Volume 3, Issue 9, September 2025 ISSN (E): 2938-3765

GILBERT SYNDROME: GENETIC FACTORS AND DIAGNOSTIC APPROACHES

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Abstract
Gilbert syndrome (GS) is an inherited disorder of bilirubin metabolism characterized by unconjugated hyperbilirubinemia. The condition is associated with a mutation in the promoter region of the UGT1A1 gene, which encodes the enzyme uridine diphosphate-glucuronosyltransferase 1A1. Although often asymptomatic, accurate diagnosis of GS is important to prevent misdiagnosis, unnecessary investigations, and overtreatment.

Introduction

The primary pathophysiological mechanism of GS involves decreased activity of UGT1A1, the enzyme responsible for conjugating unconjugated bilirubin in the liver via glucuronidation. Mutations in the promoter region, especially the increased number of TA repeats (e.g., A(TA)7TAA instead of A(TA)6TAA), lead to reduced transcriptional activity of the gene and subsequently decreased enzyme levels. This results in impaired conjugation of bilirubin, causing its accumulation in the plasma.

Decreased UGT1A1 activity manifests clinically primarily as isolated mild unconjugated hyperbilirubinemia, often presenting as intermittent jaundice during periods of physiological stress, fasting, illness, or medication use. It is typically detected in adolescence or early adulthood. The hallmark clinical feature is transient scleral icterus and jaundice without signs of hepatocellular damage or liver dysfunction. Patients are usually asymptomatic otherwise, although some may experience nonspecific symptoms such as fatigue or abdominal discomfort, which are not directly linked to GS.

Diagnosis is based on clinical presentation and laboratory findings: elevated serum total bilirubin levels (usually 85–100 μmol/L), predominantly of the unconjugated fraction, with normal liver transaminases, alkaline phosphatase, and gamma-glutamyl transpeptidase levels. Diagnostic tests such as fasting or nicotine acetal tests may be used, but molecular genetic testing for UGT1A1 promoter polymorphisms is now the gold standard.

Differential diagnosis includes hemolytic anemias, Crigler-Najjar syndrome, hepatitis, autoimmune hepatitis, Wilson's disease, and other hereditary unconjugated hyperbilirubinemias. No specific treatment is required for GS. The main approach involves patient education about the benign nature of the syndrome and avoiding precipitating factors such as fasting, certain medications, or stressful conditions. Caution is advised when prescribing drugs metabolized by UGT1A1, such as irinotecan. Gilbert syndrome does not progress to cirrhosis or other chronic liver disease. Women with GS can have successful pregnancies if proper monitoring and management are maintained. Overall, GS is a

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common benign disorder of bilirubin metabolism that requires no treatment but benefits from correct diagnosis and patient counseling to improve quality of life and prevent unnecessary investigations.

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