Available online at www.sciencedirect.com
SCIENCE DIRECT
Blood Cells, Molecules, and Diseases 36 (2006) 77 – 80
BLOOD CELLS, MOLECULES, & DISEASES
www.elsevier.com/locate/ybcmd

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

Elísio Costa

Escola Superior de Saúde do Instituto Politécnico de Bragança, Avenida D. Afonso V, 5300-121 Bragança, Portugal

Submitted 29 October 2005; revised 31 October 2005

(Communicated by E. Beutler, M.D., 31 October 2005)

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).

References

[1] M. Sampietro, A. Iolascon, Molecular pathology of Crigler–Najjar type I and II and Gilbert's syndrome, Haematologica 84 (1999) 150–157.
[2] J. Borlak, T. Thum, O. Landt, K. Erb, R. Hermann, Molecular diagnosis of a familial nonhemolytic hyperbilirubinemia (Gilbert syndrome) in healthy subjects, Hepatology 32 (2000) 792–795.
[3] G.R. Lee, T.C. Bithell, J. Foerster, J.W. Athens, J.N. Lukens, Wintrobe's Clinical Haematology, 9th ed., Lea and Febiger, Philadelphia, 1993.
[4] D.G. Nathan, S.H. Orking, Nathan and Oski's Haematology of Infancy and Childhood, 5th ed., WB Sanders Company, Philadelphia, 1998.
[5] P.J. Bosma, N.R. Chowdhury, B.G. Goldhoorn, et al., Sequence of exons and the flanking regions of human bilirubin–UDP-glucurono-

E-mail address: elisio.costa@ipb.pt.

1079-9796/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcmd.2005.10.006

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.

syltransferase gene complex and identification of a genetic mutation in a patient with Crigler–Najjar syndrome type I, Hepatology 15 (1992) 941–947.
[6] J. Sugatani, K. Yamakawa, K. Yoshinari, T. Machida, H. Takagi, M. Mori, et al., Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia, Biochem. Biophys. Res. Commun. 292 (2002) 492–497.
[7] E. Costa, E. Vieira, R. Santos, The polymorphism c.-3279T>G in the phenobarbital-responsive enhancer module of the bilirubin UDP-glucuronosyltransferase gene is associated with Gilbert syndrome, Clin. Chem. 51 (2005) 2204–2206.
[8] P.J. Bosma, J.R. Chowdhury, C. Bakker, S. Gantla, A. Boer, B.A. Oostra, et al., The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert syndrome, N. Eng. J. Med. 333 (1995) 1171–1175.
[9] A. Iolascon, M.F. Faienza, M. Centra, S. Storelli, et al., (TA)8 allele in the UGT1A1 gene promoter of a Caucasian with Gilbert's syndrome, Haematologica 84 (1999) 106–109.
[10] J. Seppen, E. Steenken, D. Lindhout, P.J. Bosma, R.P. Elferink, A mutation which disrupts the hydrophobic core of the signal peptide of bilirubin UDP-glucuronyltransferase, an endoplasmatic reticulum membrane protein, causes Crigler–Najjar type II, FEBS Lett. 390 (1996) 294–298.
[11] V. Servedio, M. d'Apolito, N. Maiorano, B. Minuti, F. Torricelli, F. Ronchi, et al., Spectrum of UGT1A1 mutations in Crigler–Najjar (CN) syndrome patients: identification of twelve novel alleles and genotype–phenotype correlation, Hum. Mutat. 25 (2005) 325.
[12] A. Kadakol, S.S. Ghosh, B.S. Sappal, G. Sharma, J.R. Chowdhury, N.R. Chowdhury, Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler–Najjar and Gilbert syndromes: correlation of genotype to phenotype, Hum. Mutat. 16 (2000) 297–306.
[13] S. Gantla, C.T. Bakker, B. Deocharan, N.R. Thummala, J. Zweiner, M. Sinaasappel, J. Roy Chowdhury, P.J. Bosma, N. Roy Chowdhury, Splice-site mutations: a novel genetic mechanism of Crigler–Najjar syndrome type 1, Am. J. Hum. Genet. 62 (1998) 585–592.
[14] Y. Maruo, S. Wada, K. Yamamoto, H. Sato, T. Yamano, M. Shimada, A case of anorexia nervos with hyperbilirubinaemia in a patient homozygous for a mutation in the bilirubin UDP/glucuronosyltransferase gene, Eur. J. Pediatr. 158 (1999) 547–549.
[15] 3R. Sutomo, V. Laosombat, A.H. Sadewa, N. Yokoyama, H. Nakamura, M. Matsuo, H. Nishio, Novel missense mutation of the UGT1A1 gene in Thai siblings with Gilbert's syndrome, Pediatr. Int. 44 (2002) 427–432.
[16] M. Ciotti, R. Obaray, M.G. Martin, I.S. Owens, Genetic defects at the UGT1 locus associated with Crigler–Najjar type I disease, including a prenatal diagnosis, Am. J. Med. Genet. 68 (1997) 173–178.
[17] E. Costa, E. Vieira, M. Martins, J. Saraiva, E. Cancela, M. Costa, R. Bauerle, T. Freitas, J.R. Carvalho, E. Santos-Silva, J. Barbot, R. dos Santos, Analysis of the UDP-glucuronosyltransferase gene in Portuguese

patients with a clinical diagnosis of Gilbert and Crigler–Najjar syndromes. Blood Cells Molecules and Disease, (in press).
[18] J.K. Ritter, M.T. Yeatman, C. Kaiser, B. Gridelli, I.S. Owens, A phenylalanine codon deletion at the UGT1 gene complex locus of a Crigler–Najjar type I patient generates a pH-sensitive bilirubin UDP-glucuronosyltransferase, J. Biol. Chem. 268 (1993) 23573–23579.
[19] J. Seppen, P.J. Bosma, B.G. Goldhoorn, C.T. Bakker, J.R. Chowdhury, P.L. Jansen, R. Oude, P. Elferink, Discrimination between Crigler–Najjar type I and II by expression of mutant bilirubin uridine diphosphate glucurononosyltransferase, J. Clin. Invest. 94 (1994) 2385–2391.
[20] P.J. Bosma, B. Goldhoorn, R.P. Oude Elferink, M. Sinaasappel, B.A. Oostra, P.L. Jansen, A mutation in bilirubin uridine 5′-diphosphate glucuronosyltransferase isoform 1 causing Crigler–Najjar syndrome type II, Gastroenterology 105 (1993) 216–220.
[21] A. Iolascon, A. Meloni, B. Coppola, M.C. Rosatelli, Crigler–Najjar syndrome type II resulting from three different mutations in the bilirubin uridine 5′-diphosphate-glucuronosyltransferase (UGT1A1) gene, J. Med. Genet. 37 (2000) 712–713.
[22] O. Koiwai, M. Nishizawa, K. Hasada, S. Aono, Y. Adachi, N. Mamiya, H. Sato, Gilbert's syndrome is caused by a heterozygous missense mutation in the gene for bilirubin UDP-glucuronosyltransferase, Hum. Mol. Genet. 4 (1995) 1183–1186.
[23] S. Aono, Y. Yamada, H. Keino, Y. Sasaoka, T. Nakagawa, S. Onishi, S. Mimura, O. Koiwai, H. Sato, A new type of defect in the gene for bilirubin uridine 5′-diphosphate-glucuronosyltransferase in a patient with Crigler–Najjar syndrome type I, Pediatr. Res. 35 (1994) 629–632.
[24] P. Labrune, A. Myara, M. Hadchouel, F. Ronchi, O. Bernard, F. Trivin, N.R. Chowdhury, J.R. Chowdhury, A. Munnich, M. Odievre, Genetic heterogeneity of Crigler–Najjar type I: a study of 14 cases, Hum. Genet. 94 (1994) 693–697.
[25] B.S. Sappal, S.S. Gosh, B. Sheneider, A. Kadakol, J.R. Chowdhury, N.R. Chowdhury, A novel intronic mutation results in the use of a cryptic splice acceptor site within the coding region of UGT1A1, causing Crigler–Najjar syndrome type I, Mol. Genet. Metab. 75 (2002) 134–142.
[26] M. Ciotti, F. Chen, F.F. Rubaltelli, I.S. Owens, Coding defect and TATA box mutation at the bilirubin UDP-glucuronosyltransferase gene cause Crigler–Najjar type I disease, Biochim. Biophys. Acta 1407 (1998) 40–50.
[27] L.T. Erps, J.K. Ritter, J.H. Hersh, D. Blossom, N.C. Martin, I.S. Owens, Identification of two single base substitutions in the UGT1 gene locus which abolish bilirubin uridine diphosphate glucuronosyltransferase activity in vitro, J. Clin. Invest. 93 (1994) 564–570.
[28] P.J. Bosma, J.R. Chowdhury, T.J. Huang, P. Lahiri, R.P. Elferink, H.H. Van Es, M. Lederstein, P.F. Whitington, P.L. Jansen, N.R. Chowdhury, Mechanisms of inherited deficiencies of multiple UDP-glucuronosyltransferase isoforms in two patients with Crigler–Najjar syndrome type I, FASEB J. 6 (1992) 2859–2863.
[29] N. Moghrabi, D.J. Clarke, M. Boxer, B. Burchell, Identification of an A-to-G missense mutation in exon 2 of the UGT1 gene complex that causes Crigler–Najjar syndrome type 2, Genomics 18 (1993) 171–173.
[30] N. Moghrabi, D.J. Clarke, B. Burchell, M. Boxer, Cosegregation of intragenic markers with a novel mutation that causes Crigler–Najjar syndrome type I: implications in carrier detection and prenatal diagnosis, Am. J. Hum. Genet. 53 (1993) 722–729.
[31] C.S. Huang, G.A. Luo, M.J. Huang, E.S. Chen, T.H. Young, Y.C. Chao, A novel compound heterozygous variation of the uridine-diphosphoglucuronosyltransferase 1A1 gene that causes Crigler–Najjar Syndrome type II, Pharmacogenetics 11 (2001) 639–642.
[32] P. Labrune, A. Myara, J. Chalas, B. Le Bihan, L. Capel, J. Francoual, Association of a homozygous (TA)8 promoter polymorphism and a N400D mutation of UGT1A1 in child with Crigler–Najjar type II syndrome, Hum. Mutat. 20 (2002) 399–401.
[33] Y. Maruo, E. Serdaroglu, M. Iwai, H. Takahashi, A. Mori, M. Bak, S. Calkavur, H. Sato, Y. Takeuchi, A novel missense mutation of the bilirubin UDP-glucuronosyltransferase gene in a Turkish patient with Crigler–Najjar syndrome type I, J. Pediatr. Gastroenterol. Nutr. 37 (2003) 627–630.
[34] N. Chalasani, N.R. Chowdhury, J.R. Chowdhury, T.D. Boyer, Kernictus in an adult who is heterozygous for Crigler–Najjar syndrome and homozygous for Gilbert-type genetic defect, Gastroenterology 112 (1997) 2099–2103.
[35] S. Aono, Y. Yamada, H. Keino, N. Hanada, T. Nakagawa, Y. Sasaoka, T. Yazawa, H. Sato, O. Koiwai, Identification of defect in the genes for bilirubin UDP-glucuronosyl-transferase in a patient with Crigler–Najjar syndrome type II, Biochem. Biophys. Res. Commun. 197 (1993) 1239–1244.