



UGT1A1 gene

UDP glucuronosyltransferase family 1 member A1

Normal Function

The *UGT1A1* gene belongs to a family of genes that provide instructions for making enzymes called UDP-glucuronosyltransferases. These enzymes perform a chemical reaction called glucuronidation, in which a compound called glucuronic acid is attached (conjugated) to one of a number of different substances.

The protein produced from the *UGT1A1* gene, called the bilirubin uridine diphosphate glucuronosyl transferase (bilirubin-UGT) enzyme, is the only enzyme that glucuronidates bilirubin, a substance produced when red blood cells are broken down. This enzyme converts the toxic form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin), making it able to be dissolved and removed from the body.

The bilirubin-UGT enzyme is primarily found in cells of the liver, where bilirubin glucuronidation takes place. Conjugated bilirubin is dissolved in bile, a fluid produced in the liver, and excreted with solid waste.

Health Conditions Related to Genetic Changes

Crigler-Najjar syndrome

At least 85 mutations in the *UGT1A1* gene that cause Crigler-Najjar syndrome have been identified. This condition occurs when both copies of the *UGT1A1* gene in each cell are altered. Crigler-Najjar syndrome is characterized by high levels of unconjugated bilirubin in the blood (unconjugated hyperbilirubinemia) and yellowing of the skin and eyes (jaundice). Some affected individuals develop a form of brain damage called kernicterus due to the accumulation of unconjugated bilirubin in the brain, which can be lethal.

Mutations in the *UGT1A1* gene that cause Crigler-Najjar syndrome result in reduced or absent function of the bilirubin-UGT enzyme. People with Crigler-Najjar syndrome type 1 (CN1) have no enzyme function, while people with Crigler-Najjar syndrome type 2 (CN2) have less than 20 percent of normal function. The signs and symptoms of CN1 are more severe than those of CN2. The loss of bilirubin-UGT function decreases glucuronidation of unconjugated bilirubin. This toxic substance then builds up in the body, causing hyperbilirubinemia, jaundice, and sometimes, kernicterus.

Gilbert syndrome

Changes in the *UGT1A1* gene can cause Gilbert syndrome. This condition is characterized by periods of mild unconjugated hyperbilirubinemia, which rarely leads to episodes of jaundice.

Gilbert syndrome occurs worldwide, but some mutations are seen more often in particular populations. In many populations, the most common genetic change that causes Gilbert syndrome occurs in an area near the *UGT1A1* gene called the promoter region, which controls the production of the bilirubin-UGT enzyme. This change must occur in both copies of the *UGT1A1* gene to cause Gilbert syndrome. The common genetic change involved in Gilbert syndrome, called UGT1A1*28, results from the addition of two DNA building blocks (nucleotides) to an important sequence in the promoter region known as the TATA box. The normal *UGT1A1* TATA box sequence is written as A(TA)₆TAA. The UGT1A1*28 sequence includes an extra TA nucleotide pair and is written as A(TA)₇TAA. This genetic change creates a longer than normal TATA box and impairs protein production.

The UGT1A1*28 change, however, is uncommon in Asian populations. Asians with Gilbert syndrome often have a mutation in one copy of the *UGT1A1* gene that results in the change of a single protein building block (amino acid) in the bilirubin-UGT enzyme. The most common mutation in this population replaces the amino acid glycine with the amino acid arginine at position 71 of the enzyme (written as Gly71Arg or G71R). This type of mutation, known as a missense mutation, results in reduced enzyme function.

People with Gilbert syndrome have approximately 30 percent of normal bilirubin-UGT enzyme function. As a result, unconjugated bilirubin is not glucuronidated quickly enough, and it builds up in the body, causing mild hyperbilirubinemia.

Warfarin resistance

Other disorders

Although jaundice is common in newborns, mutations in the *UGT1A1* gene increase the risk of developing a more severe condition called transient familial neonatal hyperbilirubinemia. In this condition, severe unconjugated hyperbilirubinemia and jaundice occur in newborns and usually disappear in 1 to 2 weeks. Some babies develop kernicterus (which can be lethal), hearing loss, or other neurological problems. The G71R mutation is the most common mutation associated with transient familial neonatal hyperbilirubinemia. Asian but not white newborns with a *UGT1A1* gene mutation seem to be at risk of developing this condition.

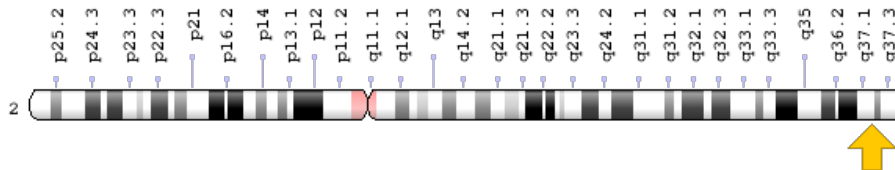
Sometimes newborn jaundice is associated with breastfeeding: Unconjugated bilirubin levels increase when the baby is breastfed, causing jaundice, and return to normal when breastfeeding is stopped for a prolonged period. This condition, often called breast milk jaundice, appears 5 or 10 days after birth and disappears at around 4 months of age. Kernicterus is not typically seen in infants with breast milk jaundice. Research suggests that a substance in the breast milk of mothers of affected infants blocks glucuronidation. In addition, many affected infants have a mutation in one copy of the *UGT1A1* gene, most commonly the G71R mutation, and the mutation is thought to underlie the unconjugated hyperbilirubinemia. The substance in the breast

milk may trigger the buildup of unconjugated bilirubin in infants with already impaired bilirubin-UGT enzyme function.

Chromosomal Location

Cytogenetic Location: 2q37.1, which is the long (q) arm of chromosome 2 at position 37.1

Molecular Location: base pairs 233,760,273 to 233,773,299 on chromosome 2 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- BILIQTL1
- bilirubin-specific UDPGT isozyme 1
- bilirubin UDP-glucuronosyltransferase 1-1
- GNT1
- HUG-BR1
- UD11_HUMAN
- UDP-glucuronosyltransferase 1-A
- UDP glucuronosyltransferase 1 family, polypeptide A1
- UDP-glucuronosyltransferase 1A1
- UDP glycosyltransferase 1 family, polypeptide A1
- UDPGT
- UDPGT 1-1
- UGT-1A
- UGT1
- UGT1-01
- UGT1*1

- UGT1.1
- UGT1A

Additional Information & Resources

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28UGT1A1%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- HYPERBILIRUBINEMIA, TRANSIENT FAMILIAL NEONATAL
<http://omim.org/entry/237900>
- UDP-GLYCOSYLTRANSFERASE 1 FAMILY, POLYPEPTIDE A1
<http://omim.org/entry/191740>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_UGT1A1.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=UGT1A1%5Bgene%5D>
- HGNC Gene Symbol Report
https://www.genenames.org/data/gene-symbol-report#!/hgnc_id/HGNC:12530
- Monarch Initiative
<https://monarchinitiative.org/gene/NCBIGene:54658>
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/54658>
- UniProt
<https://www.uniprot.org/uniprot/P22309>

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<http://omim.org/entry/191740>
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