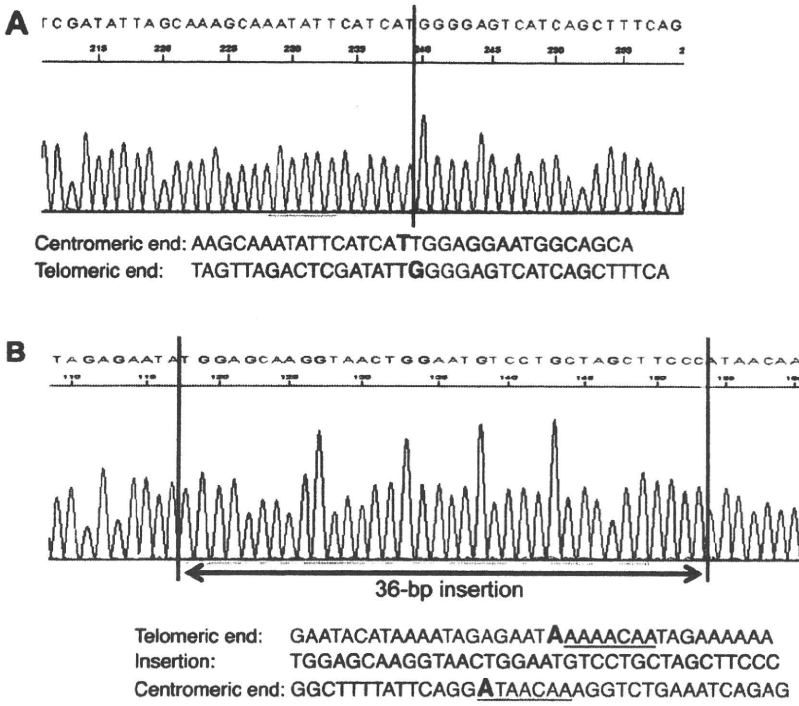

Fig. 5. The results of direct sequence analysis of the PCR products spanning the deletion breakpoints in Patient 1 (A: reverse sequence) and in Patient 2 (B: forward sequence) Red/blue letters below the sequence represent present/absent sequences around the deletion breakpoints. The sequence of the inserted 36 bases in Patient 2 is shown in black letters. Bold red letters represent the nucleotides at the breakpoints. Red vertical lines represent the deletion breakpoint in each patient. Underlined sequence in Patient 2 indicates a microhomology between the telomeric and centromeric breakpoint junctions.

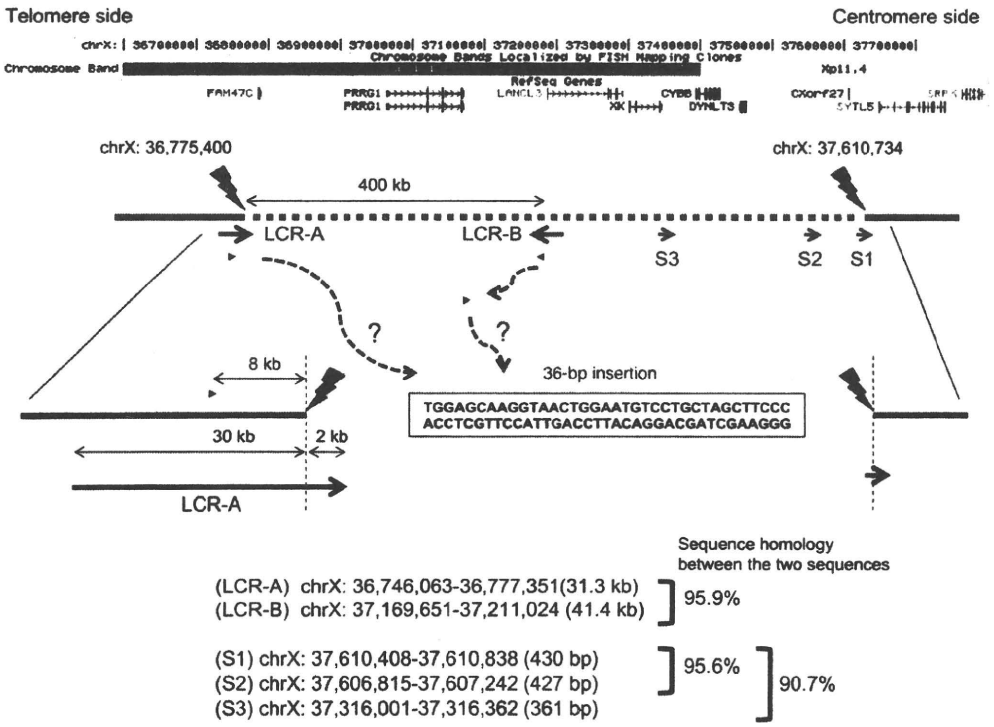

Fig. 6. Schematic representation of the deletion and significant architectural features in Patient 2 Genomic position was indicated at the top with chromosomal bands. Genes and selected transcripts are indicated. The extent of the present and absent regions in Patient 2 is shown as solid and dotted lines, respectively. Filled triangles indicate the sequence which matched the 36-bp insertion in a direct (►) and an opposite (◄) orientation. The lightning symbol (↯) indicates each deletion breakpoint.

although non-homologous end joining or other mechanisms could be also considered especially those cases in which microhomology is absent [8].

Both of the present patients had no homologous architectural features between the telomeric and centromeric breakpoint junctions except a microhomology in Patient 2, indicating their genomic rearrangements were not due to NAHR. However, the telomeric breakpoint of Patient 2 was embedded in an LCR (LCR-A) located upstream of another LCR (LCR-B) in an opposite orientation (Fig. 6). These LCRs were 30 to 40 kb long with sequence homology of 95.9%. The centromeric breakpoint of Patient 2 was also embedded in a short segment (S1) downstream of two segments (S2 and S3) which were 300 to 400 bp long with sequence homology of 90 to 95% (Fig. 6). Furthermore, UCSC Blat search showed that the sequence of 36 bases inserted between the deletion breakpoints matched a forward sequence upstream of the telomeric breakpoint and also matched a reverse sequence located within the deleted region. Interestingly, these matched sequences were located in the middle of LCR-A and LCR-B, respectively. These findings observed in Patient 2 are consistent with the characteristics of non-recurrent genomic rearrangements described above, suggesting MMBIR may have occurred in this patient [8]. Regardless of its mechanism, significant genomic architectural features at the telomeric and centromeric ends may have stimulated the genomic rearrangements observed in Patient 2.

The paucity of documented architectural features like LCRs might explain why there are only a few patients that have been described with CGS involving this region. However, many patients with this genomic disorder may have been overlooked. As was shown in the present patients, the multiple unrelated clinical features suggestive of CGS may not always be manifested at the same time. In Patient 1, the presence of CGS was considered at the age of 3 years, when signs and symptoms of CGD were appreciated, long after he survived neonatal symptoms due to OTC deficiency. In cases of OTC deficiency caused by deletions of *OTC* gene [4], the extent of the deletions may not have been accurately studied in patients who did not survive the neonatal period. In case of Patient 2, a CGS was not suspected until a molecular study was performed at the age of 18 years. Early diagnosis of McLeod syndrome is generally difficult because neurological symptoms and signs develop at a mean age of 30 to 40 years [9].

Array CGH is useful for detecting gross deletions and duplications. Its widespread use will contribute to the detection of new and possibly overlooked patients with CGS. This method is also useful as an initial step to determine deletion breakpoints. The accurate description of the deletion breakpoints has some benefits: accurate evaluation of the affected genes, carrier and prenatal diagnosis from a limited sample by PCR spanning the deletion breakpoints, and better understanding of the deletion mechanisms. Prenatal diagnosis is especially important when the deletion involves the *OTC* gene, since early treatment including liver transplantation can significantly improve the outcome in OTC deficiency [15]. This present study also shows that the DNA Walking study is effective when genomic rearrangements are complex or when there are highly homologous regions around the deletion breakpoints.

Accurate description of the deletion breakpoints in more patients is necessary for a better understanding of the mechanisms of the genomic rearrangements that occur in this genomic disorder.

Acknowledgements

The authors thank Dr. Stewart DM for reviewing the manuscript. This work was supported in part by a grant for Research on Intractable Diseases from the Japanese Ministry of Health, Labor and Welfare. All authors declare that they have no competing interests.

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Blood Cells, Molecules, and Diseases 45 (2010) 246–265

Contents lists available at ScienceDirect

Blood Cells, Molecules, and Diseases

journal homepage: www.elsevier.com/locate/ybcmd

Hematologically important mutations: X-linked chronic granulomatous disease (third update)

Dirk Roos [a,*], Douglas B. Kuhns [b], Anne Maddalena [c], Joachim Roesler [d], Juan Alvaro Lopez [e], Tadashi Ariga [f], Tadej Avcin [g], Martin de Boer [a], Jacinta Bustamante [h], Antonio Condino-Neto [i], Gigliola Di Matteo [j], Jianxin He [k], Harry R. Hill [l,m,n,o], Steven M. Holland [p], Caroline Kannengiesser [q], M. Yavuz Köker [r], Irina Kondratenko [s], Karin van Leeuwen [a], Harry L. Malech [t], László Marodi [u], Hiroyuki Nunoi [v], Marie-José Stasia [w], Anna Maria Ventura [x], Carl T. Witwer [l,m,n,o], Baruch Wolach [y], John I. Gallin [t]

[a] Sanquin Research, and Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, Plesmanlaan 125, 1066 CX, Amsterdam, The Netherlands
[b] SAIC-Frederick, Inc., NCI Frederick, Frederick, MD, USA
[c] GeneDx, Gaithersburg, MD, USA
[d] Dept. of Pediatrics, University Hospital Carl Gustav Carus, Dresden, Germany
[e] School of Microbiology, University of Antioquia, Medellin, Colombia
[f] Dept. of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[g] Dept. of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, Ljubljana, Slovenia
[h] Laboratory of Human Genetics of Infectious Diseases, INSERM, U550, and René Descartes University, Necker Medical School, Paris, France
[i] Dept. of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil
[j] Dept. of Public Health and Cellular Biology, Tor Vergata University, Rome, Italy
[k] Lung Function Lab, Pediatric Research Institute, Beijing Children's Hospital Affiliated to Capital Medical University, Beijing, People's Republic of China
[l] Dept. of Pathology, University of Utah, Salt Lake City, UT, USA
[m] Dept. of Pediatrics, University of Utah, Salt Lake City, UT, USA
[n] Dept. of Medicine, University of Utah, Salt Lake City, UT, USA
[o] ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, USA
[p] Laboratory of Clinical Infectious Disease, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA
[q] Assistance Publique des Hôpitaux de Paris, Bichat-Claude Bernard Hospital, Hormonal Biochemistry and Genetic Service, Paris, F-75018, and INSERM, Biomedical Research Center Bichat-Beaujon, U773, Paris, F-75018, France
[r] Immunology Laboratory and Cappadocia Transplant Centre, University of Erciyes, Kayseri, Turkey
[s] Dept. of Clinical Immunology, Russian Children's Clinical Hospital, Moscow, Russia
[t] Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA
[u] Dept. of Infectiology and Pediatric Immunology, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary
[v] Dept. of Reproductive and Developmental Medicine, Division of Pediatrics, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan
[w] Chronic Granulomatous Disease Diagnosis and Research Centre, University Hospital Grenoble, Therex-TIMC/Imag UMR CNRS 5525, University J. Fourrier, Grenoble, France
[x] Dept. of Biomedicine of Development Age, University of Bari, Bari, Italy
[y] Dept. of Pediatrics and Laboratory for Leukocyte Function, Meir Medical Centre, Kfar Saba, Israel

ARTICLE INFO

Article history:
Submitted 16 July 2010
Available online 21 August 2010

(Communicated by M. Lichtman, M.D., 20 July 2010)

Keywords:
gp91^{phox}
Chronic granulomatous disease
Mutation
CYBB
NADPH oxidase
X-linked disease

ABSTRACT

Chronic granulomatous disease (CGD) is an immunodeficiency disorder affecting about 1 in 250,000 individuals. The disease is caused by a lack of superoxide production by the leukocyte enzyme NADPH oxidase. Superoxide is used to kill phagocytosed micro-organisms in neutrophils, eosinophils, monocytes and macrophages. The leukocyte NADPH oxidase is composed of five subunits, of which the enzymatic component is gp91-*phox*, also called Nox2. This protein is encoded by the *CYBB* gene on the X chromosome. Mutations in this gene are found in about 70% of all CGD patients. This article lists all mutations identified in *CYBB* in the X-linked form of CGD. Moreover, apparently benign polymorphisms in *CYBB* are also given, which should facilitate the recognition of future disease-causing mutations.

* Corresponding author. Sanquin Research, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands. Fax: +31 20 5123310.
URLs: d.roos@sanquin.nl (D. Roos), HMALECH@niaid.nih.gov (H.L. Malech).

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doi:10.1016/j.bcmd.2010.07.012

The most common form of chronic granulomatous disease (CGD) is caused by mutations in the X-linked gene (*CYBB*, located at Xp21.1, OMIM *300481) for the protein gp91-*phox* (also known as Nox2). This protein is one of two subunits of flavocytochrome b_{558} (the other is p22-*phox*) and is an essential component of the phagocyte NADPH oxidase system. In previous tables we listed 343 mutations in *CYBB* known to cause X-linked CGD (X91 CGD; OMIM #306400) [1]. In the present, updated tables 338 newly identified mutations have been added (marked with * in the last column). Mutations that have not been previously published elsewhere are marked as "unpubl.". Table 1 includes missense mutations, nonsense mutations, splice site mutations, deletions and insertions that have been precisely defined. Mutations that lead to missplicing of mRNA, whether nucleotide substitutions, insertions or deletions, have all been tabulated as splice-site mutations. Table 2 includes larger deletions affecting the gp91^{phox} gene, some of which also cause other diseases. Where possible we have cross-referenced the mutations indicated here with those in an X-CGD database that lists X91 CGD patients by accession number. This database contains additional biochemical, genetic and clinical information and is available at http://www.uta.fi/imt/bioinfo/CYBBbase/. Moreover, information can also be found in the HGMD database at http://www.hgmd.cf.ac.uk/ac/search.php. Additional information about these mutations and about CGD in general can also be found in recent reviews [2–6] and in the cited literature. An update article with the mutations causing the autosomal recessive forms of CGD has recently been published separately [7]. Table 3 contains the known polymorphisms in *CYBB*. It is important to realize that SNPs and other sequence variants available on the internet are not necessarily functionally neutral. Table 4 summarizes the total number of kindreds with X-CGD patients included in this study, the total number of X-CGD patients, the total number of different mutations and the total number of mutations unique for one kindred, arranged according to type of mutation.

We have used the standard notation for differentiating the various phenotypes of X-linked CGD, X91°, X91$^-$, and X91$^+$, where the superscript denotes whether the level of gp91-*phox* protein is undetectable (°), diminished ($^-$) or normal ($^+$), as determined by immunoblot analysis and/or spectral analysis. The designation X91$^?$ indicates that the level of gp91-*phox* protein expression has not been determined. The respective proteins can be non-functional, exert residual activity, or in case of ($^-$) be fully functional. The nucleotide numbering system we have used is based on the cDNA sequence and follows the convention that +1 is the A of the ATG initiator codon. This differs from the numbering of the GenBank sequence, which starts at A−12 (subtract 12 from GenBank sequence number to make the initiator A +1). Moreover, GenBank incorrectly denotes Met65 as the start codon of protein translation. The notation of the mutations follows the recommendations of the Human Genome Variation Society [8] (see also www.hgvs.org/mutnomen). The consequences of the mutations for protein composition have been checked with the Mutalyzer program (www.lovd.nl/mutalyzer) [9].

Acknowledgments

We thank the CGD Research Trust, London, UK, for the financial support. LM thanks B. Tóth (Debrecen) for the helpful contribution to this work. ACN thanks Edgar Borges de Oliveira Jr, PhD, for the excellent work, and Fundação de Amparo a Pesquisa do Estado de São Paulo for the financial support (FAPESP, Grant 2005/59568). This work was supported in part by the Slovenian Research Agency (Grant L3-0624). CK thanks Prof. M.A. Gougerot-Pocidalo for performing the Western blot analysis of NADPH oxidase subunits and measurement of respiratory burst in patients' polymorphonuclear neutrophils. DR thanks Dr. Paul Heyworth for providing information on unpublished mutations.

This project has been funded in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract no. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Table 1
Mutations in the gp91^{phox} gene *CYBB* that cause X-linked CGD.

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.−69A>C	Promoter	NA	X91$^-$	A0089 A0090	[1,10–12]	1(2)	
c.−67T>C	Promoter	NA	X91$^-$	A0166 A0550 A0551 A0552	[1,10–13]	2(4)	
c.−67dupT	Promoter	NA	X91$^-$b		[14]	1(2)	*
c.−65C>T	Promoter	NA	X91$^-$b	A0472 A0548 A0549	[1,15–18]	2(3)	
c.−64C>T	Promoter	NA	X91$^-$b	A0546	[1,16,18] unpubl.	2(5)	
c.1A>G	Missense	p.Met1Val; startcodon lost	X91°	A0242	[1,19,20] unpubl.	4(4)	
c.2T>A	Missense	p.Met1Lys; startcodon lost	X91$^-$	A0411	[1]	1(1)	
c.2T>G	Missense	p.Met1Arg; startcodon lost	X91$^-$	A0412	[1]	1(1)	
c.6dupG	Insertion	p.Asn3GlufsX6	X91°	A0346	[21] unpubl.	2(2)	*
c.8dupA	Insertion	p.Asn3LysfsX6	X91°		[22]	1(1)	*
c.11G>A	Nonsense	p.Trp4X	X91°	A0260 A0490	[1,11,23]	3(3)	
c.12G>A	Nonsense	p.Trp4X	X91°	A0108 A0491 A0492 A0493	[1,12,19] unpubl.	5(6)	
c.14_27del14	Deletion	p.Val6LeufsX24	X91°	A0305	[1]	1(1)	
c.23_26dupAGGG	Insertion	p.Leu10GlyfsX26	X91°	A0334	[1]	1(1)	
c.27delG	Deletion	p.Leu10SerfsX12	X91$^?$		Unpubl.	1(1)	*
c.27dupG	Insertion	p.Leu10AlafsX25	X91$^?$	A0557	[24]	1(1)	*
c.40delG	Deletion	p.Val14SerfsX8	X91°	A0079	[1,19,25]	1(1)	
c.42_45dupCATT	Insertion	p.Leu16HisfsX20	X91$^?$	A0619	[20]	1(1)	*

(continued on next page)

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.45+1G>C[c]	Splice site	del. exon 1? p.Met1_Ile15del? No start protein prod.	X91°	A0223	[1,26]	1(1)	
c.45+1G>A[c]	Splice site	del. exon 1? p.Met1_Ile15del? No start protein prod.	X91°	A0592	[27,28] unpubl.	3(3)	*
c.45+1G>T[c]	Splice site	del. exon 1? p.Met1_Ile15del? No start protein prod.	X91°		[29]	1(1)	*
c.45+1delG[c]	Splice site	del. exon 1	X91°		[30]	1(1)	*
c.45+5G>A[c]	Splice site	del. exon 1? p.Met1_Ile15del No start protein prod.	X91°/−	A0003	[1,11] unpubl.	2(2)	
c.45+5_7delGTA[c]	Splice site	del. exon 1? p.Met1_Ile15del? No start protein prod.	het[d]		Unpubl.	1(1)	*
c.45+6T>C[c]	Splice site	del. exon 1? p.Met1_Ile15del? No start protein prod.	X91−	A0134 A0135	[1,12,19,31]	1(2)	
c.45+907_908ins~5800[e]	Insertion	ins.117 bp in mRNA after exon 1>p.Leu16PheX	X91°		Unpubl.	1(1)	*
c.46-14_−11delTTCT insGAA[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91°		Unpubl.	1(1)	*
c.46−11T>G[c]	Splice site	del. exon 2? p.Leu16_Gly47del?	X91°		[23]	1(1)	*
c.46−2A>G[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91?	A0498 A0499	[1] unpubl.	3(4)	
c.46−1G>A[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91°	A0224 A0500	[1,11,32]	2(2)	
c.46−1G>T[c]	Splice site	del. exon 2? p.Leu16_Gly47del?	X91?	A0593	[27]	1(1)	*
c.46−1G>C[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91?	A0625	[33]	1(1)	*
c.47delT	Deletion	p.Leu16ArgfsX6	X91°	A0214	[1,4,10,34]	1(1)	
c.49delG	Deletion	p.Val17PhefsX5	X91°	A0215	[1,11]	1(1)	
c.52dupT	Insertion	p.Trp18LeufsX17	X91°	A0349	[1]	1(1)	
c.53G>A	Nonsense	p.Trp18X	X91° 1 het[d]	A0563	[23,35]	2(2)	*
c.54G>C	Missense	p.Trp18Cys	X91−	A0083	[1,11,36]	1(1)	
c.58G>C	Missense	p.Gly20Arg	X91°	A0136 A0376	[1,11,12,37] unpubl.	2(2)	
c.58G>A	Missense	p.Gly20Arg	X91°	A0647	[20] unpubl.	2(2)	*
c.66_70delCGTCTinsA	Deletion/insertion	p.Asn22LysfsX38	X91°		[1]	1(1)	
c.64_67dupAACG	Insertion	p.Val23GlufsX13	X91?	A0298	[1,11]	1(1)	
c.80_83delTCTG	Deletion	p.Val27GlyfsX33	X91°	A0327 A0328	[1] unpubl.	5(5)	
c.83G>A	Nonsense	p.Trp28X	X91° 1 het[d]	A0483 A0575 A0563	[1,20,38] unpubl.	4(4)	
c.84G>A	Nonsense	p.Trp28X	X91° 1 het[d]	A0477 A0478	[39] unpubl.	3(3)	*
c.85delT	Deletion	p.Tyr29IlefsX32	X91?		Unpubl.	1(1)	*
c.90C>A	Nonsense	p.Tyr30X	X91?		[29]	1(1)	*
c.90_92delCCGinsGGT	Deletion/insertion	p.Tyr30X	X91° het[d]		[22,40]	1(1)	*
c.92_93insC	Insertion	p.Val32GlyfsX3	X91°		[39] unpubl.	1(2)	*
c.94delG	Deletion	p.Val32PhefsX29	X91°		Unpubl.	1(1)	*
c.99T>A	Nonsense	p.Tyr33X	X91°	A0024	[1,11]	1(1)	
c.105delT	Deletion	p.Pro36HisfsX25	X91−		Unpubl.	1(1)	*
c.112A>T	Nonsense	p.Lys38X	X91°		Unpubl.	1(1)	*
c.121delT	Deletion	p.Tyr41ThrfsX20	X91°	A0018	[1,11,34] unpubl.	2(2)	
c.121dupT	Insertion	p.Tyr41LeufsX62	X91°	A0350	[1,17]	1(1)	
c.121T>G	Missense	p.Tyr41Asp	X91−	A0495, A0544	[1,41]	1(1)	
c.125C>G	Missense	p.Thr42Arg	X91?		Unpubl.	1(1)	*
c.126_130delAAGAAinsTTTC	Deletion/insertion	p.Arg43PhefsX18	X91?		Unpubl.	1(1)	*
c.127A>T	Nonsense	p.Arg43X	X91°	A0261	[1,11,20] unpubl.	3(3)	
c.134T>G	Missense	p.Leu45Arg	X91−		Unpubl.	1(1)	*
c.141+1delG[c]	Splice site	del. exons 2+3 p.Leu16_Ala84del	X91°	A0216	[1,11,19]	1(1)	

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.141+1G>A[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91°	A0131 A0502 A0503	[1,12,19,42] unpubl.	5(5)	
c.141+1G>T[c]	Splice site	del. exon 2 p.Leu16_Gly47del	X91°	A0138 A0154	[1,12,37] unpubl.	5(5)	
c.141+2T>C[c]	Splice site	del exon 2 p.Leu16_Gly47del	X91°	A0506	[1] unpubl.	3(3)	
c.141+2T>G[c]	Splice site	del exon 2 p.Leu16_Gly47del	X91?	A0501 A0504 A0505	[1,12]	3(3)	
c.141+5G>A[c]	Splice site	del exon 2 p.Leu16_Gly47del	X91°		[1,26] unpubl.	2(2)	
c.141+5G>T[c]	Splice site	del exon 2 p.Leu16_Gly47del	X91°	A0615	[20] unpubl.	2(2)	•
c.141+5_+6delGT[c]	Splice site	del exon 2? p.Leu16_Gly47del?	X91?	A0225	[1,11]	1(1)	
c.142−12_−28del17[c]	Splice site	del exon 3 p.Ser48_Ala84del	X91°		[1]	1(1)	
c.142−12C>T[c]	Splice site	del exon 3? p.Ser48_Ala84del?	X91°		Unpubl.	1(1)	•
c.142−12delC insACCTCTTCTAG[c]	Splice site	del exon 3? p.Ser48_Ala84del?	X91°		Unpubl.	1(1)	•
c.142−2A>G[c]	Splice site	del. exon 3 p.Ser48_Ala84del	X91°	A0105	[1,43]	1(1)	
c.142−2A>T[c]	Splice site (created)	del TCAG from exon 3 p.Ile15TrpfsX6	X91°		[1]	1(1)	
c.142−1G>C[c]	Splice site	del. exon 3? p.Ser48_Ala84del?	X91°		[42]	1(2)	•
c.142−1G>A[c]	Splice site	del. exon 3 + w.t. p.Ser48_Ala84del	X91?	A0616	[20]	1(1)	•
c.142_159del18/ insCCTGCCTGAATTTC (dup173_186)T[e]	Deletion/insertion Splice site?	p.Ser48_Ala53del insProAlaX	X91°	A0599 A0600 A0601	[27] unpubl.	1(3)	•
c.143C>G[f]	Nonsense	p.Ser48X	X91°		[28] unpubl.	2(2)	•
c.158C>A	Missense	p.Ala53Asp	X91−	A0050 A0352	[1,11]	1(2)	
c.159dupC	Insertion	p.Arg54GlnfsX49	X91°	A0160	[1,12,19] unpubl.	1(1)	
c.160_165delAGGGCC	Deletion	p.Arg54_Ala55del	X91°	A0322	[39] unpubl.	2(2)	•
c.160A>G	Missense	p.Arg54Gly	X91+	A0243	[1,19]	1(1)	
c.161G>T	Missense	p.Arg54Met	X91+	A0455	[1,17,44]	2(2)	
c.162G>C	Missense	p.Arg54Ser	X91+	A0133	[1,11,45,46]	1(1)	
c.164C>A	Missense	p.Ala55Asp	X91°	A0353	[1,23,44] unpubl.	3(3)	
c.167C>T	Missense	p.Pro56Leu	X91−	A0244, A0245 A0304	[1,11,47–49]	2(3)	
c.170C>A	Missense	p.Ala57Glu	X91+	A0069	[1,4,17,44,50] unpubl.	2(2)	
c.175T>C	Missense	p.Cys59Arg	X91°	A0175, A0176	[1,12,19] unpubl.	2(3)	
c.176G>T	Missense	p.Cys59Phe	X91−	A0362	[1]	1(1)	
c.176G>A	Missense	p.Cys59Tyr	het[d]	A0363	[1]	1(1)	
c.177C>G	Missense	p.Cys59Trp	X91°	A0246 A0541	[1,19,39]	2(2)	
c.177C>A	Nonsense	p.Cys59X	X91°		Unpubl.	1(1)	•
c.185delT	Deletion	p.Phe62SerfsX5	X91°	A0614	[20]	1(1)	•
c.189C>G	Missense	p.Asn63Lys	X91°	A0413 A0414	Unpubl.	2(3)	•
c.190T>C	Missense	p.Cys64Arg	X91°	A0247	[1,19] unpubl.	2(2)	
c.192C>A	Nonsense	p.Cys64X	X91°	A0364	[1,27]	1(1)	
c.194T>G	Missense	p.Met65Arg	X91°		Unpubl.	1(2)	•
c.195dupG	Insertion	p.Leu66AlafsX37	X91°	A0196 A0197	[1,11,12]	1(2)	
c.197T>C	Missense	p.Leu66Pro	X91?		[28]	1(1)	•
c.210dupA	Insertion	p.Val71SerfsX32	X91?		Unpubl.	1(1)	•
c.217C>T	Nonsense	p.Arg73X	X91° 1 het[d]	A0008 A0188 A0262 A0263 A0456 A0457	[1,11,17,26,38,39,51–53] unpubl.	25(25)	

(*continued on next page*)

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
				A0458			
				A0459			
				A0567			
c.226delC	Deletion	p.Leu76CysfsX32	X91[?]		Unpubl.	1(2)	*
c.242delG	Deletion	p.Gly81ValfsX27	X91°	A0011	[1,11] unpubl.	2(2)	
c.242dupG	Insertion	p.Ser82PhefsX21	X91°		Unpubl.	1(1)	*
c.251delC (3′ end of exon 3)[c]	Splice site	del. exon 3 p.Ser48_Ala84del	X91°	A0110	[1,12,52,54]	1(1)	
c.252G>A (3′ end of exon 3)[c]	Splice site	del. exon 3 p.Ser48_Ala84del	X91°/− 1 het[d]	A0022 A0063 A0100 A0127 A0193 A0226 A0227 A0228 A0229 A0230 A0231 A0354 A0355 A0356 A0357 A0534 A0577 A0578 A0633 A0634 A0642	[1,11,12,17,20,23,29, 33,38,49,55–58] unpubl.	44(53)	
c.252G>T (3′ end of exon 3)[c]	Splice site	del. exon 3 p.Ser48_Ala84del	X91[?]		[23] unpubl.	2(2)	*
c.252+1G>A[c]	Splice site	del. exon 3 p.Ser48_Ala84del	X91°	A0510	[1,42] unpubl.	3(3)	
c.252+1G>T[c]	Splice site	del exon 3 p.Ser48_Ala84del	X91°	A0509	[1]	1(1)	
c.252+1G>C[c]	Splice site	del exon 3 p.Ser48_Ala84del	X91[?]		Unpubl.	1(1)	*
c.252+2T>C[c]	Splice site	del exon 3? p.Ser48_Ala84del?	X91[?]		Unpubl.	1(1)	*
c.252+2dupT[c]	Splice site	del exon 3 p.Ser48_Ala84del	X91°		[1]	2(2)	
c.252+5G>A[c]	Splice site	del exon 3 p.Ser48_Ala84del	X91°	A0023 A0507 A0508 A0594	[1,27,29,32] unpubl.	8(10)	
c.252+5G>C[c]	Splice site	del exon 3? p.Ser48_Ala84del?	X91°	A0148	[1,12,54]	1(1)	
c.253−875_336+~800del[c]	Deletion	del exon 4 p.Cys85_Ser112del	X91°		[1]	1(1)	
c.253−8A>G[c]	Splice site (created)	insTCCAAAG into exon 4 p.Cys85SerfsX20	X91°		[1,12]	1(1)	
c.253−3A>G[c]	Splice site (created)	insAG into exon 4 p.Cys85SerfsX24	het[d]		[59] unpubl.	2(2)	*
c.253−1G>A[c]	Splice site (created)	del14 from exon 4 p.Cys85SerfsX13	X91[?]	A0626	[33,55] unpubl.	2(2)	*
c.253−1G>T[c]	Splice site	del exon 4? p.Cys85ArgfsX15?	X91[?]		Unpubl.	1(1)	*
c.255C>A	Nonsense	p.Cys85X	X91°	A0365	[1]	1(1)	
c.262_263ins2.1 kb	Insertion	p.Thr88LysX?[g]	X91°	A0299	[1,19,60]	1(1)	
c.271C>T	Nonsense	p.Arg91X	X91° 1 het[d]	A0029 A0149 A0178 A0264 A0265 A0266 A0460 A0461 A0462 A0463 A0464 A0643	[1,11,12,17,22, 43,53,61,62] unpubl.	24(25)	
c.275delG	Deletion	p.Arg92AsnfsX16	X91[?]		Unpubl.	1(1)	*
c.286_290dupAGGAA	Insertion	p.Asn97LysfsX13	X91°		[39]	1(1)	*
c.295delA	Deletion	p.Thr99ProfsX9	X91°	A0097	[1,11,12]	1(1)	
c.296_306del11insTCC	Deletion/insertion	p.Thr99IlefsX21	X91°		Unpubl.	1(3)	*
c.301C>T	Missense	p.His101Tyr	X91[−]	A0381	[1,17,63,64]	1(1)	

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.302A>G	Missense	p.His101Arg	X91°	A0017	[1,11,51]	2(2)	
			1 het[d]	A0248			
c.318G>A	Nonsense	p.Trp106X	X91°	A0015	[1,11,27,61]	3(3)	
				A0479			
				A0586			
c.320T>G	Missense	p.Met107Arg	X91⁻	A0410	Unpubl.	2(2)	*
c.321dupG	Insertion	p.Ile108AspfsX15	X91°	A0057	[1,11]	1(1)	
c.327_328delAC	Deletion	p.Leu110SerfsX12	X91°	A0210	[1,11]	2(2)	
					unpubl.		
c.330_331delTC	Deletion	p.His111LeufsX11	X91?		Unpubl.	1(1)	*
c.330_331delTCinsAT	Deletion/insertion	p.His111Tyr	X91°		Unpubl.	1(1)	*
c.334T>C	Missense	p.Ser112Pro	X91?		[28]	1(1)	*
c.337+1G>C[c]	Splice site	del exon 4?	X91?	A0595	[27]	1(1)	*
		p.Cys85ArgfsX15?					
c.337+1G>A[c]	Splice site	del exon 4?	X91?		Unpubl.	1(1)	*
		p.Cys85ArgfsX15?					
c.337+1G>T[c]	Splice site	del exon 4	X91°		Unpubl.	1(1)	*
		p.Cys85ArgfsX15					
c.337+2dupT[c]	Splice site	del exon 4?	X91?		Unpubl.	1(1)	*
		p.Cys85ArgfsX15?					
c.337+5dupG[c]	Splice site	del exon 4?	X91°		Unpubl.	1(1)	*
		p.Cys85ArgfsX15?					
c.338−2A>C[c]	Splice site	del exon 5?	X91°	A0232	[1,19]	1(1)	
		p.Ala113GlufsX3?					
c.338−2A>G[c]	Splice site	del. exon 5	X91°	A0514	[1,29]	2(2)	
		p. Ala113GlufsX3			unpubl.		
c.338−1G>A[c]	Splice site	del exon 5	X91°	A0512	[1,17,44]	2(2)	
		p. Ala113GlufsX3		A0513	unpubl.		
c.339delG	Deletion	p.Ile114PhefsX14	X91°		Unpubl.	1(1)	*
c.343C>T	Missense	p.His115Tyr	X91?	A0383	Unpubl.	1(1)	*
c.345C>A	Missense	p.His115Gln	X91?	A0382	[1]	1(1)	
c.354delA	Deletion	p.His119IlefsX9	X91°	A0103	[1,12,19]	1(1)	
c.356dupA	Insertion	p.His119GlnfsX4	X91°	A0007	[1,11]	1(1)	
c.356A>G	Missense	p.His119Arg	X91°	A0384	[1,12]	2(2)	
				A0385			
c.359T>C	Missense	p.Leu120Pro	X91°	A0249	[1,11]	1(1)	
c.360_375del16	Deletion	p.Phe121ValfsX2	het[d]		Unpubl.	1(1)	*
c.370G>T	Nonsense	p.Glu124X	X91°		Unpubl.	1(1)	*
c.374G>A	Nonsense	p.Trp125X	X91?		Unpubl.	1(1)	*
c.375G>A	Nonsense	p.Trp125X	X91°	A0564	[35]	1(1)	*
c.375G>T	Missense	p.Trp125Cys	X91?	A0480	[1]	1(1)	
c.382_385dupAATG	Insertion	p.Ala129GlufsX6	X91°		Unpubl.	1(1)	*
c.388delC	Deletion	p.Arg130GlufsX10	X91?		[22]	2(2)	*
					unpubl.		
c.388C>T	Nonsense	p.Arg130X[h]	X91°	A0065	[1,11,12,17,20,22,	41(44)	
			2 het[d]	A0113	23,27,39,49,65]		
				A0267	unpubl.		
				A0268			
				A0269			
				A0270			
				A0271			
				A0272			
				A0427			
				A0428			
				A0429			
				A0430			
				A0431			
				A0432			
				A0587			
				A0596			
c.388_389insT	Insertion	p.Arg130LeufsX4	X91°	A0080	[1,19]	1(1)	
c.389G>C	Missense	p.Arg130Pro	X91°		Unpubl.	1(1)	*
c.389G>T	Missense	p.Arg130Leu + partial outsplicing exon 5	X91⁻		Unpubl.	1(1)	*
c.394_406del13	Deletion	p.Asn132LeufsX4	X91⁻		Unpubl.	1(1)	*
c.398delA	Deletion	p.Asn133IlefsX7	het[d]	A0543	[66]	1(1)	*
c.411T>A	Nonsense	p.Tyr137X	X91?		Unpubl.	1(1)	*
c.412_418delTCAGTAG	Deletion	p.Ser138HisfsX21	X91°		Unpubl.	1(1)	*
c.413C>A	Nonsense	p.Ser138X	X91°		Unpubl.	2(2)	*
c.422T>C	Missense	p.Leu141Pro	X91°	A0559	[23,24]	2(2)	*
c.424T>C	Missense	p.Ser142Pro	X91°	A0465	[1]	2(2)	
					unpubl.		
c.425C>T	Missense	p.Ser142Phe	X91°		[42]	1(1)	*
c.425_426delCT	Deletion	p.Ser142X	X91°		Unpubl.	1(2)	*

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Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.439_440delAG	Deletion	p.Arg147AlafsX3	X91$^{?}$		[27]	1(1)	*
c.442C>T	Nonsense	p.Gln148X	X91^{o}	A0273	[1,17,52]	3(3)	
				A0420	unpubl.		
c.442_443delCAinsT	Deletion/insertion	p.Gln148X	X91^{o}	A0111	[1,52]	1(1)	
c.446dupA	Insertion	p.Asn149LysfsX2	X91^{o}	A0139	[1,12,52]	1(1)	
c.448G>T	Nonsense	p.Glu150X	het[d]		Unpubl.	1(1)	*
c.450_451delAA	Deletion	p.Ser151fsX13	X91^{o}		Unpubl.	1(1)	*
c.455_456delAT	Deletion	p.Tyr152SerfsX12	X91^{o}	A0332	[1]	1(1)	
c.456T>A	Nonsense	p.Tyr152X	X91^{o}	A0124	[1,12,19,62]	2(2)	
				A0644			
c.458T>G	Missense	p.Leu153Arg	X91^{o}		Unpubl.	1(2)	*
c.461delA	Deletion	p.Asn154IlefsX7	X91^{o}		Unpubl.	1(1)	*
c.466G>A	Missense	p.Ala156Thr	X91^{-}	A0055	[1,11,12,51,52]	3(3)	
				A0137			
				A0187			
c.469C>T	Nonsense	p.Arg157X	X91^{o}	A0074	[1,11,12,20,23,	26(30)	
			1 het[d]	A0075	35,43,44,61,67]		
				A0095	unpubl.		
				A0098			
				A0152			
				A0177			
				A0274			
				A0275			
				A0276			
				A0277			
				A0433			
				A0434			
				A0565			
				A0566			
				A0567			
				A0568			
c.472_475delAAGA	Deletion	p.Lys158GlufsX2	X91^{o}	A0311	[1]	1(1)	
c.475_481delAGAATAA[f]	Deletion	p.Ile160ThrfsX10	X91$^{?}$		[28]	1(1)	
c.479dupT	Insertion	p.Asn162GlufsX3	X91$^{?}$	A0335	[1]	1(1)	
c.482A>G (3′ end of exon 5)[c]	Splice site	multiple splice products	X91^{-}	A0179	[1,52]	1(2)	
				A0180			
c.482_483+4 delAGGTAA[c]	Splice site	del exon 5?	X91^{o}	A0181	[1,12]	1(1)	
		p. Ala113GlufsX3?					
c.483G>T (3′ end of exon 5)[c]	Splice site	del exon 5	X91^{o}	A0233	[1,11]	1(1)	
		p. Ala113GlufsX3					
c.483+1G>A[c]	Splice site	del exon 5	X91^{o}	A0515	[1,23,42]	4(5)	
		p. Ala113GlufsX3			unpubl.		
c.483+1G>T[c]	Splice site	del exon 5	X91^{o}	A0115	[1,11,12,19,49]	6(6)	
		p. Ala113GlufsX3		A0234	unpubl.		
				A0516			
				A0517			
c.483+2T>C[c]	Splice site	del exon 5?	X91^{o}	A0164	[1,43]	1(1)	
		p Ala113GlufsX3?					
c.483+3A>T[c]	Splice site	del exon 5	X91^{o}	A0009	[1,32]	1(1)	
		p. Ala113GlufsX3					
c.483+5G>A[c]	Splice site	del exon 5?	X91^{-}	A0140	[1,19,26]	1(2)	
		p Ala113GlufsX3?		A0141			
c.483+978G>T[c]	Splice site (created)	ins parts of intron 5	X91$^{?}$	A0606	[68,69]	2(2)	*
		multiple splice products					
c.483+1880_+1881ins836[c,g]	Splice site (created)	multiple splice products	X91^{o}		[1,70]	1(1)	
c.484−100_674+291del581[c]	Deletion	del. exon 6 (p.Asn162ThrfsX15	X91$^{?}$		[20]	1(1)	*
c.484−?_897+?dup[i]	Insertion	p.Asn162_Lys299dup	X91^{o}		Unpubl.	1(1)	*
c.484−3C>A[c]	Splice site	del exon 6	X91^{-}		Unpubl.	1(2)	*
		p.Asn162ThrfsX15					
c.484−2A>T[c]	Splice site	del exon 6?	X91$^{?}$		Unpubl.	1(1)	*
		p.Asn162ThrfsX15?					
c.517delC	Deletion	p.Leu173CysfsX16	X91^{o}	A0217	[1,11]	1(1)	
c.535G>A	Missense	p.Gly179Arg	X91^{o}	A0375	[1,25]	1(1)	
c.535G>T	Nonsense	p.Gly179X	X91^{o}		Unpubl.	2(2)	*
c.536G>A	Missense	p.Gly179Glu	X91$^{?}$		Unpubl.	1(1)	*
c.548_559del12	Deletion	p.Thr183_Leu186del	X91$^{?}$		Unpubl.	1(1)	*
c.553T>C	Missense	p.Cys185Arg	X91$^{?}$		Unpubl.	1(1)	*
c.554delG	Deletion	p.Cys185SerfsX4	X91^{o}	A0218	[1,19]	1(1)	
c.555C>A	Nonsense	p.Cys185X	X91^{o}	A0182	[1,12,19]	3(3)	
				A0358	unpubl.		
c.555_560dupCCTCAT	Insertion	p.Leu188_Ile189dup	X91$^{?}$	A0585	[27]	1(1)	*
c.5561_569delATTAATTAT	Deletion	p.Leu188_Ile190del	X91^{-}		[1]	1(1)	
c.565_568delATTA	Deletion	p.Ile189SerfsX24	X91^{o}	A0309	[1]	3(3)	
					unpubl.		
c.573_581dupTTCCTCCAC	Insertion	p.Thr191_Ser193dup	X91^{-}		Unpubl.	1(1)	*

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.577T>C	Missense	p.Ser193Pro	X91°	A0627	[23,33] unpubl.	3(3)	*
c.578C>T	Missense	p.Ser193Phe	X91⁻	A0466	[1,27] unpubl.	2(2)	
c.583_588dupAAAACC	Insertion	p.Lys195_Thr196 dup	X91⁻		Unpubl.	1(1)	*
c.591_592ins41	Insertion	p.Arg198ThrfsX30	X91°		[1]	1(1)	
c.592delC	Deletion	p.Arg198GlyfsX16	X91°		Unpubl.	1(1)	*
c.595delA	Deletion	p.Arg199GlyfsX15	X91°	A0320	[1,12]	1(1)	
c.597_604dup8[f]	Insertion	p.Phe202CysfsX15	X91?		[28]	1(1)	*
c.603C>G	Nonsense	p.Tyr201X	X91?		Unpubl.	1(1)	*
c.603delC	Deletion	p.Phe202LeufsX12	X91°	A0333	[1]	1(1)	
c.606_608delTGAinsGG	Deletion/insertion	p.Phe202LeufsX12	X91°		[1,17]	1(1)	
c.607G>T	Nonsense	p.Glu203X	X91°	A0278	[1,11] unpubl.	2(2)	
c.613T>A	Missense	p.Phe205Ile	X91°	A0060	[1,33,55]	1(1)	
c.614_632del19	Deletion	p.Phe205SerfsX4	X91°		Unpubl.	1(2)	*
c.618G>A	Nonsense	p.Trp206X	het[d]		Unpubl.	1(1)	*
c.621C>A	Splice site (created)	del. part exon 6 p.Tyr207X	X91°	A0012	[1,11,32]	1(1)	
c.625C>T	Missense	p.His209Tyr	X91⁻/°	A0006 A0387 A0388 A0389	[1,11,50] unpubl.	5(5)	
c.625_626delCA	Deletion	p.His209SerfsX16	X91?	A0211	[1,19]	1(1)	
c.626A>G	Missense	p.His209Arg	X91°	A0386	[1,17] unpubl.	2(2)	
c.627T>A	Missense	p.His209Gln	X91°	A0125	[1,12,23,52]	2(2)	
c.628_631dupCATC	Insertion	p.Leu211ProfsX16	X91° het[d]	A0597	[65]	1(1)	*
c.632T>C	Missense	p.Leu211Pro	X91?		Unpubl.	1(1)	*
c.632T>G	Missense	p.Leu211Arg	het[d]		Unpubl.	1(1)	*
c.636delT	Deletion	p.Phe212LeufsX1	X91°		[29] unpubl.	2(2)	*
c.646_648delTTC	Deletion	p.Phe216del	X91⁻	A0010 A0058 A0085	[1,19,47,55,71]	3(3)	
c.664C>A	Missense	p.His222Asn	X91°	A0390	[1,12]	1(1)	
c.664C>T	Missense	p.His222Tyr	X91°	A0394	[1,12]	1(1)	
c.665A>G	Missense	p.His222Arg	X91°	A0250 A0391 A0392 A0393	[1,11,12,23,26] unpubl.	6(6)	
c.665A>T	Missense	p.His222Leu	X91?		Unpubl.	1(1)	*
c.667G>T	Nonsense	p.Gly223X[h]	X91°		[72]	1(1)	*
c.667_668delGG/insTT	Deletion/insertion	p.Gly223Leu	X91?	A0109	[1,12,19]	1(1)	
c.671C>G	Missense	p.Ala224Gly	X91°	A0351	[1,17]	1(1)	
c.674A>T	Missense	p.Glu225Val	X91°		[42,61]	2(2)	*
c.674+1G>T[c]	Splice site	del exon 6? p.Asn162ThrfsX15?	X91°		Unpubl.	1(1)	*
c.674+1G>A[c]	Splice site	del exon 6 p.Asn162ThrfsX15	X91°		Unpubl.	2(2)	*
c.674+3G>C[c]	Splice site	del exon 6? p.Asn162ThrfsX15	X91?		Unpubl.	1(1)	*
c.674+4A>G[c]	Splice site	del exon 6 p.Asn162ThrfsX15	X91°		[29] unpubl.	2(2)	*
c.674+4A>T[c]	Splice site	del exon 6? p.Asn162ThrfsX15	X91°		Unpubl.	1(2)	*
c.674+4A>C[c]	Splice site	del. exon 6? p.Asn162ThrfsX15?	X91?		[28]	1(2)	*
c.674+4_+7delAGTG[c]	Splice site	multiple splice products	X91°	A0106	[1,12,19] unpubl.	5(6)	
c.674+5G>A[c]	Splice site	del exon 6 p.Asn162ThrfsX15	X91?	A0235	[1,11]	1(1)	
c.674+5G>C[c]	Splice site	del exon 6 p.Asn162ThrfsX15	X91°	A0519 A0561 A0562	[1,42]	4(7)	
c.674+6T>A[c]	Splice site	del exon 6? p.Asn162ThrfsX15?	X91°	A0518	[1,12]	1(1)	
c.674+6T>C[c]	Splice site	del exon 6 p.Asn162ThrfsX15	X91?		Unpubl.	1(1)	*
c.674+?_804+?del[c]	Deletion	del exon 7 p.Arg226LeufsX5	X91°		[20]	1(1)	*
c.674+921A>G[c]	Splice site (created)	ins 56 of intron 6 into mRNA p.Glu225AspfsX2	X91?	A0581	[73]	1(1)	*

(*continued on next page*)

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.675−999A>G[c]	Splice site (created)	ins 94 of intron 6 into mRNA multiple splice products	X91°		[1,74]	1(1)	
c.675−24_690dup40	Insertion	p.Gln231SerfsX23	X91°	A0301	[1,75]	1(1)	
c.675−2A>C[c]	Splice site	del exon 7? p.Arg226LeufsX5?	X91°		Unpubl.	1(1)	*
c.675−1G>A[c]	Splice site	del exons 6_7 p.Asn162_Met268del	X91°		Unpubl.	1(1)	*
c.676C>T	Nonsense	p.Arg226X	X91° 1 het[d]	A0132, A0150, A0279, A0280 A0281, A0282, A0283, A0284 A0435 A0436 A0437 A0438 A0439 A0440 A0441 A0442 A0588	[1,11,12,17,22,23, 27,39,53,76,77] unpubl.	57(63)	
c.691C>T	Nonsense	p.Gln231X	X91° 1 het[d]	A0421 A0422	[1,20,39] unpubl.	4(4)	
c.700G>T	Nonsense	p.Glu234X	X91°	A0607	[78]	1(1)	*
c.703_704delAG	Deletion	p.Ser235PhefsX5	X91°	A0120, A0212 A0323	[1,11,29,52,53] unpubl.	5(5)	
c.706_707dupTT	Insertion	p.Leu236PhefsX7	X91°	A0344	[1,17,44]	1(1)	
c.713delT	Deletion	p.Val238GlyfsX4	X91[?]	A0628	[33]	1(1)	*
c.716_720delATAAT	Deletion	p.Ile241SerfsX3	X91°	A0117	[1,12,52]	1(1)	
c.730T>A	Missense	p.Cys244Ser	X91[?]		[29]	1(1)	*
c.730T>C	Missense	p.Cys244Arg	X91⁻	A0171	[1,12,52] unpubl.	2(2)	
c.730T>G	Missense	p.Cys244Gly	X91⁻	A0359	[26]	1(1)	*
c.731G>C	Missense	p.Cys244Ser	X91⁻	A0251	[1,11,49,51]	1(1)	
c.731G>A	Missense	p.Cys244Tyr	X91⁻	A0252	[1,61,79] unpubl.	3(3)	
c.732T>A	Nonsense	p.Cys244X	het[d]		[23]	1(1)	*
c.733G>T	Nonsense	p.Glu245X	X91°		Unpubl.	1(1)	*
c.736C>T	Nonsense	p.Gln246X	X91°	A0122 A0123 A0186 A0423	[1,12,19,23,78] unpubl.	7(10)	
c.740_741delAAinsT	Deletion/insertion	p.Lys247IlefsX8	X91°	A0021	[1,19]	1(1)	
c.742dupA	Insertion	p.Ile248AsnfsX36	X91° 1 het[d]	A0002 A0061 A0062 A0121 A0126 A0146 A0162 A0170 A0189 A0337 A0338 A0339 A0340 A0341 A0342 A0343 A0602 A0603 A0604	[1,11,12,17,23, 33,52,54,55] unpubl.	30(32)	
c.752G>A	Nonsense	p.Trp251X	X91°	A0285	[1,11] unpubl.	2(2)	
c.754G>T	Nonsense	p.Gly252X	X91[?]		Unpubl.	1(1)	*
c.755delG	Deletion	p.Gly252GlufsX3	X91°	A0195 A0219 A0220	[1,12,19,20] unpubl.	4(5)	
c.755_756delGA	Deletion	p.Gly252GlufsX31	X91°		[42]	1(1)	*
c.760dupA	Insertion	p.Ile254AsnfsX30	X91°	A0128	[1,12,54]	1(1)	
c.769T>C	Missense	p.Cys257Arg	X91°		Unpubl.	1(2)	*
c.773delC	Deletion	p.Pro258GlnfsX11	X91°		[42]	1(1)	*

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.771C>A	Nonsense	p.Cys257X	het[d]		[1]	1(1)	
c.779C>G	Missense	p.Pro260Arg	X91°		Unpubl.	1(1)	*
c.781_782delCA	Deletion	p.Gln261ValfsX22	X91°	A0001	[1,11]	1(1)	
c.781C>T	Nonsense	p.Gln261X	X91°	A0020 A0286 A0424 A0425	[1,11] unpubl.	5(5)	
c.785_804+1dup21del9ins2[c]	Splice site	del. exon7 p.Arg226LeufsX5	X91?		Unpubl.	1(1)	*
c.788delC	Deletion	p.Ala263ValfsX6	X91°	A0582	[27]	1(1)	*
c.797delC	Deletion	p.Pro266LeufsX3	X91°	A0316	[1,23]	2(2)	
c.799_800insAA	Insertion	p.Pro267GlnfsX3	X91?		Unpubl.	1(1)	*
c.804+1G>A[c]	Splice site	del exon 7 p.Arg226LeufsX5	X91°	A0522	[1,77,80]	2(2)	
c.804+1G>T[c]	Splice site	del exon 7 p.Arg226LeufsX5	X91°	A0523	[1] unpubl.	3(3)	
c.804+2T>A[c]	Splice site	del. exon 7 p.Arg226LeufsX5	X91°	A0005	[1,32]	1(1)	
c.804+2T>C[c]	Splice site	del. exon 7 p.Arg226LeufsX5	X91°	A0236 A0237	[1,11] unpubl.	3(4)	
c.805−2A>C[c]	Splice site	del exon 8? p.Thr269_Lys299del?	X91°	A0238	[1,19]	1(1)	
c.805−2A>T[c]	Splice site	del. exon 8? p.Thr269_Lys299del?	X91°		Unpubl.	1(1)	*
c.805−2A>G[c]	Splice site	del exon 8 p.Thr269_Lys299del	X91°	A0520	[1,17,44]	1(1)	
c.805−1G>A[c]	Splice site	del exon 8? p.Thr269_Lys299del?	X91°	A0521	[1,12] unpubl.	2(2)	
c.805−1G>C[c]	Splice site	del. exon 8? p.Thr269_Lys299del?	X91?		Unpubl.	1(1)	*
c.805−?[c]	Splice site	del exon 8 p.Thr269_Lys299del	X91°		[1,25]	1(1)	
c.810G>A	Nonsense	p.Trp270X	X91°	A0624	[53] unpubl.	2(2)	*
c.811A>T	Nonsense	p.Lys271X	X91°		Unpubl.	1(1)	*
c.815G>A	Nonsense	p.Trp272X.	X91°	A0099 A0287 A0482	[1,12,19]	3(3)	
c.816G>A	Nonsense	p.Trp272X	X91°	A0047	[1,11]	1(1)	
c.831_853del23	Deletion	p.Met277IlefsX63	X91?		Unpubl.	1(1)	*
c.840T>A	Nonsense	p.Tyr280X	X91?		Unpubl.	1(1)	*
c.844_874del31	Deletion	p.Cys282AsnfsX21	X91°	A0536	Unpubl.	1(1)	*
c.845dupG	Insertion	p.Cys282TrpfsX2	X91°		Unpubl.	1(1)	*
c.867G>A	Nonsense	p.Trp289X	het[d]		[81]	1(1)	*
c.868C>T	Nonsense	p.Arg290X	X91° 2 het[d]	A0045 A0046 A0145 A0159 A0194 A0198 A0288 A0289 A0443 A0444 A0445 A0446 A0447 A0448 A0449 A0450 A0451 A0452 A0453 A0639	[1,11,12,20,23,29,33,39,42,43,49,53,61] unpubl.	38(42)	
c.871_880del10	Deletion	p.Ser291ArgfsX19	X91°	A0321	[1,17]	1(1)	
c.883_887dupGTGGT	Insertion	p.Ile297TrpfsX18	X91?		Unpubl.	1(1)	*
c.890_904del15	Deletion	p.Ile297_Val301del	X91+	A0310	[1,25]	1(1)	
c.894delC	Deletion	p.Lys299ArgfsX14	het[d]		[82]	1(2)	*
c.897G>C	Missense Splice site?	p.Lys299Asn	X91−		Unpubl.	1(1)	*
c.897G>T	Missense Splice site?	p.Lys299Asn	X91?	A0402	[1]	1(1)	
c.897G>A (3′ end of exon 8)[c]	Splice site	del exon 8 p.Thr269_Lys299del	X91?		[23] unpubl.	2(2)	*

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Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.897+1G>A[c]	Splice site	del exon 8 p.Thr269_Lys299del	X91°	A0524	[1,29]	2(2)	
c.897+1G>T[c]	Splice site	del. exon 8 p.Thr269_Lys299del	X91°	A0239 A0240 A0303	[1,11,23]	3(4)	
c.898−1G>A[c]	Splice site	del exon 9? p.Val300AspfsX4?	X91⁷		Unpubl.	2(2)	*
c.903dupC	Insertion	p.Thr302HisfsX46	X91°		Unpubl.	1(1)	*
c.904A>C	Missense	p.Thr302Pro	X91⁷		[23]	1(1)	*
c.906_909delTCAC	Deletion	p.His303LeufsX9	X91⁷		Unpubl.	1(1)	*
c.907C>T	Missense	p.His303Tyr	X91⁺		Unpubl.	1(1)	*
c.[907C>A;911C>G]	Missense	p.[His303Asn; Pro304Arg]	X91⁺	A0538	[1,83,84]	1(2)	
c.909C>A	Missense	p.His303Gln	X91°		Unpubl.	1(7)	*
c.911C>T	Missense	p.Pro304Leu	X91⁷		Unpubl.	1(2)	*
c.915delC	Deletion	p.Phe305LeufsX8	X91⁷	A0558	[24]	1(1)	*
c.916A>T	Nonsense	p.Lys306X	X91°	A0290	[1,11]	1(1)	
c.919A>C	Missense	p.Thr307Pro	X91°	A0469 A0590	[27,39]	2(2)	*
c.919delA	Deletion	p.Thr307ProfsX6	X91°	A0221	[1,11]	1(1)	
c.[922_923insCCTTTCA; 935_937delTGA][f]	Deletion/insertion	p.Ile308ProfsX39	X91⁷		[1,12]	1(1)	
c.922_923insGTTTC	Insertion	p.Ile308SerfsX7	X91°		[39]	1(1)	*
c.925G>A	Missense	p.Glu309Lys	X91⁻	A0101 A102 A0368 A0369 A0370 A0371 A0372	[1,17,20,43] unpubl.	9(15)	
c.925G>T	Nonsense	p.Glu309X	X91°		Unpubl.	1(2)	*
c.929T>C	Missense	p.Leu310Pro	X91°		Unpubl.	1(1)	*
c.931delC	Deletion	p.Gln311ArgfsX2	X91⁷		Unpubl.	1(1)	*
c.935T>G	Missense	p.Met312Arg	X91⁷	A0253	[1,11] unpubl.	2(2)	
c.935T>A	Missense	p.Met312Lys	X91⁷	A0629	[33]	1(1)	*
c.943_945delAAG	Deletion	p.Lys315del	X91⁻	A0163 A0208 A0209	[1,11,12,43,48,79] unpubl.	3(4)	
c.948delG	Deletion	p.Phe317SerfsX26	X91°	A0222	[1,19]	1(1)	
c.958delG	Deletion	p.Glu320LysfsX23	X91⁷		Unpubl.	1(1)	*
c.[958delG;962T>G]	Deletion/missense	p.Glu320LysfsX23	X91°		Unpubl.	1(1)	*
c.958G>T	Nonsense	p.Glu320X	X91°	A0569	[35]	1(1)	*
c.960delA	Deletion	p.Val321TrpfsX22	X91°	A0306	[1]	1(1)	
c.965delG	Deletion	p.Gly322AspfsX21	X91°	A0118	[1,12,52]	1(1)	
c.965G>A	Missense	p.Gly322Glu	X91⁻	A0377	[1,12] unpubl.	2(2)	
c.967C>T	Nonsense	p.Gln323X	X91°	A0067	[1,17,19]	1(1)	
c.972C>A	Nonsense	p.Tyr324X	X91°		Unpubl.	1(1)	*
c.973A>T	Missense	p.Ile325Phe	X91⁻	A0401	[1,12]	1(1)	
c.979delG	Deletion	p.Val327SerfsX16	X91°	A0584	[27]	1(1)	*
c.981_985delCAAGT	Deletion	p.Lys328ProfsX18	X91°		Unpubl.	1(1)	*
c.985T>C	Missense	p.Cys329Arg	X91°		[42]	1(1)	*
c.992_997 delAGGTGTinsGGGGG	Deletion/insertion	p.Lys331ArgfsX12	X91°		Unpubl.	1(1)	*
c.994delG	Deletion	p.Val332CysfsX11	X91°	A0571	[35]	1(1)	*
c.997T>C	Missense	p.Ser333Pro	X91⁷	A0200	[1,12,52] unpubl.	2(2)	
c.1006G>T	Nonsense	p.Glu336X	X91°	A0087 A088 A0291	[1,20,52]	4(5)	
c.1010G>A	Nonsense	p.Trp337X	X91°	A0292 A0535	[1,11] unpubl.	3(3)	
c.1011G>A	Nonsense	p.Trp337X	X91⁷ 1 het[d]		[53] unpubl.	3(3)	*
c.1012C>T	Missense	p.His338Tyr	X91⁻	A0014 A0084 A0254 A0397 A0398	[1,11,26,49,80,85] unpubl.	7(7)	
c.1012C>A	Missense	p.His338Asn	X91⁷	A0396	[1]	1(1)	
c.1013A>G	Missense	p.His338Arg	X91⁺		Unpubl.	2(4)	*
c.1014C>A	Missense	p.His338Gln	X91⁷		Unpubl.	3(3)	*
c.1016C>A	Missense	p.Pro339His	X91⁺/⁻	A0070 A0096 A0416 A0417	[1,11,12,17,19, 22,26,29,44,86] unpubl.	11(13)	
c.1016C>T	Missense	p.Pro339Leu	X91⁷		Unpubl.	1(1)	*

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.1016delC	Deletion	p.Pro339LeufsX4	X91$^{?}$	A0317	[1]	1(1)	
c.1016dupC	Insertion	p.Thr341TyrfsX7	X91^{o}	A0347	[1,22,87]	1(2)	
c.1022C>A	Missense	p.Thr341Lys	X91^{+}	A0255	[1,19,88]	1(1)	
c.1022C>T	Missense	p.Thr341Ile	X91^{-}	A0470	[1]	1(1)	
c.1025T>A	Missense	p.Leu342Gln	X91^{o}	A0064 A0256 A0404	[1,11,33,55] unpubl.	4(4)	
c.1027A>C	Missense	p.Thr343Pro	X91^{o}	A0591	[27] unpubl.	2(2)	*
c.1030T>C	Missense	p.Ser344Pro	X91^{o}		Unpubl.	2(2)	*
c.1030_1031insCT	Insertion	p.Ala345ProfsX42	X91^{o}		Unpubl.	1(2)	*
c.1031C>T	Missense	p.Ser344Phe	X91^{o}	A0467 A0468	[1,17,44] unpubl.	3(4)	
c.1032delC	Deletion	p.Ala345ProfsX41	X91^{o}	A0324 A0325	[1]	2(2)	
c.1038delT	Deletion	p.Glu347ArgfsX39	X91^{o}	A0129 A130 A0161 A0318	[1,12,19,54] unpubl.	5(6)	
c.1046delA	Deletion	p.Asp349AlafsX37	X91$^{?}$		Unpubl.	1(1)	*
c.1061A>C	Missense	p.His354Pro	X91^{o}		Unpubl.	2(2)	*
c.1061A>G	Missense	p.His354Arg	X91^{-}	A0399	Unpubl.	1(2)	*
c.1062_1071del10	Deletion	p.His354GlnfsX29	X91^{o}	A0207	[1,11]	1(1)	
c.1063delA	Deletion	p.Ile355SerfsX31	X91^{o}		[23]	1(1)	*
c.1063_1070delATCCGCAT	Deletion	p.Ile355ArgfsX15	X91$^{?}$		Unpubl.	1(1)	*
c.1067G>C	Missense	p.Arg356Pro	X91$^{?}$	A0454	[12]	1(1)	*
c.1075G>A	Missense	p.Gly359Arg	X91^{o}	A0056 A0378	[1,11,23] unpubl.	3(4)	
c.1076G>T	Missense	p.Gly359Val	X91$^{?}$	A0379	[1]	1(1)	
c.1076G>C	Missense	p.Gly359Ala	X91^{-}	A0611	[20]	1(1)	*
c.1081T>C	Missense	p.Trp361Arg	X91^{o}		[22] unpubl.	3(3)	*
c.1082G>A	Nonsense	p.Trp361X	X91$^{?}$		Unpubl.	1(1)	*
c.1083G>A	Nonsense	p.Trp361X	X91^{o}	A0484	[1,23,28]	3(3)	
c.1085C>T	Missense	p.Thr362Ile	X91^{o}		Unpubl.	2(3)	*
c.1085C>G	Missense	p.Thr362Arg	X91$^{?}$		Unpubl.	1(1)	*
c.1094T>C	Missense	p.Leu365Pro	X91^{o}	A0405	[1] unpubl.	2(2)	
c.1094dupT	Insertion	p. Phe366ValfsX7	X91^{o}		Unpubl.	1(1)	*
c.1095delG	Deletion	p.Phe366SerfsX20	X91$^{?}$		Unpubl.	1(1)	*
c.1105T>C	Missense	p.Cys369Arg	X91^{+} het[d]	A0257	[1,11,88]	1(1)	
c.1120C>T	Nonsense	p.Gln374X	X91^{o}		Unpubl.	2(2)	*
c.1123G>T	Nonsense	p.Glu375X	X91^{o}	A0610	[20] unpubl.	3(3)	*
c.1129C>T	Nonsense	p.Gln377X	X91^{o}	A0293	[1,11]	1(1)	
c.1136dupC	Insertion	p.Trp380ValfsX5	X91$^{?}$		Unpubl.	1(1)	*
c.1139G>A	Nonsense	p.Trp380X	X91^{o}	A0086 A0174	[1,12,52] unpubl.	3(3)	
c.1140G>A	Nonsense	p.Trp380X	X91^{o}		Unpubl.	3(3)	*
c.1144_1145insAGGT	Insertion	p.Leu382GlnfsX4	het[d]		Unpubl.	1(1)	*
c.1147_1150delCCTA	Deletion	p.Pro383ArgfsX2	X91$^{?}$	A0315	[1]	1(1)	
c.1150_1151+2delAAGT[c]	Splice site	del exon 9? p.Val300AspfsX4?	X91^{o}	A0156	Unpubl.	9(9)	
c.1151+4A>T[c]	Splice site	del exon 9? p.Val300AspfsX4?	X91$^{?}$		Unpubl.	1(1)	*
c.1151+5G>A[c]	Splice site	del exon 9? p.Val300AspfsX4	X91^{o}	A0525	[1] unpubl.	2(2)	
c.1152−11T>G[c]	Splice site	del exon 10/ins10 into exon 10> pAla488PhefsX12	X91^{-}		[1,26]	1(2)	
c.1152−2A>G[c]	Splice site	del exon 10? p.Ile385SerfsX63?	X91$^{?}$	A0580	[38]	1(1)	*
c.1152−2A>T[c]	Splice site	del exon 10? p.Ile385SerfsX63?	X91^{o}		Unpubl.	2(2)	*
c.1152−1G>A[c]	Splice site	alt splice site>1 nt del p.Ile385X	X91^{o}		Unpubl.	2(2)	*
c.1154T>G	Missense	p.Ile385Arg	X91^{o}		Unpubl.	1(1)	*
c.1163delA	Deletion	p.Asp388ValfsX17	X91$^{?}$		Unpubl.	1(1)	*
c.1165G>A	Missense	p.Gly389Arg	X91$^{?}$		Unpubl.	1(1)	*
c.1166G>A	Missense	p.Gly389Glu	X91^{o}	A0380	[1,17] unpubl.	2(2)	
c.1166G>C	Missense	p.Gly389Ala	X91^{-}	A0004	[1,11,49,51]	1(1)	
c.1166G>T	Missense	p.Gly389Val	X91$^{?}$		Unpubl.	1(1)	*
c.1166_1170del insTGTTCAGC	Deletion/insertion	p.Gly389_Pro390del insValPheSer	X91$^{?}$		Unpubl.	1(1)	*

(*continued on next page*)

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.1167delG	Deletion	p.Phe391LeufsX14	X91$^{?}$		Unpubl.	1(1)	*
c.1169C>T	Missense	p.Pro390Leu	X91^{o}	A0258 A0259	[1,11] unpubl.	2(3)	
c.1177delA	Deletion	p.Thr393LeufsX12	X91$^{?}$		Unpubl.	1(1)	*
c.1180_1182delGCC/ ins ATGTGATGAACACAT	Deletion/insertion	p.Ala394MetX2	X91^{o}	A0072 A0073	[1,89]	1(2)	
c.1186_1195del10	Deletion	p.Glu396SerfsX6	X91?		Unpubl.	1(1)	*
c.1190_1191delAT	Deletion	p.Asp397GlyfsX5	X91^{o}	A0213	[1,11]	1(1)	
c.1214T>G	Missense	p.Met405Arg	X91^{o}	A0142	[1,12,19]	1(1)	
c.1222G>A	Missense	p.Gly408Arg	X91$^{?}$	A0157 A0158	[1,12,19]	2(3)	
c.1222G>C	Missense	p.Gly408Arg	X91^{+}		[90]	1(1)	*
c.1223G>A	Missense	p.Gly408Glu	X91^{+} 1 het[d]	A0013 A0016 A0190 A0191	[1,11,12,19,88]	3(4)	
c.1234G>A	Missense	p.Gly412Arg	X91$^{?}$		Unpubl.	1(1)	*
c.1234G>C	Missense	p.Gly412Arg	X91^{+}		Unpubl.	1(2)	*
c.1235G>A	Missense	p.Gly412Glu	X91$^{?}$		Unpubl.	1(1)	*
c.1234_1257dup24	Insertion	p.Gly412Ile419dup	X91$^{?}$		[1]	1(1)	
c.1237dupG	Insertion	p.Val413GlyfsX18	X91^{o} 1 het[d]	A0144	[1,12,19] unpubl.	2(2)	
c.1244C>A	Missense	p.Pro415His	X91^{+}	A0048 A049 A0076 A077 A0107	[1,11,12,91]	3(5)	
c.1244C>G	Missense	p.Pro415Arg	X91$^{?}$	A0419	[1]	1(1)	
c.1244C>T	Missense	p.Pro415Leu	X91^{+}	A0112	[1,3,12,19] unpubl.	3(3)	
c.1253C>A	Missense	p.Ser418Tyr	X91^{o}		Unpubl.	1(1)	*
c.1255dupA	Insertion	p.Ile419AsnfsX12	X91$^{?}$	A0574	[38]	1(1)	*
c.1259T>C	Missense	p.Leu420Pro	X91^{o}	A0406	[1,17,64]	1(1)	
c.1264T>C	Missense	p.Ser422Pro	X91$^{?}$	A0202	[1,12,19]	1(1)	
c.1265C>A[f]	Nonsense	p.Ser422X	X91$^{?}$		[23]	1(1)	*
c.1265_1273delTCAGTCTGG	Deletion	p.Ser422_Trp424del	X91^{-}		Unpubl.	1(1)	*
c.1271G>A	Nonsense	p.Trp424X	het[d]		Unpubl.	1(1)	*
c.1272delG	Deletion	p.Trp424CysfsX11	X91^{o}	A0330	[1,12]	1(1)	
c.1272G>A	Nonsense	p.Trp424X	X91^{o}	A0622 A0623	[53] unpubl.	4(4)	*
c.1275C>G	Nonsense	p.Tyr425X	X91$^{?}$	A0496	[1]	1(1)	
c.1281T>G	Nonsense	p.Tyr427X	X91$^{?}$		Unpubl.	1(1)	*
c.1284C>A	Nonsense	p.Cys428X	X91^{o}	A0598	Unpubl.	1(1)	*
c.[1287delT;1290delC]	Deletion	p.Asn429LysfsX23	X91^{o}	A0617	[20]	1(1)	*
c.1294delA	Deletion	p.Thr432ProfsX3	X91^{o}		Unpubl.	1(1)	*
c.1309A>T	Nonsense	p.Lys437X	X91^{o}	A0403	[1,17] unpubl.	2(2)	
c.1313delA[c]	Deletion Splice site?	p.Lys438ArgfsX64	X91^{o}	A0053 A0054	[1,11] unpubl.	2(3)	
c.1313_1314delAGinsT[c]	Deletion/insertion Splice site?	p.Lys438IlefsX64	X91^{o}	A0091	[1,12,19]	1(1)	
c.1314delG[c]	Deletion Splice site?	p.Ile439SerfsX63	X91$^{?}$		Unpubl.	2(2)	*
c.1314+1G>A[c]	Splice site	del exon 10? p.Ile385SerfsX63?	X91$^{?}$ 1 het[d]	A0526 A0579	[1,12,38]	2(2)	
c.1314+1G>T[c]	Splice site	del exon 10 p.Ile385SerfsX63	X91$^{?}$	A0529	[1]	1(1)	
c.1314+1G>C[c]	Splice site	del exon 10 p.Ile385SerfsX63	X91^{o}		Unpubl.	1(1)	*
c.1314+2T>A[c]	Splice site	del exon 10 p.Ile385SerfsX63	X91^{o}	A0527	[1]	1(1)	
c.1314+2T>G[c]	Splice site	del exon 10 p.Ile385SerfsX63	het[d]		Unpubl.	1(1)	*
c.1314+4_+5AG>GC[c]	Splice site	del exon 10 p.Ile385SerfsX63	X91^{-}		Unpubl.	1(1)	*
c.1315−2A>C[c]	Splice site	del exon 11? p.Ile439_Gln487del?	X91$^{?}$		Unpubl.	2(2)	*
c.1315−1G>C[c]	Splice site	del exon 11 p.Ile439_Gln487del	X91^{o}	A0528	[1,12]	1(1)	
c.1315−1G>T[c]	Splice site	del. exon 11? p.Ile439_Gln487del?	X91$^{?}$		Unpubl.	1(1)	*
c.1315delA[c]	Deletion Splice site?	p.Ile439SerfsX63	X91^{o}	A0081	[1,19,25]	1(1)	
c.1320C>A	Nonsense	p.Tyr440X	X91$^{?}$	A0151	[1,12,52]	1(1)	
c.1320C>G	Nonsense	p.Tyr440X	X91$^{?}$		Unpubl.	1(1)	*
c.1326C>G	Nonsense	p.Tyr442X	X91^{o}	A0589	[27]	1(1)	*

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.1327delT	Deletion	p.Trp443GlyfsX59	X91$^{?}$	A0630	[33]	1(1)	*
c.1329G>A	Nonsense	p.Trp443X	X91°	A0168	[1,12,52]	2(2)	
				A0485			
c.1333T>C	Missense	p.Cys445Arg	X91$^{?}$	A0605	Unpubl.	1(1)	*
c.1335C>A	Nonsense	p.Cys445X	X91°	A0361	[1]	2(3)	
					unpubl.		
c.1340delA	Deletion	p.Asp447AlafsX55	X91°		[23]	1(1)	*
c.1348_1352delGCCTT	Deletion	p.Ala450X	X91$^{?}$	A0308	[1]	1(1)	
c.1350delC	Deletion	p.Phe451LeufsX51	X91$^{?}$	A0192	[1,12,19]	1(1)	
c.1354G>T	Nonsense	p.Glu452X	X91°	A0373	[1,17]	1(1)	
c.1357T>C	Missense	p.Trp453Arg	X91°	A0486	[1,12,23]	3(3)	
				A0487	unpubl.		
				Kuhns unp			
c.1357T>A	Missense	p.Trp453Arg	X91°	A0613	[20]	1(2)	*
c.1357_1358delTG	Deletion	p.Trp453ValfsX32	X91°		Unpubl.	1(1)	*
c.1358G>A	Nonsense	p.Trp453X	X91°	A0488	[1,12,19]	1(1)	
c.1359G>A	Nonsense	p.Trp453X	X91°	A0489	[1]	2(3)	
					unpubl.		
c.1363_1375del13	Deletion	p.Ala455AsnfsX43	X91°		Unpubl.	1(1)	*
c.1375C>T	Nonsense	p.Gln459X	X91°		Nunoi unp	1(1)	*
c.1382delT	Deletion	p.Leu461ArgfsX41	X91$^{?}$		Unpubl.	1(1)	*
c.1384G>T	Nonsense	p.Glu462X[b]	X91°	A0374	[39,72]	2(2)	*
c.1396C>T	Nonsense	p.Gln466X	X91°	A0426	[1,17]	2(2)	
					unpubl.		
c.1399G>T	Nonsense	p.Glu467X	X91^{-}		Unpubl.	1(2)	*
c.1407−1414del8/ins TGTTGTA[f]	Deletion/insertion	p.Asn470ValfsX14	X91°		[1]	1(2)	
					unpubl.		
c.1415delG	Deletion	p.Gly472AlafsX30	X91°	A0092	[1,12,19]	1(2)	
				A0493			
c.1421T>G	Missense	p.Leu474Arg	X91^{-}		Unpubl.	1(1)	*
c.1428C>A	Nonsense	p.Tyr476X	X91°	A0071	[1,11,17,44,86]	1(1)	
c.1437C>A	Nonsense	p.Tyr479X	X91$^{?}$	A0631	[33]	3(3)	*
					unpubl.		
c.1441A>C	Missense	p.Thr481Pro	X91^{+}		Unpubl.	1(1)	*
c.1447_1459del13	Deletion	p.Trp483ArgfsX15	X91°	A0331	[1,17]	1(1)	
c.1448G>A	Nonsense	p.Trp483X	X91°		Unpubl.	3(3)	*
c.1449G>A	Nonsense	p.Trp483X	X91°	A0294	[1,19]	1(1)	
c.1455delG	Deletion	p.Glu485AspfsX17	X91$^{?}$	A0165	[1,12,19]	1(1)	
c.1456dupT	Insertion	p.Ser486PhefsX11	X91°	A0184	[1,12,19]	2(3)	
				A0185	unpubl.		
c.1461+1G>A[c]	Splice site	del exon 11?	X91$^{?}$	A0241	[1,19]	2(2)	
		p.Ile439_Gln487del?			unpubl.		
c.1461+1G>T[c]	Splice site	del exon 11	X91°	A0530	[1,24]	3(4)	
		p.Ile439_Gln487del		A0560	unpubl.		
c.1461+2delT[c]	Splice site	del exon 11?	X91$^{?}$		[29]	1(1)	*
		p.Ile439_Gln487del?					
c.1461+668_1462−807del1558	Deletion	intronic deletion; no phenotype	het[d,j]		[68]	1(1)	*
c.1462−809_1586+819	Deletion/insertion	del exon 12	X91°		[1,68]	1(1)	
del1753ins12		p.Ala488TyrfsX11					
c.1462−2A>G[c]	Splice site	partial del exon 12	X91^{+}	A0078	[1,92]	3(4)	
		p.Ala488_Glu497del		A0104	unpubl.		
				A0531			
c.1462−2A>C[c]	Splice site	(partial) del exon 12?	X91^{+}		Unpubl.	1(1)	*
		p.Ala488_Glu497del?					
c.1462−1G>A[c]	Splice site	altern. splicing exon 12	X91°	A0532	[1]	1(1)	
		G del exon 12>p.Ala488ProfsX14					
c.1462−?[c]	Splice site	del exon 12	X91°		[1,17]	1(1)	
		p.Ala488TyrfsX11					
c.1464delC	Deletion	p.Asn489IlefsX13	X91°	A0114	[1,12,19]	1(1)	
c.1484A>C	Missense	p.His495Pro	X91^{-}		Unpubl.	1(2)	*
c.1488_1490delTGA	Deletion	p.Asp496del	X91^{+}		Unpubl.	1(1)	*
c.1497delA	Deletion	p.Asp500MetfsX2	X91°	A0312	[1,17]	1(1)	
c.1498G>A	Missense	p.Asp500Asn	X91^{-}	A0366	Unpubl.	1(3)	*
c.1498G>C	Missense	p.Asp500His	X91$^{?}$	A0632	[23,33]	2(2)	*
c.1498G>T	Missense	p.Asp500Tyr	X91^{+}	A0367	[23,56]	2(3)	*
c.1499A>G	Missense	p.Asp500Gly	X91^{+}	A0019	[1,93]	1(1)	
c.1500T>G	Missense	p.Asp500Glu	X91^{+}		[23]	1(1)	*
c.1509delA	Deletion	p.Gly504AlafsX2	X91°		[23] unpubl.	2(2)	*
c.1514T>G	Missense	p.Leu505Arg	X91^{+}	A0408	[35,39]	3(3)	*
				A0573	unpubl.		
c.1514T>C	Missense	p.Leu505Pro	X91^{-}	A0407	[1]	1(2)	
c.1515_1525del11	Deletion	p.Lys506PhefsX9	X91$^{?}$		Unpubl.	1(1)	*
c.1519C>T	Nonsense	p.Gln507X	X91°	A0116	[1,12,52]	2(5)	
c.1521_1525delAAAGA/	Deletion/insertion	p.Gln507_Thr509del/	X91^{+}	A0068	[1,94]	1(1)	
ins CATCTGGG		insHisIleTrpAla					

(*continued on next page*)

Table 1 (*continued*)

cDNA nucleotide (or splice site) change	Mutation	Amino acid change	CGD type	Accession number	Ref.	Kindred (patients)[a]	
c.1522_1523delAA	Deletion	p.Lys508AspfsX10	X91$^{?}$	A0313	[1]	1(1)	
c.1523delA	Deletion	p.Lys508ArgfsX25	X91^{o}	A0314	[1,23]	2(3)	
c.1524_1527delGACT	Deletion	p.Lys508AsnfsX24	X91$^{?}$		Unpubl.	1(1)	*
c.1528_1529delTT	Deletion	p.Leu510ValfsX8	X91^{o}	A0143	[1,19] unpubl.	3(3)	
c.1532_1538delATGGACGinsTTCA	Deletion/insertion	p.Tyr511_Arg513del/insPheGln	X91$^{?}$	A0645	[95]	1(1)	*
c.1533T>A	Nonsense	p.Tyr511X	X91^{o}		[23]	1(1)	*
c.1546T>A	Missense	p.Trp516Arg	X91$^{?}$		[23]	1(1)	*
c.1546T>C	Missense	p.Trp516Arg	X91^{o}	A0494	[1,64]	1(1)	
c.1547G>A	Nonsense	p.Trp516X	X91^{o}	A0570	[35] unpubl.	3(3)	*
c.1548G>T	Missense	p.Trp516Cys	X91$^{?}$	A0094	[1,12,19]	1(1)	
c.1548G>A	Nonsense	p.Trp516X	X91^{o}	A0295 A0296	[1,19] unpubl.	3(3)	
c.1549delG	Deletion	p.Asp517IlefsX16	X91^{o}		Unpubl.	1(1)	*
c.1555G>T	Nonsense	p.Glu519X	X91^{o}	A0059	[1,33,55]	1(1)	
c.1561A>T	Nonsense	p.Lys521X	X91^{o}	A0025	[1,11]	1(1)	
c.1565delC	Deletion	p.Thr522LysfsX11	X91^{o}	A0326	[1,12,34]	1(1)	
c.1570_1586+?del	Deletion	p.Ala524X	X91^{o}		Unpubl.	1(1)	*
c.1571C>T	Missense	p.Ala524Val	X91^{o}		[96] unpubl.	2(2)	*
c.1578delA	Deletion	p.Gln526HisfsX7	X91^{o}	A0319	[56]	1(1)	*
c.1579dupC	Insertion	p.His527ProfsX3	X91^{o}		[23]	1(1)	*
c.1585_1586+9del11[c]	Splice site	del 17 from 3′ exon 12 p.Ala524TyrfsX11	X91^{-}	A0572	[35]	1(1)	*
c.1586+1G>C[c]	Splice site	del exon 12? p.Ala488TyrfsX11?	X91$^{?}$		Unpubl.	1(1)	*
c.1586+3A>T[c]	Splice site	del exon 12? p.Ala488TyrfsX11?	X91$^{?}$		Unpubl.	1(1)	*
c.1587−2A>G[c]	Splice site	altern. splicing G insert exon 13>p.Asn529LysfsX12	X91^{o}	A0533	[1,17,61] unpubl.	3(4)	
c.1598_1600delGAG	Deletion	p.Gly533del	X91^{-}		[28] unpubl.	2(2)	*
c.1600_1614del15	Deletion	p.Val534_Gly538del	X91^{-}	A0329	[1]	1(1)	
c.1601T>A	Missense	p.Val534Asp	X91$^{?}$	A0147	[1,12,19]	1(1)	
c.1603_1609delTTCCTCT	Deletion	p.Phe535ValfsX10	X91^{o}		Unpubl.	1(1)	*
c.1607dupT	Insertion	p.Cys537LeufsX4	X91$^{?}$	A0345	[1]	1(1)	
c.1609T>C	Missense	p.Cys537Arg	X91^{+}	A0199 A0545	[1,12,19,41] unpubl.	2(2)	
c.1611_1612delTG	Deletion	p.Cys537TrpfsX3	X91^{o}		[23]	1(1)	*
c.1618delG	Deletion	p.Glu540LysfsX7	X91^{o}	A0537	[97] unpubl.	2(3)	*
c.1622_1625dupCCTT	Insertion	p.Leu542PhefsX4	X91^{o}	A0183	[1,12,19]	1(1)	
c.1625T>C	Missense	p.Leu542Ser	X91^{o}	A0082	[1,19,26]	1(1)	
c.1637T>C	Missense	p.Leu546Pro	X91^{+}	A0409	[1,26]	1(1)	
c.1637T>G	Missense	p.Leu546Arg	X91^{-}		Unpubl.	1(1)	*
c.1642A>T	Nonsense	p.Lys548X	X91$^{?}$		Unpubl.	1(1)	*
c.1645C>T	Nonsense	p.Gln549X	X91$^{?}$	A0297	[1,19]	1(1)	
c.1658delA	Deletion	p.Ser554LeufsX24	X91$^{?}$		Unpubl.	1(1)	*
c.1661_1662delCT	Deletion	p.Ser554X	X91$^{?}$		[29]	1(1)	*
c.1662dupT	Insertion	p.Glu555X	X91^{o}	A0302 A0348 A0556	[1,19,24] unpubl.	3(5)	
c.1662_1663insGT	Insertion	p.Glu555ValfsX23	X91$^{?}$		Unpubl.	1(1)	*
c.1663_1693dup31	Insertion	p.Phe565X	X91$^{?}$	A0300	[1,39,79]	2(2)	
c.1678G>T	Nonsense	p.Gly560X	X91$^{?}$		Unpubl.	1(1)	*
c.1679delG	Deletion	p.Gly560GlufsX17	X91^{o}	A0307	[77,80,98]	3(3)	*
c.1682−1712del31	Deletion	p.Val561AspfsX6	X91^{o}	A0155	[1,12,19] unpubl.	2(2)	
c.1694dupT	Insertion	p.Asn566GlnfsX28	X91^{-}		Unpubl.	1(1)	*
c.1702G>A	Missense	p.Glu568Lys	X91^{+}	A0259	[1,19,88]	1(1)	

Acc. #, accession number in the X-CGD database (see text); *mutation added since last tabulation; unpubl., not previously published; ND, not determined; NA, not applicable; del, deletion; ins, insertion; dup, duplication; bp, base pairs; AA, amino acids; w.t., wild type.

[a] Number of unrelated kindreds and (number of patients).

[b] These promoter mutations lead to loss of gp91-*phox* expression on neutrophils and monocytes, but normal expression on eosinophils [14–16,18].

[c] Position of introns in *CYBB*: intron 1 c.45_46; intron 2 c.141_142; intron 3 c.252_253; intron 4 c.337_338; intron 5 c.483_484; intron 6 c.674_675; intron 7 c.804_805; intron 8 c.897_898; intron 9 c.1151_1152; intron 10 c.1314_1315; intron 11 c.1461_1462; and intron 12 c.1586_1587.

[d] Female heterozygote patient or female heterozygote relative of a deceased patient.

[e] This patient has a *TMF1* retrogene insertion in *CYBB* intron 1, resulting in an extra exon between exons 1 and 2 in the *CYBB* mRNA. This extra exon contains TAG as the second codon (De Boer et al., unpublished).

[f] Corrected after consultation of the author.

[g] Due to insertion of a LINE-1 element [60,70].

[h] Two patients with c.388C>T (Kuhns et al., unpubl.), one patient with c.667G>T and one patient with c.1384G>T [72] have somatic mosaicisms of cells with the mutated *CYBB* sequence and a small proportion of reverse mutated cells with the wild-type *CYBB* sequence.

[i] Due to unequal crossing over between a GT repetition at the 3′ region of intron 5 and a GT repetition at the 5′ region of intron 8 (Van Leeuwen, Stasia, et al., unpublished).

[j] This woman is a triple mosaic carrier of two different mutations and the wild-type of *CYBB* [68].

Table 2
Large (≥ 1 exon) deletions in the *CYBB* region known to cause X-linked CGD.

Approximate size of deletion (associated disease)	Affected exon(s)	CGD type	Acc. #	Ref	Kindred (patients)	
~6000 kb (+DMD, McLeod)	NA	X91°		Unpubl.	1(1)	*
~5650 kb (+DMD, RP, McLeod)	NA	X91°		[99]	1(1)	*
~5000 kb (+DMD, RP, McLeod)	NA	X91°	A0030	[1,100]	1(1)	
~4000 kb (+DMD, McLeod)	NA	X91°	A0031	[1,101]	1(1)	
~3900 kb (+OTC, RP, McLeod)	NA	X91$^{?}$		[102]	1(1)	*
~3500 kb (+OTC, McLeod)	NA	X91°		Unpubl.	1(1)	*
913 kb	del promoter_exon 1	X91°		[1,12]	1(1)	
~800 kb (+McLeod)	NA	X91°	A0032	[1,103]	1(1)	
~800 kb (+McLeod)	NA	X91°		Unpubl.	1(1)	*
~550 kb (+McLeod)	NA	X91°		[20]	1(1)	*
~500 kb (+RP, McLeod)	NA	X91°		[1,104]	1(1)	
~500 kb (+RP, McLeod)	NA	X91°	A0066	[1,17]	1(1)	
~500 kb	NA	X91°		[20]	1(1)	*
ND (+RP, McLeod)	NA	X91°	A0033	[1,105]	1(1)	
~450 kb (+McLeod)	NA	X91°		Unpubl.	3(4)[a]	*
ND (+McLeod)	NA	X91°		Unpubl.	1(1)	*
ND (+McLeod)	NA	X91°		[29]	1(1)	*
ND (+McLeod)	NA	X91°		[29]	1(1)	*
ND (+McLeod)	del exons 1_13	X91$^{?}$		[106]	1(1)	*
ND (+McLeod)	del exons 1_13	X91$^{?}$		[106]	1(1)	*
ND (+McLeod)	del exons 1_13	X91$^{?}$		[106]	1(1)	*
ND (+McLeod)	del exons 1_13	X91$^{?}$		[106]	1(1)	*
~320 kb (+DMD, McLeod)	NA	X91°		[1,12]	1(1)	
~320 kb (+McLeod)	NA	X91°		Unpubl.	1(1)	*
>300 kb (+McLeod)	del exons 1_13	X91°		Unpubl.	1(1)	*
>300 kb (+McLeod)	del exons 1_13	X91°		Unpubl.	1(1)	*
>150 kb (+McLeod)	del exons 1_13	X91°		Unpubl.	1(1)	*
>150 kb (+McLeod)	del exons 1_13	X91°		Unpubl.	1(1)	*
>100 kb (+McLeod)	del exons 1_3	X91°		Unpubl.	1(1)	*
>100 kb (+McLeod)	del exons 1_13	X91°		[107]	1(3)	*
~100 kb	del exons 1_13	X91°		Unpubl.	1(1)	*
~80 kb	del exons 1_13	X91°		Unpubl.	1(2)	*
>60 kb (+McLeod)	del exons 1_3	X91$^{?}$		[20]	1(2)	*
≫30 kb (+DMD+McLeod)	NA	X91°	A0119	[1,12]	1(1)	
>27 kb (+McLeod)	del. exons 1_13	X91o	A0035	[1,11,19]	1(1)	
>27 kb	del exons 1_13[a]	X91°	A0034	[1,11,12,20,23,29,54]	30[a](32)	
			A0036	unpubl.		
			A0037			
			A0038[b]			
			A0119			
			A0153			
			A0167			
			A0169			
			A0201			
25 kb	del promoter_exon 7	X91°		[1,17,108,109]	1(1)	
>20 kb	del exons 1_10	X91°	A0039[b]	[1,11]	1(1)	
>20 kb	del exons 1_10	X91°		Unpubl.	1(1)	*
ND	del promoter_exon 4	X91°		Unpubl.	1(1)	*
~19 kb	del exons 6_13	X91°		[1]	1(3)	
>15 kb	del exons 4_13	X91°	A0040	[1,19]	1(1)	
~14 kb	del exons 4_9	X91°	A0026	[1,34]	1(1)	
>13 kb	del exons 6_13	X91°	A0041	[1,110]	1(2)	
>13 kb	del exons 6_13	X91°		Unpubl.	1(1)	*
ND	del exons 7_13	X91$^{?}$		Unpubl.	1(1)	*
>10 kb	del exons 8_13	X91°	A0042	[1,11]	1(1)	
>10 kb	del exons 8_13	X91°		[1]	1(1)	
~10 kb	del exons 7_12	X91° (het[b])		Unpubl.	1(1)	*
~10 kb	del exons 7_11	X91°		[1]	1(1)	
>9 kb	del exons 9_13	X91°		[1]	1(1)	
ND	del exons 6_8	X91°		[29]	1(1)	*
ND	del. exons 4_6	X91$^{?}$		Unpubl.	1(1)	*
7 kb	del exons 3_4	X91°		[1,17]	1(1)	
>6.5 kb	del exons 11_13	X91°	A0043	[1,11]	1(1)	
~6 kb	del exons 12_13	X91°	A0044	[1,67]	1(1)	
>5.3 kb	del exons 1_3	X91°	A0204	[1,19]	1(1)	
ND	del exons 1_3	X91°		[56]	1(2)	*
~4.3 kb	del exons 11_13	X91°	A0172	[1,52]	1(2)	
			A0173			
ND	del. exons 11–13	X91$^{?}$		Unpubl.	1(1)	*
ND	del exons 7_8	X91°		Unpubl.	1(1)	*
~3.5 kb	del exons 6_7	X91°	A0028[c]	[1,34,111]	1(1)	
~3.2 kb	del exon 6	X91°		[1]	1(1)	
~3.2 kb	del exon 7	X91$^{?}$	A0205	[1,11]	1(1)	
~3 kb	del exon 5	X91°	A0027[c]	[1,34,111]	1(1)	

(continued on next page)

Table 2 (*continued*)

Approximate size of deletion (associated disease)	Affected exon(s)	CGD type	Acc. #	Ref	Kindred (patients)	
~3 kb	del exon 7	X91$^{?}$		Unpubl.	1(2)	*
~2.2 kb	del exon 5	X91^{o}	A0206	[1,19]	1(1)	
~2 kb	del exon 3	X91^{o}		[1]	1(1)	
~2 kb	del exon 7	X91^{o}		[23]	1(1)	*
ND	del exon 3	X91$^{?}$		Unpubl.	1(1)	*
~2 kb	del promoter_exon 1	X91^{o}		[1]	1(1)	
ND	del promoter_exon 1	X91$^{?}$		[23]	1(1)	*
~2 kb	del exon 8	X91^{o}		[1] unpubl.	2(2)[a]	
2 kb	del exons 12_13	X91^{o}		[1,17]	1(1)	
~2 kb	del. exon 7	X91^{o}		[23]	1(1)	*
ND	del. exon 7	X91$^{?}$		Unpubl.	1(1)	*
~1.1 kb	del exon 6	X91$^{?}$		[23]	1(2)	*
~1 kb	del intron 12_ 3′UTR	X91^{o}	A0203	[1,101] unpubl.	1(1)	
ND	del exon 9	X91$^{?}$		Unpubl.	1(1)	*
ND	del. exon 9	X91$^{?}$		Unpubl.	1(1)	*
0.35 kb	del exon 3	X91^{o}		[1]	1(2)	
0.22 kb	del promoter	X91^{o}		[1]	1(1)	

DMD, Duchenne muscular dystrophy; RP, X-linked retinitis pigmentosa; OTC, ornithine transcarbamylase deficiency; McLeod, McLeod hemolytic anemia; 3′UTR, 3′ untranslated region.

[a] These mutations are not necessarily identical.

[b] Patients A0038 and A0039 are brothers with different deletions.

[c] Patients A0027 and A0028 are brothers with different deletions; their mother has both mutations and the wild-type *CYBB* sequence (triple mosaic) [34,111].

Table 3
Known polymorphisms in the *CYBB* gene.

Nucleotide change	Effect	Approximate frequency
c.−270C/A	N.A.	Unknown [112]
c.141+48C/G	N.A.	Unknown (Maddalena, unpubl.)
c.142−12C/T	N.A.	Unknown (internet, unpubl.)
c.484−60delT	N.A.	Unknown (Jianxin He, unpubl.)
c.484−4G/A	Splice	Unknown [1]
c.654C/A	Silent (p.Gly218)	2% A in sub-Sahara Africans (internet, unpubl.)
c.804+118A/G	N.A.	Unknown (Maddalena, unpubl.)
c.1002G/A	Silent (p.Lys334)	4% A in sub-Sahara Africans (internet, unpubl.) [1]
c.1090G/C	p.364Gly/Arg	Unknown [1,113]
c.1414G/A	p.472Gly/Ser	2% A in Asians (internet, unpubl.)
c.1551T/A	p.517Asp/Glu	Unknown (Hill, unpubl.) [1]
c.1581C/T	Silent (p.His527)	Unknown (Di Matteo, unpubl.)

Table 4
Total number of kindreds with X-CGD patients, total number of X-CGD patients, total number of different mutations and total number of mutations unique for one kindred.

	Kindreds	Mutations
Deletions	281 (22.2%)	242 (35.6%)
Insertions	89 (7.0%)	54 (7.9%)
Deletion/insertions	19 (1.5%)	19 (2.8%)
Splice site mutations	247 (19.5%)	120 (17.6%) (2 undefined)
Missense mutations	246 (19.4%)	145 (21.3%)
Nonsense mutations	377 (29.8%)	96 (14.1%)
Promoter mutations	8 (0.6%)	5 (0.7%)
	Total 1267 unrelated kindreds with 1415 patients	Total 681 different mutations in the patients (all large deletions considered different). Of these 681 mutations, 498 (73.1%) are unique for one kindred.

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