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Hematologically important mutations: Bilirubin UDP-glucuronosyltransferase gene mutations in Gilbert and Crigler–Najjar syndromes

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Abstract

Gilbert and Crigler–Najjar syndromes are familial unconjugated hyperbilirubinemias caused by genetic lesions involving a single complex locus encoding for bilirubin UDP-glucuronosyltransferase (UGT1A1) gene. Over the last years, a number of different mutations affecting this gene have been characterized. In this report is provided a summary of reported Gilbert and Crigler–Najjar syndromes-associated UGT1A1 gene mutations.

Keywords: Gilbert syndrome; UGT1A1; Hyperbilirubinemia; Mutations

Water-insoluble bilirubin, which results from breakdown products of heme, is a toxic compound. Hepatic glucuronization of this insoluble bilirubin is catalyzed by isoenzyme 1A1 of UDP-glucuronosyltransferase (UGT1A1), which is essential for efficient biliary excretion of bilirubin [1,2]. Mutations in the UGT1A1 gene (UGT1A1; MIM#191740) are responsible for both Gilbert and Crigler–Najjar syndromes. Genetic alterations causing absence, or severe reduction, of UGT1A1 enzymatic activity, result respectively in Crigler–Najjar syndrome type I and type II [1–5]. The clinical classification of Crigler–Najjar syndrome types I and II is based on the bilirubin levels, the presence of kernictus and the reduction of the bilirubin levels upon administration of phenobarbital or other enzyme-inducing agents [3,4]. Type I Crigler–Najjar syndrome is characterized by almost complete absence of UGT1A1 enzyme activity, with serum bilirubin levels of 340–685 μmol/l or higher and is refractory to phenobarbital treatment. In type II Crigler–Najjar syndrome, enzyme activity is severely reduced, with a serum bilirubin level of 100–340 μmol/l. Enzyme activity can be induced by phenobarbital treatment [3,4]. Mild hyperbilirubinemia, usually less than 50 μmol/l, is associated with Gilbert Syndrome and thought to reflect a small reduction in UGT1A1 activity (approximately 30%) [2]. UGT1A1 protein is encoded by five consecutive exons located at the 3′ end of the UGT1A locus [5].

Gilbert and Crigler–Najjar Syndromes gene mutations are shown in Table 1. The nucleotide numbers shown in this table are based on the cDNA sequence in the GenBank, accession number NM_000463.2. The recommended numbering convention used in this tabulation assigns "1" to the A of the initiator ATG codon. Mutations are described according to the recommendations of the Human Genome Variation Society (www.hgvs.org).

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Table 1
Bilirubin UDP-glucuronosyltransferase gene mutations in Gilbert and Crigler–Najjar syndromes

cDNA nucleotide substitution	Amino acid substitution	Mutation type	Phenotype associated[a]	References	Comments
c.−3279T > G	–	Substitution	GS	[6,7]	Described also associated with c.−41_−40dupTA
c.−41_−40dupTA	–	Duplication	GS	[8]	Described as (TA)7 allele. The most common mutation associated with GS in Caucasian population. Also associated with neonatal hyperbilirubinemia
c.−43_−40dupTATA	–	Duplication	GS	[9]	Described as (TA)8 allele
c.44T > G	p.L15R	Substitution	CN2	[10]	b
c.101C > A	p.P34Q	Substitution	CN2	[11]	c
c.115C > G	p.H39D	Substitution	CN1	[12]	d
c.145C > T	p.Q49X	Substitution	CN1	[13]	c
c.211G > A	p.G71R	Substitution	SG	[14]	The most common mutation associated with GS in Asian population. Also associated with neonatal hyperbilirubinemia
c.222C > A	p.Y74X	Substitution	CN1	[12]	d
c.247T > C	p.F83L	Substitution	GS	[15]	Homozygosity was described in association with GS
c.357_358delCT	p. S120CfsX25	Deletion, frameshift	CN1	[16]	d
c.488_491dupACCT	p.S165PfsX18	Duplication, frameshift	GS	[17]	Described in *trans* with c.− 41_− 40dupTA mutation
c.508_510delTTC	p.F170del	Deletion	CN2	[18]	d
c.517delC	p.H173MfsX31	Deletion, frameshift	CN1	[12]	d
c.524T > A	p.L175Q	Substitution	CN2	[19]	c
c.529T > C	p.C177R	Substitution	CN1	[19]	c
c.576C > G	p.Y192X	Substitution	CN1, CN2	[11]	This mutation in *trans* with c.1184G > T mutation was associated with CN1 and in *trans* with c.1130G > T mutation was associated with CN2
c.625C > T	p.R209W	Substitution	CN2	[20]	b
c.674T > G	p.V225G	Substitution	CN2	[21,17]	Also associated with GS in *cis* with c.− 41_− 40dupTA mutation
c.686C > A	p.P229Q	Substitution	GS	[22]	Detected in heterozygosity
c.717_718delAG	p.E241GfsX15	Deletion, frameshift	CN2	[21]	Described in association with two other mutations
c.801delC	p.I268SfsX97	Deletion, frameshift	CN1	[11]	d
c.835A > T	p.N279Y	Substitution	CN1	[19]	c
c.840C > A	p.C280X	Substitution	CN1	[23]	d
c.864 + 1G > C	Splicing alteration	Substitution frameshift	CN1	[13]	d
c.865 − ?_997 + ?del	p. E288_T332del	Deletion	CN1	[19]	Alteration detected only at RNA level
c.865 − 1G > A	Splicing alteration	Substitution frameshift	CN1	[11]	c
c.875C > T	p.A292V	Substitution	CN1	[24]	c
[c.877T > A + c.878_890del]	p.I294_S297delY293MfsX68	Substitution, deletion, frameshift	CN2	[11,25]	d
c.878_890del	p.I294_S297delY293LfsX68	Deletion, frameshift	CN2	[11,25]	c
c.881T > C	p.I294T	Substitution	CN2	[26]	c
c.923G > A	p.G308E	Substitution	CN1	[27,17]	Also associated with GS and CN2 in *trans* with c.− 41_− 40dupTA mutation
c.973delG	p.A325LfsX40	Deletion, frameshift	CN2	[19]	c
c.991C > T	p.Q331X	Substitution	CN1	[28]	d
c.992A > G	p.Q331R	Substitution	CN2	[29]	b
c.997 − 2A > G	Splicing alteration	Substitution frameshift	CN1	[25]	c
c.1005G > A	p.W335X	Substitution	CN1	[24]	c
c.1006C > T	p.R336W	Substitution	CN1	[26]	c
c.1007G > A	p.R336Q	Substitution	CN1	[11]	c
c.1021C > T	p.R341X	Substitution	CN1	[30]	d
c.1043delA	p.N348TfsX17	Deletion, frameshift	CN1	[12]	d
c.1060T > C	p.W354T	Substitution	CN2	[11]	c
c.1069C > T	p.Q357X	Substitution	CN1	[24]	d

Table 1 (*continued*)

cDNA nucleotide substitution	Amino acid substitution	Mutation type	Phenotype associated[a]	References	Comments
c.1070A > G	p.Q357R	Substitution	CN1	[24]	d
c.1085 − 1G > A	Splicing alteration	Substitution	CN1	[25]	c
c.1099C > G	p.R367G	Substitution	GS	[22]	Detected in heterozygosity
c.1102G > A	p.A368T	Substitution	CN1	[24]	c
c.1124C > T	p.S375F	Substitution	CN1	[27]	d
c.1127A > G	p.H376R	Substitution	CN2	[12]	c
c.1130G > T	p.G377V	Substitution	CN2	[12]	d
c.1143C > G	p.S381R	Substitution	CN1	[24]	d
c.1157_1158indelsGT	p.V386G	Insertion, deletion	CN1	[16]	d
c.1159C > T	p.P387S	Substitution	CN1	[11]	c
c.1184G > T	p.G395V	Substitution	CN1	[11]	d
c.1186delG	p.D396IfsX15	Deletion, frameshift	CN2	[31]	c
c.1198A > G	p.N400D	Substitution	CN2	[32]	Associated with homozygosity for the c.− 43_− 40dupTATA mutation
c.1201G > C	p.A401P	Substitution	CN1	[24]	c
c.1207C > T	p.R403C	Substitution	CN2	[11]	c
c.1220delA	p.K407RfsX4	Deletion, frameshift	CN1	[12]	c
c.1223insG	p.A409SfsX12	Insertion, frameshift	CN1	[24]	c
c.1282A > G	p.K428E	Substitution	CN1	[24]	c
c.1304 + 1G > T	Splicing alteration	Substitution	CN1	[11]	c
c.1309A > T	p.K437X	Substitution	CN1	[24]	c
c.1381T > C	p.W461R	Substitution	CN1	[33]	d
c.1388A > C	p.E463A	Substitution	CN2	[34]	Associated with homozygosity for the c.− 41_− 40dupTA mutation
c.1433C > A	p.A478D	Substitution	CN2	[11]	b
c.1448G > A	p.W483X	Substitution	CN1	[12]	d
c.1449G > A	p.W483X	Substitution	CN1	[12]	d
c.1456T > G	p.Y486D	Substitution	CN2	[35]	Associated with homozygosity to the c.211G > A mutation
c.1463C > T	p.S488F	Substitution	CN1	[28]	d
c.1487T > A	p.L496X	Substitution	CN1	[12]	c

b) Homozygosity for this mutation was described in association with CN2.
c) This mutation was described in *trans* with other mutation.
d) Homozygosity for this mutation was described in association with CN1.
GS: Gilbert syndrome. CN1: Crigler–Najjar Syndrome type I. CN2: Crigler–Najjar Syndrome type II.
[a] The phenotype associated is related with the first description of the mutation.

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