and viral hepatitis markers were negative. Abdominal ultrasonography was normal, and a liver biopsy obtained during an earlier evaluation had shown normal hepatic histopathology.

An initial *UGT1A1* promoter polymorphism assay showed a 6/6 TA-repeat genotype (*UGT1A1**1/*1), i.e. a wild-type promoter. Because this assay interrogates only the promoter TATA box (Fig. 2) and the degree of hyperbilirubinemia exceeded that usually seen in Gilbert syndrome, comprehensive genetic testing(Whole exome sequencing test) was undertaken. This identified a homozygous missense variant in exon 5 of *UGT1A1* (NM_000463.3): c.1456T > G, p.(Tyr486Asp) (Y486D). The variant was classified as likely pathogenic according to American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria [13] and is associated with autosomal recessive *UGT1A1*-related unconjugated hyperbilirubinemia.

2.4 Differential diagnosis

Hemolytic disorders and ineffective erythropoiesis were excluded by the normal hemoglobin, peripheral smear, G6PD and LDH. Acquired liver disease was excluded by normal liver enzymes, negative viral markers, normal imaging and normal histology. Among the inherited conjugation disorders, Gilbert syndrome was considered unlikely because bilirubin was persistently well above the range typical for that condition and the commonest Gilbert genotype (*UGT1A1**28) was absent. CNS-I was considered unlikely in view of the adult presentation and moderate hyperbilirubinemia. The clinical, biochemical and genetic findings were therefore most consistent with CNS-II (Fig. 3).

2.5 Therapeutic intervention: graded phenobarbitone challenge

To confirm the functional phenotype, a graded phenobarbitone challenge was performed (Fig. 4B). Phenobarbitone was started at 30 mg at bedtime on days 1–3, increased to 30 mg twice daily on days 4–7, and then to 60 mg twice daily as tolerated. Liver function tests, particularly serum bilirubin, were monitored twice weekly.

2.6 Follow-up and outcomes

Serum total bilirubin declined progressively on phenobarbitone, from a baseline of 9.8 mg/dL on 19 September 2026 to 5.26 mg/dL (46% reduction) and, three days later, to 4.1 mg/dL — a cumulative reduction of 5.7 mg/dL (58%) (Fig. 4C). This response comfortably exceeds the 25–30% reduction that is generally regarded as characteristic of CNS-II, demonstrating inducible residual UGT1A1 activity and confirming the diagnosis. Phenobarbitone was well tolerated, and the patient reported no drowsiness. He was initiated on Phenobarbitone tablet at a starting dose of 30mg once daily at bedtime for 3 days,

followed by 30mg twice daily for next three days and dose was later titrated up to 60mg twice daily since he reported good tolerability and no adverse effects. The overall clinical course is summarized in Fig. 4A.

Table 1
Laboratory, imaging, histological and molecular findings at presentation (19 September 2026)

Investigation	Patient value	Reference interval[a]
Hematology		
Hemoglobin	14.3 g/dL	13.0–17.0 g/dL
Total leukocyte count	5.98 × 10^3/mm^3	4.0–11.0 × 10^3/mm^3
Platelet count	281 × 10^3/mm^3	150–410 × 10^3/mm^3
Peripheral blood smear	No evidence of hemolysis	—
G6PD	Normal	—
Lactate dehydrogenase	168 U/L	140–280 U/L
Liver biochemistry		
Total bilirubin	**9.8 mg/dL**	0.2–1.2 mg/dL
Direct (conjugated) bilirubin	1.2 mg/dL	0.0–0.3 mg/dL
Indirect bilirubin (calculated)	**8.6 mg/dL (88% of total)**	< 1.0 mg/dL
AST / ALT	23 / 23 U/L	< 40 U/L
Alkaline phosphatase	60 U/L	40–129 U/L
Gamma-glutamyl transferase	13 U/L	< 60 U/L
Total protein / albumin	7.0 / 4.1 g/dL	6.4–8.3 / 3.5–5.2 g/dL
Renal function and serology		
BUN	8 mg/dL	7–20 mg/dL
Creatinine	0.8 mg/dL	0.7–1.3 mg/dL
Viral hepatitis markers	Negative	—
Imaging and histology		
Ultrasonography, abdomen	Normal study	—
Liver biopsy (earlier evaluation)	Normal histopathology	—

Investigation	Patient value	Reference interval[a]
Hematology		
Molecular genetics		
UGT1A1 promoter TA-repeat assay	6/6 TA repeats (*UGT1A1**1/*1); wild-type	—
Comprehensive UGT1A1 analysis	Homozygous c.1456T > G, p.(Tyr486Asp), exon 5 (NM_000463.3); likely pathogenic	—

[a]Typical adult reference intervals shown for orientation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; G6PD, glucose-6-phosphate dehydrogenase.

3. Discussion

This case illustrates two practical points: a normal *UGT1A1* promoter genotype does not exclude a clinically significant UGT1A1 defect, and the combination of full-gene molecular analysis with a phenobarbitone challenge allows CNS-II to be diagnosed definitively without invasive investigation.

3.1 Interpreting a normal promoter genotype

UGT1A1 lies within the complex *UGT1A* locus on chromosome 2q37, in which a unique first exon, encoding the substrate-binding amino-terminal domain, is spliced to four common exons (exons 2–5) shared by all UGT1A isoforms and encoding the UDP-glucuronic acid-binding carboxy-terminal domain [4, 11] (Fig. 2). The promoter TA-repeat assay determines only the number of TA repeats in the TATA box. A 6/6 result excludes the commonest Gilbert genotype but provides no information about the many coding, splice-site and other pathogenic variants described in Crigler–Najjar syndrome [3, 11]. The normal promoter result and the exon 5 variant in our patient are therefore complementary rather than contradictory: the two tests interrogated different regions of the gene. Moreover, in some populations — notably East Asian — Gilbert syndrome is frequently caused by a coding variant (p.Gly71Arg, *UGT1A1**6) rather than *UGT1A1**28 [14], a further limitation of promoter-only testing.

The magnitude of hyperbilirubinemia is the key clinical clue. Bilirubin in Gilbert syndrome is usually below 4 mg/dL, even with fasting or intercurrent illness [4, 15]; persistent values of 6–10 mg/dL, as in our patient, should prompt full-gene analysis irrespective of the promoter result. Early comprehensive testing might also have rendered the earlier liver biopsy unnecessary, since hepatic histology is characteristically normal in inherited disorders of bilirubin conjugation (Table 2).

3.2 The p.Tyr486Asp (Y486D) variant

The c.1456T > G transversion substitutes aspartate for tyrosine at codon 486, within the common carboxy-terminal region encoded by exon 5. In expression studies, homozygous Y486D retained only

about 7.6% of wild-type bilirubin-glucuronidating activity, a level within the CNS-II range [14]. The variant has been reported predominantly in East and Southeast Asian patients with CNS-II, often in compound heterozygosity with other *UGT1A1* variants or in cis with p.Gly71Arg [14, 16–19], and has also been described in European series [20].To our knowledge, homozygous Y486D has rarely been reported from the Indian subcontinent. Our patient's phenotype — moderate unconjugated hyperbilirubinemia presenting beyond infancy, with a robust phenobarbitone response — is concordant with the general genotype–phenotype rule that missense variants retaining partial activity cause CNS-II, whereas truncating or null variants cause CNS-I [3, 21]. Homozygosity for a rare variant raises the possibility of parental consanguinity or a founder allele, however there is no such family history of parental consanguinity.

3.3 Phenobarbitone challenge as a functional test

The therapeutic effect of phenobarbitone is transcriptional: the drug triggers nuclear translocation of the constitutive androstane receptor (CAR), which then engages an enhancer element (PBREM) located upstream of *UGT1A1* and up-regulates expression of the gene [22, 23]. Because more enzyme is only useful if the enzyme works at all, a meaningful fall in bilirubin — conventionally at least 25–30% — is expected in CNS-II, whereas little or no change occurs in CNS-I [8, 19]. The 58% reduction in our patient (9.8 to 4.1 mg/dL), with a continuing downward trend on serial measurement, clearly exceeds this threshold and provides strong functional confirmation of CNS-II; the residual elevation on treatment is also in keeping with the incomplete correction typically seen in CNS-II, in contrast to the near-normalization expected in Gilbert syndrome. This distinction has direct clinical consequences: CNS-I requires prolonged daily phototherapy and usually liver transplantation, whereas CNS-II generally carries a good prognosis [4, 9]. A phenobarbitone challenge is inexpensive and non-invasive, and is a practical alternative to bile pigment analysis, which is not widely available. The graded, low-dose regimen used here (maximum 120 mg/day) was sufficient to elicit a clear response.

3.4 Implications for management and counseling

Although CNS-II is usually benign, bilirubin can rise sharply during fasting, intercurrent illness or pregnancy, and bilirubin encephalopathy has rarely been reported in older children and adults with CNS-II [4, 5]. Management therefore includes:

- long-term phenobarbitone (single bedtime dosing to minimize sedation) when bilirubin remains persistently elevated or during periods of increased risk;
- avoidance of prolonged fasting and caution with drugs that are UGT1A1 substrates or inhibitors (e.g. irinotecan, atazanavir), with the diagnosis recorded prominently in the patient's medical record;
- periodic surveillance, including for pigment gallstones; and
- genetic counseling — both parents are presumed heterozygous carriers, each sibling has a 25% risk of being affected, and all of the patient's offspring will be obligate carriers. Cascade testing of siblings is recommended.

3.5 Strengths and limitations

The diagnosis in this patient rests on concordant clinical, biochemical, molecular and functional evidence, with systematic exclusion of hemolytic and acquired causes. Limitations include the absence of direct measurement of hepatic UGT1A1 activity or bile pigment composition, reliance on published expression data rather than patient-specific functional studies of the variant, absence of parental segregation analysis.

Table 2
Comparison of inherited unconjugated hyperbilirubinemias with the features of the present patient

Feature	CNS-I	CNS-II (Arias syndrome)	Gilbert syndrome	Present patient
Inheritance	Autosomal recessive	Autosomal recessive	Usually autosomal recessive	Homozygous variant
Age at onset	Neonatal	Infancy to adulthood	Adolescence/adulthood; often incidental	Approximately 16 years
Serum bilirubin	Typically 20–50 mg/dL	Typically ~ 6–20 mg/dL	Usually < 4 mg/dL	6–10 mg/dL
Residual UGT1A1 activity	Absent	Usually < 10%	~ 30%	Not measured (~ 7.6% predicted for homozygous Y486D)
Typical genetic lesion	Truncating/null or severely deleterious variants	Missense variants retaining partial activity	Promoter $A(TA)_7TAA$ (*28); p.Gly71Arg (*6) in East Asia	Homozygous c.1456T > G, p.(Tyr486Asp); promoter 6/6
Response to phenobarbitone	None or minimal	Fall of ≥ 25–30%	Bilirubin falls/normalizes	Fall of 58% (9.8 → 4.1 mg/dL)
Kernicterus risk	High	Low (precipitated by stress)	Negligible	None
Liver enzymes and histology	Normal	Normal	Normal	Normal
Treatment	Phototherapy; liver transplantation	Phenobarbitone if required; avoid precipitants	Reassurance	Phenobarbitone
Prognosis	Life-threatening without definitive treatment	Generally good	Excellent	—

Data compiled from references [3–5, 8, 14]. Activity is expressed as a percentage of normal hepatic UGT1A1 activity.

4. Learning Points

- Persistent isolated unconjugated hyperbilirubinemia above ~ 5–6 mg/dL, after exclusion of hemolysis and liver disease, should raise suspicion of CNS-II rather than Gilbert syndrome.
- A normal (6/6) *UGT1A1* promoter TA-repeat genotype does not exclude a pathogenic *UGT1A1* defect; full-gene analysis, including all five exons and their flanking intronic regions, is required.
- A graded phenobarbitone challenge is a simple, non-invasive functional test: a ≥ 25–30% fall in bilirubin distinguishes CNS-II from CNS-I.
- Liver biopsy is seldom required when molecular and functional testing are available.
- Diagnosis should prompt counseling on drug interactions (e.g. irinotecan, atazanavir), precipitating factors and family cascade testing.

5. Conclusion

In an adolescent or young adult whose jaundice is due solely to unconjugated bilirubin, and in whom hemolysis and acquired hepatic disease have been ruled out, CNS-II deserves explicit consideration. In this patient, a normal *UGT1A1* promoter genotype initially obscured the diagnosis, which was established by identification of a homozygous likely pathogenic c.1456T > G (p.Tyr486Asp) variant and confirmed functionally by a 58% fall in serum bilirubin (9.8 to 4.1 mg/dL) with phenobarbitone. Comprehensive *UGT1A1* analysis should be undertaken whenever the biochemical phenotype exceeds that expected for Gilbert syndrome, irrespective of the promoter result.

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR, constitutive androstane receptor; CNS-I/-II, Crigler–Najjar syndrome type I/II; G6PD, glucose-6-phosphate dehydrogenase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; PBREM, phenobarbital-responsive enhancer module; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

Declarations

Consent for publication: Written informed consent for publication was obtained from the patient. The consent covers this case report and all the clinical, laboratory, imaging, histological and genetic information it contains, including the results of whole exome sequencing and the identified UGT1A1 variant, as well as the accompanying figures. The report has been anonymized and contains no

information that could identify the patient. A copy of the signed consent form is available to the Editor on request.

Ethics approval and consent to participate: This report is a retrospective description of the routine clinical care of a single patient and does not constitute research involving human participants. The Institutional Ethics Committee, Army Hospital Research and Referral, New Delhi, reviewed the report and determined that formal ethics approval was not required, because the report describes diagnostic tests and treatment performed solely for the patient's clinical benefit, with no experimental intervention or research protocol, and is published in anonymized form with the patient's written consent (waiver reference number- IC/GEAHRR/2026/08, dated 08/08/2026). All investigations, including genetic testing and the phenobarbitone challenge, were performed as part of standard clinical care with the patient's informed consent, in accordance with the Declaration of Helsinki.

Conflicts of interest: The authors declare no conflicts of interest.

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Use of artificial intelligence: During the preparation of this manuscript, the authors used Claude Opus 5.5 (Anthropic; accessed October 2026), a large language model, to assist with language editing, restructuring of the manuscript according to the CARE guidelines, drafting of portions of the Introduction and Discussion, identification of supporting literature, and preparation of the schematic illustrations (Figures 1–4) from the authors' clinical data. AI tools were not used to generate patient data, perform laboratory or genetic analyses, or determine the diagnosis. The authors reviewed, edited and verified all content, including every reference, and take full responsibility for the accuracy and integrity of the published work.

Author contributions: A1: clinical care, data collection and manuscript drafting; A2: genetic interpretation and critical revision; A3: supervision and final approval. All authors approved the final manuscript.

Data availability: The UGT1A1 (NM_000463.3) c.1456T>G, p.(Tyr486Asp) variant identified in this patient, together with its clinical interpretation and the associated phenotype, has been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) under submission ID SUB16634920. The ClinVar accession number is pending and will be provided before publication. The raw whole exome sequencing data (FASTQ, BAM and VCF files) are not publicly available, because they constitute potentially identifiable germline genetic information and the patient's consent does not extend to open public release. These data are available from the corresponding author on reasonable request, subject to approval by the Institutional Ethics Committee, Army Hospital Research and Referral, New Delhi and a data access agreement. The authors are willing to deposit the raw data in a controlled-access repository, such as the European Genome-phenome Archive, if required. All other data supporting the findings of this case are included in the article.

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References

1. Bosma PJ. Inherited disorders of bilirubin metabolism. J Hepatol. 2003;38(1):107–17.
2. Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology. 2014;146(7):1625–38.
3. Kadakol A, Ghosh SS, Sappal BS, Sharma G, Chowdhury JR, Chowdhury NR. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. Hum Mutat. 2000;16(4):297–306.
4. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). Best Pract Res Clin Gastroenterol. 2010;24(5):555–71.
5. Memon N, Weinberger BI, Hegyi T, Aleksunes LM. Inherited disorders of bilirubin clearance. Pediatr Res. 2016;79(3):378–86.
6. Crigler JF Jr, Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics. 1952;10(2):169–80.
7. Arias IM. Chronic unconjugated hyperbilirubinemia without overt signs of hemolysis in adolescents and adults. J Clin Invest. 1962;41(12):2233–45.
8. Arias IM, Gartner LM, Cohen M, Ezzer JB, Levi AJ. Chronic nonhemolytic unconjugated hyperbilirubinemia with glucuronyl transferase deficiency: clinical, biochemical, pharmacologic and genetic evidence for heterogeneity. Am J Med. 1969;47(3):395–409.
9. Dhawan A, Lawlor MW, Mazariegos GV, McKiernan P, Squires JE, Strauss KA, et al. Disease burden of Crigler-Najjar syndrome: systematic review and future perspectives. J Gastroenterol Hepatol. 2020;35(4):530–43.
10. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med. 1995;333(18):1171–5.
11. Canu G, Minucci A, Zuppi C, Capoluongo E. Gilbert and Crigler Najjar syndromes: an update of the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene mutation database. Blood Cells Mol Dis. 2013;50(4):273–80.
12. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218–35.
13. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24.
14. Yamamoto K, Sato H, Fujiyama Y, Doida Y, Bamba T. Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (UGT1A1) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II. Biochim Biophys Acta. 1998;1406(3):267–73.
15. Fevery J. Bilirubin in clinical practice: a review. Liver Int. 2008;28(5):592–605.

16. Maruo Y, et al. Compound heterozygote of a novel missense mutation (p.K402T) and a double missense mutation (p.[G71R;Y486D]) in type II Crigler-Najjar syndrome. J Pediatr Gastroenterol Nutr. 2011;52(3):362–5.
17. Zheng B, et al. Crigler-Najjar syndrome type II in a Chinese boy resulting from three mutations in the bilirubin uridine 5'-diphosphate-glucuronosyltransferase (UGT1A1) gene and a family genetic analysis. BMC Pediatr. 2014;14:267.
18. Tesapirat L, et al. Compound heterozygosity of a novel exon 3 frameshift (p.R357P fs*24) mutation and Y486D mutation in exon 5 of the UGT1A1 gene in a Thai infant with Crigler-Najjar syndrome type 2. Genet Mol Res. 2015;14(1):3293–9.
19. He T, Geng X, Zhu L, et al. Type II Crigler-Najjar syndrome: a case report and literature review. Front Med (Lausanne). 2024;11:1354514.
20. Sneitz N, Bakker CT, de Knegt RJ, Halley DJ, Finel M, Bosma PJ. Crigler-Najjar syndrome in the Netherlands: identification of four novel UGT1A1 alleles, genotype-phenotype correlation, and functional analysis of 10 missense mutants. Hum Mutat. 2010;31(1):52–9.
21. Seppen J, Bosma PJ, Goldhoorn BG, Bakker CT, Chowdhury JR, Chowdhury NR, et al. Discrimination between Crigler-Najjar type I and II by expression of mutant bilirubin uridine diphosphate-glucuronosyltransferase. J Clin Invest. 1994;94(6):2385–91.
22. Sugatani J, Kojima H, Ueda A, Kakizaki S, Yoshinari K, Gong QH, et al. The phenobarbital response enhancer module in the human bilirubin UDP-glucuronosyltransferase UGT1A1 gene and regulation by the nuclear receptor CAR. Hepatology. 2001;33(5):1232–8.
23. Huang W, Zhang J, Chua SS, Qatanani M, Han Y, Granata R, et al. Induction of bilirubin clearance by the constitutive androstane receptor (CAR). Proc Natl Acad Sci U S A. 2003;100(7):4156–61.

Figures

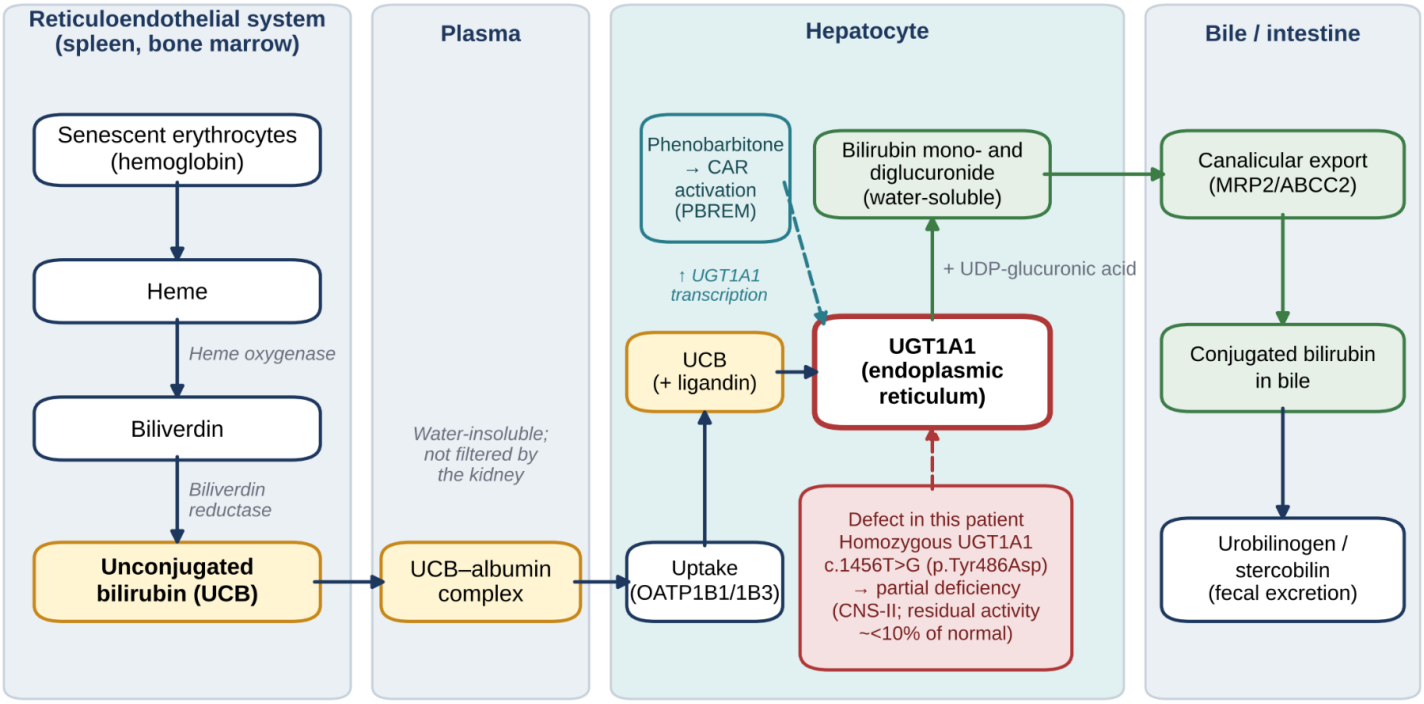


Figure 1

Bilirubin metabolism and the site of the defect. Unconjugated bilirubin generated from heme in the reticuloendothelial system circulates bound to albumin, is taken up by hepatocytes and is conjugated with glucuronic acid by UGT1A1 before canalicular excretion via MRP2. In this patient, homozygosity for p.Tyr486Asp results in partial UGT1A1 deficiency (CNS-II). Phenobarbitone activates CAR, which binds the PBREM enhancer and up-regulates *UGT1A1* transcription, increasing residual activity. CAR, constitutive androstane receptor; MRP2, multidrug resistance-associated protein 2; OATP, organic anion-transporting polypeptide; PBREM, phenobarbital-responsive enhancer module.

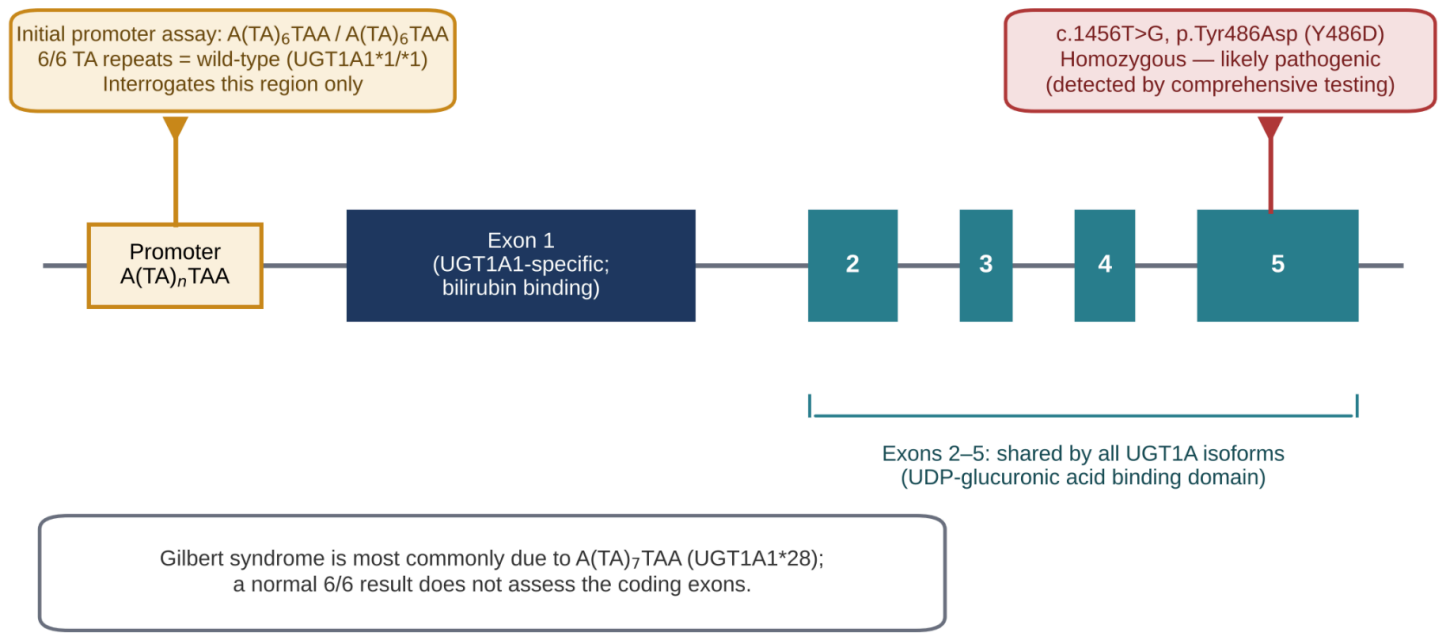


Figure 2

Schematic of the *UGT1A1*gene (not to scale) showing the regions interrogated by each test. The initial promoter assay examined only the TATA-box TA-repeat (6/6, wild-type). Comprehensive analysis identified the homozygous c.1456T>G, p.(Tyr486Asp) variant in exon 5, one of four common exons shared by all UGT1A isoforms.

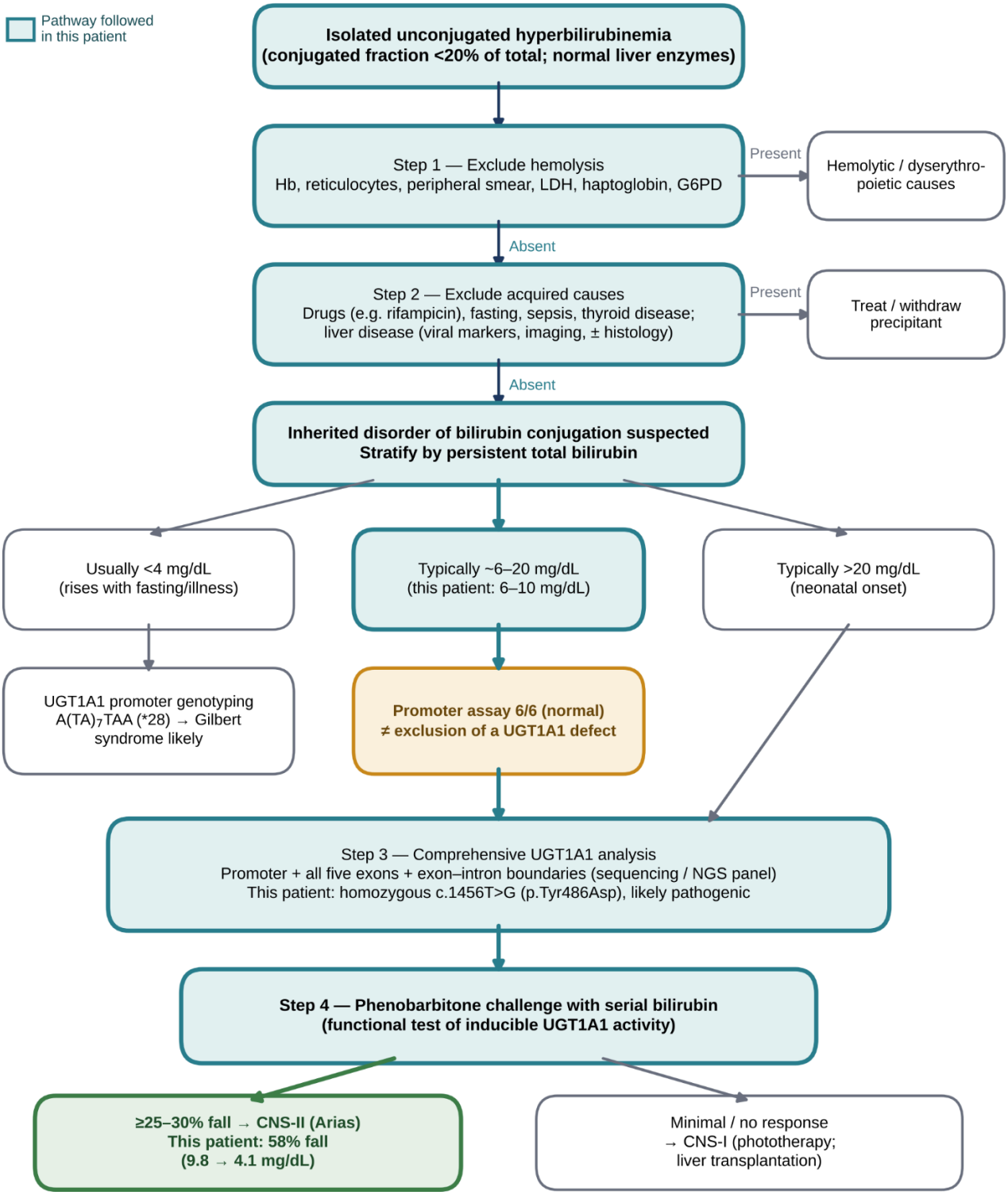


Figure 3

Proposed stepwise diagnostic approach to isolated unconjugated hyperbilirubinemia. The pathway followed in this patient is highlighted. Bilirubin ranges are indicative and overlap between conditions; a normal promoter assay should not terminate the evaluation when bilirubin exceeds the range typical of Gilbert syndrome. CNS, Crigler–Najjar syndrome; G6PD, glucose-6-phosphate dehydrogenase; LDH, lactate dehydrogenase; NGS, next-generation sequencing.

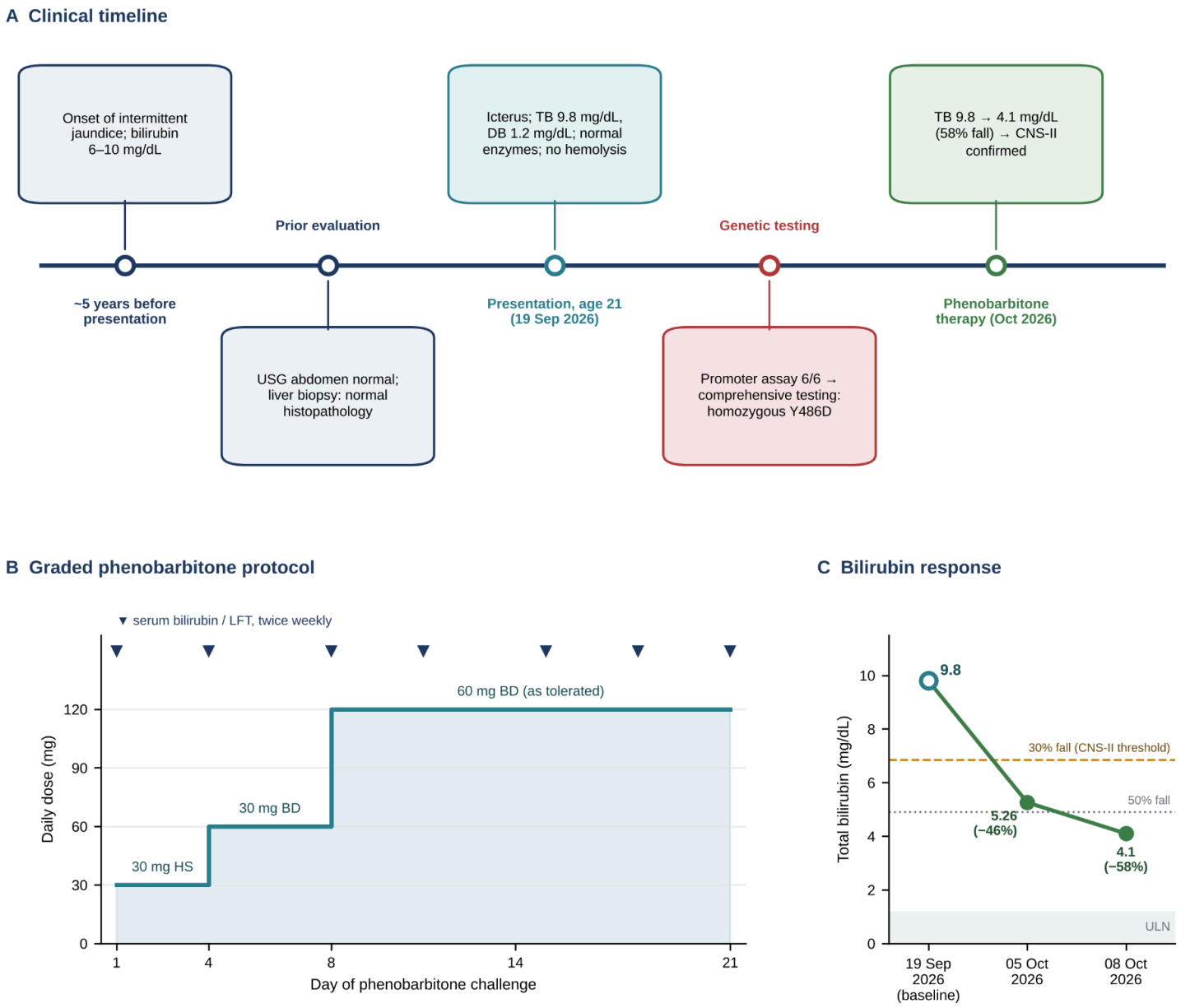


Figure 4

(A) Timeline of the clinical course (intervals schematic). (B) Graded phenobarbitone challenge protocol showing the dose schedule and twice-weekly bilirubin monitoring. (C) Serum total bilirubin at baseline on 19 September 2026 (9.8 mg/dL) and on phenobarbitone on 5 October 2026 (5.26 mg/dL; −46%) and 8 October 2026 (4.1 mg/dL; −58%). The dashed line marks a 30% reduction from baseline, the threshold generally used to support CNS-II; the dotted line marks a 50% reduction; the shaded band indicates the upper limit of normal. BD, twice daily; HS, at bedtime; LFT, liver function tests; ULN, upper limit of normal; TB, total bilirubin; DB, direct bilirubin; USG, ultrasonography.