

Survivin Is a Downstream Target of E2A-HLF

15. Li, F., and Ling, X. (2006) *J. Cell. Physiol.* **208**, 476–486
16. Altieri, D. C. (2003) *Nat. Rev. Cancer* **3**, 46–54
17. Li, F., Ambrosini, G., Chu, E. Y., Plescia, J., Tognin, S., Marchisio, P. C., and Altieri, D. C. (1998) *Nature* **396**, 580–584
18. Li, F., and Altieri, D. C. (1999) *Biochem. J.* **344**, 305–311
19. Kurosawa, H., Goi, K., Inukai, T., Inaba, T., Chang, K. S., Shinjyo, T., Rakestraw, K. M., Naeve, C. W., and Look, A. T. (1999) *Blood* **93**, 321–332
20. Kikuchi, J., Furukawa, Y., Iwase, S., Terui, Y., Nakamura, M., Kitagawa, S., Kitagawa, M., Komatsu, N., and Miura, Y. (1997) *Blood* **89**, 3980–3990
21. Robinson, D. A., Dillon, C. P., Kwiatkowski, A. V., Sievers, C., Yang, L., Kopinja, J., Rooney, D. L., Zhang, M., Ihrig, M. M., McManus, M. T., Gertler, F. B., Scott, M. L., and Van Parijs, L. (2003) *Nat. Genet.* **33**, 401–406
22. Kikuchi, J., Shimizu, R., Wada, T., Ando, H., Nakamura, M., Ozawa, K., and Furukawa, Y. (2007) *Stem Cells* **25**, 2439–2447
23. Gu, C. M., Zhu, Y. K., Ma, Y. H., Zhang, M., Liao, B., Wu, H. Y., and Lin, H. L. (2006) *Neoplasia* **53**, 206–212
24. Inaba, T., Shapiro, L. H., Funabiki, T., Sinclair, A. E., Jones, B. G., Ashmun, R. A., and Look, A. T. (1994) *Mol. Cell. Biol.* **14**, 3403–3413
25. Kobayashi, K., Hatano, M., Otaki, M., Ogasawara, T., and Tokuhisa, T. (1999) *Proc. Natl. Acad. Sci. U.S.A.* **96**, 1457–1462
26. Deleted in proof
27. Moubarak, R. S., Yuste, V. J., Artus, C., Bouharrou, A., Greer, P. A., Menissier-de Murcia, J., and Susin, S. A. (2007) *Mol. Cell. Biol.* **27**, 4844–4862
28. Susin, S. A., Lorenzo, H. K., Zamzami, N., Marzo, I., Snow, B. E., Brothers, G. M., Mangion, J., Jacotot, E., Costantini, P., Loeffler, M., Larochette, N., Goodlett, D. R., Aebersold, R., Siderovski, D. P., Penninger, J. M., and Kroemer, G. (1999) *Nature* **397**, 441–446
29. Modjtahedi, N., Giordanetto, F., Madeo, F., and Kroemer, G. (2006) *Trends Cell Biol.* **16**, 264–272
30. Shinjyo, T., Kurosawa, H., Miyagi, J., Ohama, K., Masuda, M., Nagasaki, A., Matsui, H., Inaba, T., Furukawa, Y., and Takasu, N. (2008) *Tohoku J. Exp. Med.* **216**, 25–34
31. Carter, B. Z., Kornblau, S. M., Tsao, T., Wang, R. Y., Schober, W. D., Milella, M., Sung, H. G., Reed, J. C., and Andreeff, M. (2003) *Blood* **102**, 4179–4186
32. Liu, T., Brouha, B., and Grossman, D. (2004) *Oncogene* **23**, 39–48
33. Liu, T., Biddle, D., Hanks, A. N., Brouha, B., Yan, H., Lee, R. M., Leachman, S. A., and Grossman, D. (2006) *J. Invest. Dermatol.* **126**, 2247–2256
34. Croci, D. O., Cogno, I. S., Vittar, N. B., Salvatierra, E., Trajtenberg, F., Podhajcer, O. L., Osinaga, E., Rabinovich, G. A., and Rivarola, V. A. (2008) *J. Cell. Biochem.* **105**, 381–390
35. Yu, S. W., Wang, H., Poitras, M. F., Coombs, C., Bowers, W. J., Federoff, H. J., Poirier, G. G., Dawson, T. M., and Dawson, V. L. (2002) *Science* **297**, 259–263
36. Inukai, T., Inoue, A., Kurosawa, H., Goi, K., Shinjyo, T., Ozawa, K., Mao, M., Inaba, T., and Look, A. T. (1999) *Mol. Cell* **4**, 343–352
37. Metzstein, M. M., and Horvitz, H. R. (1999) *Mol. Cell* **4**, 309–319
38. Metzstein, M. M., Hengartner, M. O., Tsung, N., Ellis, R. E., and Horvitz, H. R. (1996) *Nature* **382**, 545–547
39. Inoue, A., Seidel, M. G., Wu, W., Kamizono, S., Ferrando, A. A., Bronson, R. T., Iwasaki, H., Akashi, K., Morimoto, A., Hitzler, J. K., Pestina, T. I., Jackson, C. W., Tanaka, R., Chong, M. J., McKinnon, P. J., Inukai, T., Grosveld, G. C., and Look, A. T. (2002) *Cancer Cell* **2**, 279–288
40. Tu, S. P., Jiang, X. H., Lin, M. C., Cui, J. T., Yang, Y., Lum, C. T., Zou, B., Zhu, Y. B., Jiang, S. H., Wong, W. M., Chan, A. O., Yuen, M. F., Lam, S. K., Kung, H. F., and Wong, B. C. (2003) *Cancer Res.* **63**, 7724–7732
41. Kanwar, J. R., Shen, W. P., Kanwar, R. K., Berg, R. W., and Krissansen, G. W. (2001) *J. Natl. Cancer Inst.* **93**, 1541–1552
42. Schimmer, A. D. (2004) *Cancer Res.* **64**, 7183–7190
43. Altieri, D. C. (2008) *Nat. Rev. Cancer* **8**, 61–70
44. Fukuda, S., and Pelus, L. M. (2006) *Mol. Cancer Ther.* **5**, 1087–1098

BRIEF REPORT

Successful Treatment of Refractory Donor Lymphocyte Infusion-Induced Immune-Mediated Pancytopenia with Rituximab

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A 6-year-old male with chronic granulomatous disease, who was transplanted with bone marrow and exhibited increasing mixed chimerism, subsequently received two donor lymphocyte infusions (DLI). Two weeks after the second DLI, the patient developed acute graft-versus-host disease (GVHD) and progressive pancytopenia that was associated with autoantibody production. Conventional treatment did not improve the pancytopenia. However, administration of

Rituximab (RTX) (375 mg/m²/week for four consecutive weeks) resulted in a rapid resolution of the pancytopenia. The patient achieved full donor chimerism without GVHD symptoms. RTX can be valuable for managing immune-mediated cytopenias that arise after DLI and are refractory to conventional therapies. *Pediatr Blood Cancer* 2010;54:329–331. © 2009 Wiley-Liss, Inc.

Key words: allogeneic stem cell transplantation; antibodies; graft rejection; graft-versus-host disease; immune responses; Rituximab

INTRODUCTION

Donor leukocyte infusion (DLI) is used as an immunotherapy not only for preventing the reemergence of malignancies, but also for preventing graft rejection after allogeneic hematopoietic stem cell transplantation (hSCT) that results in the development of mixed increasing chimerism [1]. However, DLI treatment is also associated with substantial toxicity. For example, it has been shown that up to 41% of patients receiving DLI suffer from myelosuppression, which could lead to death from causes other than the underlying disease [2,3]. Like the cytopenias associated with graft-versus-host disease (GVHD), the cytopenias that can arise after DLI are conventionally treated by steroids, intravenous immunoglobulin (IVIG), and splenectomy. However, the prognosis of cases that are refractory to conventional treatments remains dismal as the treatment of such cases has not been established. Anti-CD20 antibody (Rituximab, RTX), a humanized murine monoclonal antibody that is often used to treat B-cell malignancies, has been shown to effectively treat various autoimmune diseases that arise after hSCT [4–6]. Here, we describe a patient with severe immune-mediated pancytopenia after DLI who responded well to RTX therapy.

CASE REPORT

A 4-month-old male was diagnosed with X-linked chronic granulomatous disease on the basis of his reduced NADPH oxidase levels (<5%) and the complete absence of gp91-phox. Despite prophylactic treatment with trimethoprim–sulfamethoxazole and itraconazole, and interferon- γ , he suffered repeatedly from severe bacterial and fungal infections, including multiple episodes of pulmonary aspergillosis. Therefore, allogeneic hSCT was planned, and the patient was transferred at 6 years of age to our hospital for bone marrow transplantation (BMT) from a genotypically HLA-matched, blood-type compatible unrelated donor. The HLA type of the donor and the patient was HLA-A 33/24, -B 58/52, -DR 1302/1502. The conditioning regimen included fludarabine 30 mg/m²/day for 6 days from day –7 to –2, cyclophosphamide 30 mg/kg/day for

4 days from day –6 to –3, anti-T lymphocyte globulin 2.5 mg/kg/day for 4 days from day –6 to –3, and total body irradiation 300 cGy on day –1. To prevent GVHD, the patient received tacrolimus and short-methotrexate (day 1: 10 mg/m², day 3.6: 7 mg/m²), as previously reported [7]. Subsequently, 4.8×10^8 /kg mononucleated cells were infused without T-cell depletion. The patient's bone marrow (BM) was analyzed serially for chimerism by micro-satellite PCR, and the presence of oxidase-positive neutrophils in the peripheral blood (PB) was determined by fluorescence-activated cell sorting using a dihydrorhodamine oxidation assay. Hematopoietic engraftment occurred rapidly. The neutrophil count exceeded 0.5×10^9 /L on day 10, the reticulocyte count exceeded 10% on day 17, and the platelet counts did not drop below 40×10^9 /L during this period. However, the donor chimerism of the patient was unstable. After the dosage of tacrolimus was reduced on day 25, grade II acute GVHD of the skin developed on day 37, which was resolved by a short course of prednisolone (PSL) treatment. Subsequently, the patient achieved full donor chimerism of BM on day 61, and the oxidase-positivity of PB neutrophils was 100% on day 82. The GVHD did not worsen after treatment with PSL and tacrolimus was discontinued on days 98 and 361, respectively.

Although the patient was asymptomatic and there were no abnormal laboratory findings, the oxidase-positivity of PB neutrophils gradually decreased to 50% and 13% on days 404 and 758,

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Received 1 May 2009; Accepted 10 August 2009

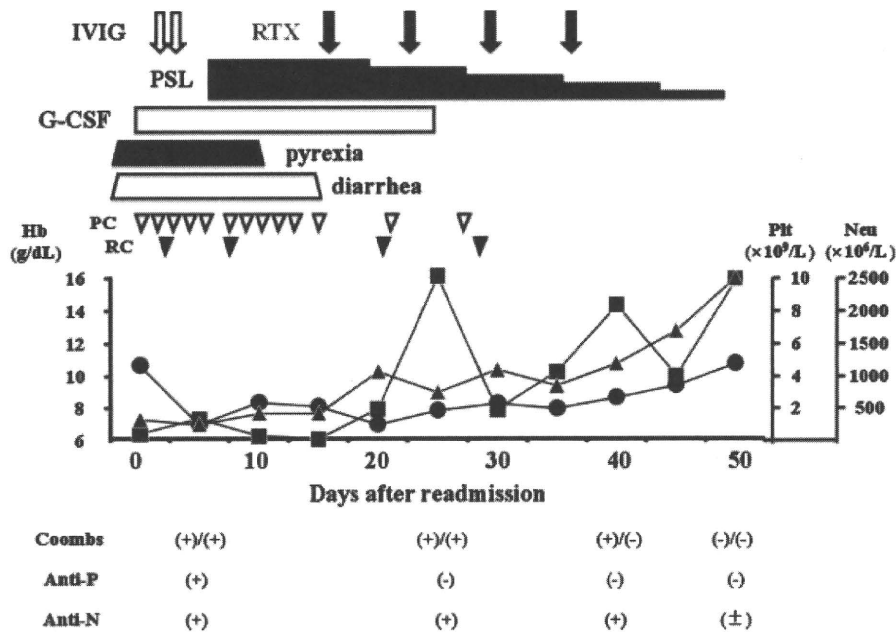


Fig. 1. The clinical course after readmission. IVIG, intravenous immunoglobulin; RTX, Rituximab; PSL, prednisolone; G-CSF, granulocyte colony-stimulating factor; RC, packed red blood cell concentrate; PC, packed platelet concentrate; Plt, platelet counts; Neu, neutrophil counts; Coombs, direct/indirect Coombs test; Anti-P, anti-platelet antibody; Anti-N, anti-neutrophil antibody. Closed circles, triangles, and squares indicate Hb levels, platelet counts (Plt), and neutrophil counts (Neu), respectively.

respectively. In an attempt to induce his return to full donor chimerism, the patient was given frozen 1.0×10^7 and 5.0×10^7 PB lymphocytes/kg on days 805 and 850, respectively, which had been harvested from the same donor who had provided the BM. Before this second DLI, the patient had not undergone any notable events such as contracting an infectious disease, medication changes or vaccinations. The clinical course after the second DLI is shown in Figure 1. Two weeks after it was delivered, the patient developed a skin rash, diarrhea, fever, elevated serum liver enzyme value, and thrombocytopenia. The patient was diagnosed clinically as having GVHD. Since restarting the patient on tacrolimus did not improve

his symptoms, he was readmitted to our hospital on day 44 after the second DLI.

On readmission, the physical examination revealed no abnormal symptoms except for a persistent high fever. The results of the laboratory investigations are shown in Table I. Antibody screening tests revealed strong positivity in the direct and indirect Coombs test, and the presence of anti-platelet antibodies and anti-neutrophil antibodies specific for HNA-1a and 1b. However, other antibody screening tests were negative. There was no fungal infection or recurrence of CMV and EBV. An examination of the BM on day 896 after the BMT revealed a hypocellular marrow, but no

TABLE I. Laboratory Data on Readmission

	Value	Unit	Normal range		Value	Unit	Normal range		Value	Normal range
WBC	3.1	$10^9/L$	3.6–9.8	AST	38	IU/L	13–33	CMVpp65	(–)	(–)
Neu	0.93	$10^9/L$	1.6–6.0	ALT	36	IU/L	8–42	EBV-DNA PCR	(–)	(–)
Lymph	2.2	$10^9/L$	1.1–3.9	LDH	273	IU/L	129–241	Aspergillus-Ag	(–)	(–)
Hb	10.6	g/dl	11.3–13.7	ALP	473	IU/L	115–359	Candida-Ag	(–)	(–)
Reti	7.1	$10^9/L$	2.7–9.3	T.Bil	0.8	mg/dl	0.3–1.3	Direct Coombs Test	(+)	(–)
Plt	12	$10^9/L$	192–456	TP	7.3	mg/dl	6.3–8.1	Indirect Coombs Test	(+)	(–)
Haptoglobin	102.4	mg/dl	14–294	Alb	4.3	mg/dl	3.9–5.1			
CRP	4.9	mg/dl	<0.2	Soluble IL2	972	U/ml	145–519	Anti-neutrophil antibodies	(+)	(–)
β -DG	7.473	ng/ml	<11	Ferritin	7.3	ng/ml	<155	Anti-HNA-a	(+)	(–)
Endotoxin	<1.76	pg/ml	<5	Triglycerides	58	mg/dl	34–173	Anti-HNA-b	(+)	(–)
								Anti-platelet antibodies	(+)	(–)

WBC, white blood cell; Neu, neutrophil; Lymph, lymphocyte; Hb, hemoglobin; Reti, reticulocyte; Plt, platelet; CRP, C-reactive protein; β -DG, β -D-glucan; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; T.Bil, total bilirubin; TP, total protein; Alb, albumin; CMVpp65, Cytomegalovirus pp65; EBV, Epstein–Barr virus; Ag, antigen; HNA, human neutrophil antigen.

evidence of malignancy or hemophagocytosis. Chimerism studies of the BM revealed 55% of the cells were composed of donor cells. Only 17% of the PB neutrophils were oxidase-positive. The patient was first treated with IVIG (1 g/kg/day for 2 days), PSL (2 mg/kg/day daily), and granulocyte colony-stimulating factor (G-CSF). Although this initial treatment resolved the pyrexia and diarrhea, the patient's pancytopenia gradually progressed and multiple transfusions became necessary. Given his refractory autoimmune pancytopenia, he was treated with RTX (375 mg/m²/week for four consecutive weeks). The neutrophil counts rose markedly within a few days after the first RTX infusion, which was followed by the gradual increase in Hb and platelet counts. The patient became transfusion-independent after the third RTX course, and pancytopenia did not recur when the patient stopped receiving G-CSF and PSL. The hematological values normalized 21 days after the initial RTX infusion. The autoimmune antibody levels dropped during RTX treatment and eventually disappeared almost completely. Both BM chimerism studies and analysis of the oxidase-positivity of the PB neutrophils revealed 100% donor chimerism 80 days after the initial RTX infusion. Three years after the RTX treatment, the patient was alive and free of disease and showed no signs of mixed chimerism or GVHD.

DISCUSSION

Cytopenias that follow allogeneic hSCT can be immune-mediated and are frequently associated with GVHD. Autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) occur frequently, but immune-mediated cytopenias, including autoimmune neutropenia (AIN), are relatively rare [4,5]. Cytopenias are also often seen in patients after DLI and are thought to be mediated by autoimmune mechanisms, as with GVHD. In our case, pancytopenia developed soon after DLI, along with acute GVHD and the emergence of autoantibodies against multilineage blood cells. Notably, the levels of these antibodies decreased in parallel with the improvement of the pancytopenia, while the blood and BM analyses suggested that other possible causes of cytopenias, such as viral infections and hemophagocytic histiocytosis, were unlikely. However, the BM examination also showed a hypocellular marrow, which suggested that the pancytopenia did not arise from antibody-mediated cell destruction alone. Our findings suggest that autoimmunity was the major cause of the severe pancytopenia exhibited by our patient.

Most patients with autoimmune cytopenias are rescued by the administration of high-dose IVIG and standard immunosuppressive agents such as steroids [8,9]. Furthermore, RTX has been demonstrated to be useful for treating the AIHA and ITP that follow GVHD, which is refractory to conventional treatment [5,6,10–13]. However, the prognosis of patients who develop autoimmune pancytopenia remains to be determined. Page et al. [4] reported two cases that developed pancytopenia after umbilical cord blood transplantation. Despite receiving immunosuppressive treatment, including RTX, one patient continued to need the therapy while the other required a second transplantation because of pancytopenia.

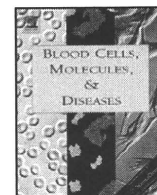
Despite the fact that our patient was initially treated with PSL, high-dose IVIG, and G-CSF, and showed improvements in the other symptoms of acute GVHD, his pancytopenia progressed. Given this rapid and potentially fatal progression, we chose to start a salvage therapeutic approach rather than continue such

conventional treatments, which would result in a slower response. The institution of RTX resulted in the resolution of the pancytopenia and the almost complete disappearance of the autoimmune antibodies. Furthermore, the response to RTX was already obvious 1 week after the first RTX infusion, which is consistent with a study that showed that RTX induces a prompt response in a subpopulation of patients [14].

Although no definite conclusions can be drawn from a single case with a relatively short period of follow-up, this case strengthens the hypothesis that RTX can be a beneficial treatment for refractory DLI-induced immune-mediated pancytopenia. This case suggests that further clinical research examining the merits of RTX in such cases is warranted.

REFERENCES

- Slavin S, Morecki S, Weiss L, et al. Donor lymphocyte infusion: The use alloreactive and tumor-reactive lymphocytes for immunotherapy of malignant and nonmalignant diseases in conjunction with allogeneic stem cell transplantation. *J Hematother Stem Cell Res* 2002;11:265–276.
- Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood* 1995;86:2041–2050.
- Collins RHJR, Shpiberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol* 1997;15:433–444.
- Page KM, Mendizabal AM, Prasad VK, et al. Posttransplant autoimmune hemolytic anemia and other autoimmune cytopenias are increased in very young infants undergoing unrelated donor umbilical cord blood transplantation. *Biol Blood Marrow Transplant* 2008;14:1108–1117.
- Raj K, Narayanan S, Auguston B, et al. Rituximab is effective in the management of refractory autoimmune cytopenias occurring after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2005;35:299–301.
- Zaja F, Bacigalupo A, Patriaca F, et al. Treatment of refractory chronic GVHD with rituximab: A GITMO study. *Bone Marrow Transplant* 2007;40:273–277.
- Kojima S, Matsuyama T, Kato S, et al. Outcome of 154 patients with severe aplastic anemia who received transplants from unrelated donors: The Japan Marrow Donor Program. *Blood* 2002;100:799–803.
- Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005;106:2244–2251.
- Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. *Am J Hematol* 2002;69:258–271.
- Stasi R, Pagano A, Stipa E, et al. Rituximab chimeric CD20 antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001;98:952–957.
- Ratanatharathorn V, Carson E, Reynolds C, et al. Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. *Ann Intern Med* 2000;133:275–279.
- Hongeng S, Tardong P, Worapongpaiboon S, et al. Successful treatment of refractory autoimmune hemolytic anaemia in a post-unrelated bone marrow transplant paediatric patient with Rituximab. *Bone Marrow Transplant* 2002;29:871–872.
- Corti P, Bonanini S, Vallinoto C, et al. Rituximab for immune hemolytic anaemia following T and B cell depleted hematopoietic stem cell transplantation. *Acta Haematol* 2003;109:43–45.
- Mohty M, Marchetti N, El-Cheikh J, et al. Rituximab as salvage therapy for refractory chronic GVHD. *Bone Marrow Transplant* 2008;41:909–911.



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

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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.

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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 A0546	[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.Asn3GlnfsX6	X91°	A0346	[21] unpubl.	2(2)	*
c.8dupA	Insertion	p.Asn3LysfsX6	X91°		[22]	1(1)	*
c.11G>A	Nonsense	p.Trp4X	X91°	A0260 A0490 A0108 A0491 A0492 A0493	[1,11,23]	3(3)	
c.12G>A	Nonsense	p.Trp4X	X91°		[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°	A0483 A0575	[1,20,38] unpubl.	4(4)
c.84G>A	Nonsense	p.Trp28X	1 het ^d X91°	A0563 A0477	[39]	3(3) *
c.85delT	Deletion	p.Tyr29IlefsX32	1 het ^d X91 [?]	A0478	unpubl.	1(1) *
c.90C>A	Nonsense	p.Tyr30X	X91 [?]		Unpubl.	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] unpubl.	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] unpubl.	1(1)
c.142–12_–28del17 ^c	Splice site	del exon 3 p.Ser48_Ala84del	X91°		[1] Unpubl.	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] unpubl.	1(1)
c.142–2A>T ^c	Splice site (created)	del TCAG from exon 3 p.Ile15TrpfsX6	X91°		[1] unpubl.	1(1)
c.142–1G>C ^c	Splice site	del. exon 3? p.Ser48_Ala84del?	X91°		[42] unpubl.	1(2) *
c.142–1G>A ^c	Splice site	del. exon 3 + w.t. p.Ser48_Ala84del	X91 [?]	A0616	[20] unpubl.	1(1) *
c.142_159del18/ insCCTGCCTGAATTTC (dup173_186) ^{Tf}	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] unpubl.	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] unpubl.	1(1)
c.161G>T	Missense	p.Arg54Met	X91 ⁺	A0455	[1,17,44] unpubl.	2(2)
c.162G>C	Missense	p.Arg54Ser	X91 ⁺	A0133	[1,11,45,46] unpubl.	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] unpubl.	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] unpubl.	1(1)
c.176G>A	Missense	p.Cys59Tyr	het ^d	A0363	[1] unpubl.	1(1)
c.177C>G	Missense	p.Cys59Trp	X91°	A0246 A0541	[1,19,39] unpubl.	2(2)
c.177C>A	Nonsense	p.Cys59X	X91°		Unpubl.	1(1) *
c.185delIT	Deletion	p.Phe62SerfsX5	X91°	A0614	[20] unpubl.	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] unpubl.	1(1)
c.194T>G	Missense	p.Met65Arg	X91°		Unpubl.	1(2) *
c.195dupG	Insertion	p.Leu66AlafsX37	X91°	A0196 A0197	[1,11,12] unpubl.	1(2)
c.197T>C	Missense	p.Leu66Pro	X91 [?]		[28] unpubl.	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	
c.226delC	Deletion	p.Leu76CysfsX32	X91 [?]	A0458	Unpubl.	1(2)	*
c.242delG	Deletion	p.Gly81ValfsX27	X91°	A0459	[1,11] unpubl.	2(2)	
c.242dupG	Insertion	p.Ser82PhefsX21	X91°	A0011	Unpubl.	1(1)	*
c.251delC (3' end of exon 3) ^c	Splice site	del. exon 3	X91°	A0110	[1,12,52,54]	1(1)	
c.252G>A (3' end of exon 3) ^c	Splice site	p.Ser48_Ala84del 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 A0148	[1,27,29,32] unpubl.	8(10)	
c.252+5G>C ^c	Splice site	del exon 3? p.Ser48_Ala84del?	X91°		[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° 1 het ^d	A0017 A0248	[1,11,51]	2(2)
c.318G>A	Nonsense	p.Trp106X	X91°	A0015 A0479 A0586	[1,11,27,61]	3(3)
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] unpubl.	2(2)
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) *
c.337+1G>A ^c	Splice site	p.Cys85ArgfsX15? del exon 4?	X91°		Unpubl.	1(1) *
c.337+1G>T ^c	Splice site	p.Cys85ArgfsX15? del exon 4	X91°		Unpubl.	1(1) *
c.337+2dupT ^c	Splice site	p.Cys85ArgfsX15? del exon 4?	X91°		Unpubl.	1(1) *
c.337+5dupG ^c	Splice site	p.Cys85ArgfsX15? del exon 4?	X91°		Unpubl.	1(1) *
c.338–2A>C ^c	Splice site	p.Cys85ArgfsX15? del exon 5?	X91°	A0232	[1,19]	1(1)
c.338–2A>G ^c	Splice site	p.Ala113GlufsX3? del. exon 5	X91°	A0514	[1,29] unpubl.	2(2)
c.338–1G>A ^c	Splice site	p. Ala113GlufsX3 del exon 5	X91°	A0512 A0513	[1,17,44] unpubl.	2(2)
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 A0385 A0249	[1,12]	2(2)
c.359T>C	Missense	p.Leu120Pro	X91°		[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] unpubl.	2(2) *
c.388C>T	Nonsense	p.Arg130X ^h	X91° 2 het ^d	A0065 A0113 A0267 A0268 A0269 A0270 A0271 A0272 A0427 A0428 A0429 A0430 A0431 A0432 A0587 A0596 A0080	[1,11,12,17,20,22, 23,27,39,49,65] unpubl.	41(44)
c.388_389insT	Insertion	p.Arg130LeufsX4	X91°		[1,19]	1(1)
c.389G>C	Missense	p.Arg130Pro	X91°		Unpubl.	1(1) *
c.389G>T	Missense	p.Arg130Leu + partial outslicing 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] unpubl.	2(2)
c.425C>T	Missense	p.Ser142Phe	X91°		[42]	1(1) *
c.425_426delCT	Deletion	p.Ser142X	X91°		Unpubl.	1(2) *

(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.439_440delAG	Deletion	p.Arg147AlafsX3	X91 [?]		[27]	1(1) *
c.442C>T	Nonsense	p.Gln148X	X91°	A0273	[1,17,52]	3(3)
				A0420	unpubl.	
c.442_443delCAinsT	Deletion/insertion	p.Gln148X	X91°	A0111	[1,52]	1(1)
c.446dupA	Insertion	p.Asn149LysfsX2	X91°	A0139	[1,12,52]	1(1)
c.448G>T	Nonsense	p.Glu150X	het ^d		Unpubl.	1(1) *
c.450_451delAA	Deletion	p.Ser151fsX13	X91°		Unpubl.	1(1) *
c.455_456delAT	Deletion	p.Tyr152SerfsX12	X91°	A0332	[1]	1(1)
c.456T>A	Nonsense	p.Tyr152X	X91°	A0124	[1,12,19,62]	2(2)
				A0644		
c.458T>G	Missense	p.Leu153Arg	X91°		Unpubl.	1(2) *
c.461delA	Deletion	p.Asn154IlefsX7	X91°		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°	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°	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°	A0181	[1,12]	1(1)
		p. Ala113GlufsX3?				
c.483G>T (3' end of exon 5) ^c	Splice site	del exon 5	X91°	A0233	[1,11]	1(1)
		p. Ala113GlufsX3				
c.483+1G>A ^c	Splice site	del exon 5	X91°	A0515	[1,23,42]	4(5)
		p. Ala113GlufsX3			unpubl.	
c.483+1G>T ^c	Splice site	del exon 5	X91°	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°	A0164	[1,43]	1(1)
		p Ala113GlufsX3?				
c.483+3A>T ^c	Splice site	del exon 5	X91°	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°		[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°		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°	A0217	[1,11]	1(1)
c.535G>A	Missense	p.Gly179Arg	X91°	A0375	[1,25]	1(1)
c.535G>T	Nonsense	p.Gly179X	X91°		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°	A0218	[1,19]	1(1)
c.555C>A	Nonsense	p.Cys185X	X91°	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°	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_648delITTC	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_+7delAGTC ^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 A0518	[1,42]	4(7)	
c.674+6T>A ^c	Splice site	del exon 6? p.Asn162ThrfsX15?	X91°		[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)	*

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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.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?	X91°		Unpubl.	1(1) *
c.675–1G>A ^c	Splice site	p.Arg226LeufsX5? del exons 6_7	X91°		Unpubl.	1(1) *
c.676C>T	Nonsense	p.Asn162_Met268del 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 A0285	[1,11,12,17,23, 33,52,54,55] unpubl.	30(32)
c.752G>A	Nonsense	p.Trp251X	X91°		[1,11] unpubl.	2(2)
c.754G>T	Nonsense	p.Gly252X	X91?		Unpubl.	1(1) *
c.755delG	Deletion	p.Gly252GluufsX3	X91°	A0195 A0219 A0220	[1,12,19,20] unpubl.	4(5)
c.755_756delGA	Deletion	p.Gly252GluufsX31	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 ^o		Unpubl.	1(1) *
c.781_782delCA	Deletion	p.Gln261ValfsX22	X91 ^o	A0001	[1,11]	1(1)
c.781C>T	Nonsense	p.Gln261X	X91 ^o	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 ^o	A0582	[27]	1(1) *
c.797delC	Deletion	p.Pro266LeufsX3	X91 ^o	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 ^o	A0522	[1,77,80]	2(2)
c.804+1G>T ^c	Splice site	del exon 7 p.Arg226LeufsX5	X91 ^o	A0523	[1] unpubl.	3(3)
c.804+2T>A ^c	Splice site	del. exon 7 p.Arg226LeufsX5	X91 ^o	A0005	[1,32]	1(1)
c.804+2T>C ^c	Splice site	del. exon 7 p.Arg226LeufsX5	X91 ^o	A0236 A0237	[1,11] unpubl.	3(4)
c.805–2A>C ^c	Splice site	del exon 8? p.Thr269_Lys299del?	X91 ^o	A0238	[1,19]	1(1)
c.805–2A>T ^c	Splice site	del. exon 8? p.Thr269_Lys299del?	X91 ^o		Unpubl.	1(1) *
c.805–2A>G ^c	Splice site	del exon 8 p.Thr269_Lys299del	X91 ^o	A0520	[1,17,44]	1(1)
c.805–1G>A ^c	Splice site	del exon 8? p.Thr269_Lys299del?	X91 ^o	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 ^o		[1,25]	1(1)
c.810G>A	Nonsense	p.Trp270X	X91 ^o	A0624	[53] unpubl.	2(2) *
c.811A>T	Nonsense	p.Lys271X	X91 ^o		Unpubl.	1(1) *
c.815G>A	Nonsense	p.Trp272X	X91 ^o	A0099 A0287 A0482 A0047	[1,12,19]	3(3)
c.816G>A	Nonsense	p.Trp272X	X91 ^o		[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 ^o	A0536	Unpubl.	1(1) *
c.845dupG	Insertion	p.Cys282TrpfsX2	X91 ^o		Unpubl.	1(1) *
c.867G>A	Nonsense	p.Trp289X	het ^d		[81]	1(1) *
c.868C>T	Nonsense	p.Arg290X	X91 ^o 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 ^o	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	p.Lys299Asn	X91 [–]		Unpubl.	1(1) *
c.897G>T	Splice site?					
c.897G>T	Missense	p.Lys299Asn	X91 [?]	A0402	[1]	1(1)
c.897G>A (3' end of exon 8) ^c	Splice site?					
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 97 p.Val300AspfsX4?	X91 [?]		Unpubl.	2(2) *
c.903dupC	Insertion	p.Thr302HisfsX46	X91°		Unpubl.	1(1) *
c.904A>C	Missense	p.Thr302Pro	X91 [?]		[23]	1(1) *
c.906_909delTCAC	Deletion	p.His303LeufsX9	X91 [?]		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	X91 [?]		Unpubl.	1(2) *
c.915delC	Deletion	p.Phe305LeufsX8	X91 [?]	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	X91 [?]		[1,12]	1(1)
c.922_923insGT TTC	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	X91 [?]		Unpubl.	1(1) *
c.935T>G	Missense	p.Met312Arg	X91 [?]	A0253	[1,11] unpubl.	2(2)
c.935T>A	Missense	p.Met312Lys	X91 [?]	A0629	[33]	1(1) *
c.943_945delAAG	Deletion	p.Lys315del	X91–	A0163 A0208 A0209 A0222	[1,11,12,43,48,79] unpubl.	3(4)
c.948delG	Deletion	p.Phe317SerfsX26	X91°		[1,19]	1(1)
c.958delG	Deletion	p.Glu320LysfsX23	X91 [?]		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	X91 [?]	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	X91 [?]		[53] unpubl.	3(3) *
c.1012C>T	Missense	p.His338Tyr	X91– 1 het ^d	A0014 A0084 A0254 A0397 A0398 A0396	[1,11,26,49,80,85] unpubl.	7(7)
c.1012C>A	Missense	p.His338Asn	X91 [?]		[1]	1(1)
c.1013A>G	Missense	p.His338Arg	X91+		Unpubl.	2(4) *
c.1014C>A	Missense	p.His338Gln	X91 [?]		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	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.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	[1,11,33,55]	4(4)
				A0256	unpubl.	
				A0404		
c.1027A>C	Missense	p.Thr343Pro	X91 ^o	A0591	[27]	2(2)
					unpubl.	
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	[1,17,44]	3(4)
				A0468	unpubl.	
c.1032delC	Deletion	p.Ala345ProfsX41	X91 ^o	A0324	[1]	2(2)
				A0325		
c.1038delT	Deletion	p.Glu347ArgfsX39	X91 ^o	A0129	[1,12,19,54]	5(6)
				A130	unpubl.	
				A0161		
				A0318		
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	[1,11,23]	3(4)
				A0378	unpubl.	
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]	3(3)
					unpubl.	
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]	2(2)
					unpubl.	
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 ⁺	A0257	[1,11,88]	1(1)
			het ^d			
c.1120C>T	Nonsense	p.Gln374X	X91 ^o		Unpubl.	2(2)
c.1123G>T	Nonsense	p.Glu375X	X91 ^o	A0610	[20]	3(3)
					unpubl.	
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	[1,12,52]	3(3)
				A0174	unpubl.	
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?	X91 ^o	A0156	Unpubl.	9(9)
		p.Val300AspfsX4?				
c.1151+4A>T ^c	Splice site	del exon 9?	X91 [?]		Unpubl.	1(1)
		p.Val300AspfsX4?				
c.1151+5G>A ^c	Splice site	del exon 9?	X91 ^o	A0525	[1]	2(2)
		p.Val300AspfsX4			unpubl.	
c.1152−11T>G ^c	Splice site	del exon 10/ins10 into exon 10>	X91 [−]		[1,26]	1(2)
		p.Ala488PhefsX12				
c.1152−2A>G ^c	Splice site	del exon 10?	X91 [?]	A0580	[38]	1(1)
		p.Ile385SerfsX63?				
c.1152−2A>T ^c	Splice site	del exon 10?	X91 ^o		Unpubl.	2(2)
		p.Ile385SerfsX63?				
c.1152−1G>A ^c	Splice site	alt splice site>1 nt del	X91 ^o		Unpubl.	2(2)
		p.Ile385X				
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]	2(2)
					unpubl.	
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	[1,11]	2(3)
				A0259	unpubl.	
c.1177delA	Deletion	p.Thr393LeufsX12	X91 [?]		Unpubl.	1(1) *
c.1180_1182delGCC/ ins ATGTGATGAACACAT	Deletion/insertion	p.Ala394MetX2	X91 ^o	A0072	[1,89]	1(2)
				A0073		
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	[1,12,19]	2(3)
				A0158		
c.1222G>C	Missense	p.Gly408Arg	X91 ⁺		[90]	1(1) *
c.1223G>A	Missense	p.Gly408Glu	X91 ⁺	A0013	[1,11,12,19,88]	3(4)
			1 het ^d	A0016		
				A0190		
				A0191		
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	A0144	[1,12,19]	2(2)
			1 het ^d		unpubl.	
c.1244C>A	Missense	p.Pro415His	X91 ⁺	A0048	[1,11,12,91]	3(5)
				A049		
				A0076		
				A077		
				A0107		
c.1244C>G	Missense	p.Pro415Arg	X91 [?]	A0419	[1]	1(1)
c.1244C>T	Missense	p.Pro415Leu	X91 ⁺	A0112	[1,3,12,19]	3(3)
					unpubl.	
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	[53]	4(4) *
				A0623	unpubl.	
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]	2(2)
					unpubl.	
c.1313delA ^c	Deletion	p.Lys438ArgfsX64	X91 ^o	A0053	[1,11]	2(3)
c.1313_1314delAGinsT ^c	Deletion/insertion	p.Lys438IlefsX64	X91 ^o	A0054	unpubl.	
	Splice site?			A0091	[1,12,19]	1(1)
c.1314delG ^c	Deletion	p.Ile439SerfsX63	X91 [?]		Unpubl.	2(2) *
	Splice site?					
c.1314+1G>A ^c	Splice site	del exon 10?	X91 [?]	A0526	[1,12,38]	2(2)
		p.Ile385SerfsX63?	1 het ^d	A0579		
c.1314+1G>T ^c	Splice site	del exon 10	X91 [?]	A0529	[1]	1(1)
		p.Ile385SerfsX63				
c.1314+1G>C ^c	Splice site	del exon 10	X91 ^o		Unpubl.	1(1) *
		p.Ile385SerfsX63				
c.1314+2T>A ^c	Splice site	del exon 10	X91 ^o	A0527	[1]	1(1)
		p.Ile385SerfsX63				
c.1314+2T>G ^c	Splice site	del exon 10	het ^d		Unpubl.	1(1) *
		p.Ile385SerfsX63				
c.1314+4_+5AG>GC ^c	Splice site	del exon 10	X91 ⁻		Unpubl.	1(1) *
		p.Ile385SerfsX63				
c.1315-2A>C ^c	Splice site	del exon 11?	X91 [?]		Unpubl.	2(2) *
		p.Ile439_Gln487del?				
c.1315-1G>C ^c	Splice site	del exon 11	X91 ^o	A0528	[1,12]	1(1)
		p.Ile439_Gln487del				
c.1315-1G>T ^c	Splice site	del exon 11?	X91 [?]		Unpubl.	1(1) *
		p.Ile439_Gln487del?				
c.1315delA ^c	Deletion	p.Ile439SerfsX63	X91 ^o	A0081	[1,19,25]	1(1)
	Splice site?					
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 ^o	A0168 A0485	[1,12,52]	2(2)
c.1333T>C	Missense	p.Cys445Arg	X91 [?]	A0605	Unpubl.	1(1) *
c.1335C>A	Nonsense	p.Cys445X	X91 ^o	A0361	[1] unpubl.	2(3)
c.1340delA	Deletion	p.Asp447AlafsX55	X91 ^o		[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 ^o	A0373	[1,17]	1(1)
c.1357T>C	Missense	p.Trp453Arg	X91 ^o	A0486 A0487	[1,12,23] unpubl.	3(3)
c.1357T>A	Missense	p.Trp453Arg	X91 ^o	A0613	[20] Kuhns unp	1(2) *
c.1357_1358delITG	Deletion	p.Trp453ValfsX32	X91 ^o		Unpubl.	1(1) *
c.1358G>A	Nonsense	p.Trp453X	X91 ^o	A0488	[1,12,19]	1(1)
c.1359G>A	Nonsense	p.Trp453X	X91 ^o	A0489	[1] unpubl.	2(3)
c.1363_1375del13	Deletion	p.Ala455AsnfsX43	X91 ^o		Unpubl.	1(1) *
c.1375C>T	Nonsense	p.Gln459X	X91 ^o		Nunoi unp	1(1) *
c.1382delT	Deletion	p.Leu461ArgfsX41	X91 [?]		Unpubl.	1(1) *
c.1384G>T	Nonsense	p.Glu462X ^h	X91 ^o	A0374	[39,72]	2(2) *
c.1396C>T	Nonsense	p.Gln466X	X91 ^o	A0426	[1,17] unpubl.	2(2)
c.1399G>T	Nonsense	p.Glu467X	X91 ^o		Unpubl.	1(2) *
c.1407–1414del8/ins TGTGTGA ^f	Deletion/insertion	p.Asn470ValfsX14	X91 ^o		[1] unpubl.	1(2)
c.1415delG	Deletion	p.Gly472AlafsX30	X91 ^o	A0092 A0493	[1,12,19]	1(2)
c.1421T>G	Missense	p.Leu474Arg	X91 ^o		Unpubl.	1(1) *
c.1428C>A	Nonsense	p.Tyr476X	X91 ^o	A0071	[1,11,17,44,86]	1(1)
c.1437C>A	Nonsense	p.Tyr479X	X91 [?]	A0631	[33] unpubl.	3(3) *
c.1441A>C	Missense	p.Thr481Pro	X91 ⁺		Unpubl.	1(1) *
c.1447_1459del13	Deletion	p.Trp483ArgfsX15	X91 ^o	A0331	[1,17]	1(1)
c.1448G>A	Nonsense	p.Trp483X	X91 ^o		Unpubl.	3(3) *
c.1449G>A	Nonsense	p.Trp483X	X91 ^o	A0294	[1,19]	1(1)
c.1455delG	Deletion	p.Glu485AspfsX17	X91 [?]	A0165	[1,12,19]	1(1)
c.1456dupT	Insertion	p.Ser486PhefsX11	X91 ^o	A0184 A0185	[1,12,19] unpubl.	2(3)
c.1461+1G>A ^c	Splice site	del exon 11? p.Ile439_Gln487del?	X91 [?]	A0241	[1,19] unpubl.	2(2)
c.1461+1G>T ^c	Splice site	del exon 11 p.Ile439_Gln487del	X91 ^o	A0530 A0560	[1,24] unpubl.	3(4)
c.1461+2delT ^c	Splice site	del exon 11? p.Ile439_Gln487del?	X91 [?]		[29]	1(1) *
c.1461+668_1462–807del1558	Deletion	intronic deletion; no phenotype	het ^{d,j}		[68]	1(1) *
c.1462–809_1586+819 del1753ins12	Deletion/insertion	del exon 12 p.Ala488TyrfsX11	X91 ^o		[1,68]	1(1)
c.1462–2A>G ^c	Splice site	partial del exon 12 p.Ala488_Glu497del	X91 ⁺	A0078 A0104 A0531	[1,92] unpubl.	3(4)
c.1462–2A>C ^c	Splice site	(partial) del exon 12? p.Ala488_Glu497del?	X91 ⁺		Unpubl.	1(1) *
c.1462–1G>A ^c	Splice site	altern. splicing exon 12 G del exon 12>p.Ala488ProfsX14	X91 ^o	A0532	[1]	1(1)
c.1462–7 ^c	Splice site	del exon 12 p.Ala488TyrfsX11	X91 ^o		[1,17]	1(1)
c.1464delC	Deletion	p.Asn489IlefsX13	X91 ^o	A0114	[1,12,19]	1(1)
c.1484A>C	Missense	p.His495Pro	X91 ^o		Unpubl.	1(2) *
c.1488_1490delTGA	Deletion	p.Asp496del	X91 ⁺		Unpubl.	1(1) *
c.1497delA	Deletion	p.Asp500MetfsX2	X91 ^o	A0312	[1,17]	1(1)
c.1498G>A	Missense	p.Asp500Asn	X91 ^o	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 ^o		[23] unpubl.	2(2) *
c.1514T>G	Missense	p.Leu505Arg	X91 ⁺	A0408 A0573	[35,39] unpubl.	3(3) *
c.1514T>C	Missense	p.Leu505Pro	X91 ^o	A0407	[1]	1(2)
c.1515_1525del11	Deletion	p.Lys506PhefsX9	X91 [?]		Unpubl.	1(1) *
c.1519C>T	Nonsense	p.Gln507X	X91 ^o	A0116	[1,12,52]	2(5)
c.1521_1525delAAAGA/ ins CATCTGGG	Deletion/insertion	p.Gln507_Thr509del/ insHisIleTrpAla	X91 ⁺	A0068	[1,94]	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.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]	3(3)
c.1532_1538delATGGACGinsTTCA	Deletion/insertion	p.Tyr511_Arg513del/insPheGln	X91 [?]	A0645	unpubl. [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]	3(3) *
c.1548G>T	Missense	p.Trp516Cys	X91 [?]	A0094	[1,12,19]	1(1)
c.1548G>A	Nonsense	p.Trp516X	X91 ^o	A0295	[1,19]	3(3)
				A0296	unpubl.	
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]	2(2) *
					unpubl.	
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	X91 [−]	A0572	[35]	1(1) *
		p.Ala524TyrfsX11				
c.1586+1G>C ^c	Splice site	del exon 12?	X91 [?]		Unpubl.	1(1) *
		p.Ala488TyrfsX11?				
c.1586+3A>T ^c	Splice site	del exon 12?	X91 [?]		Unpubl.	1(1) *
		p.Ala488TyrfsX11?				
c.1587−2A>G ^c	Splice site	altern. splicing	X91 ^o	A0533	[1,17,61]	3(4)
		G insert exon 13>p.Asn529LysfsX12			unpubl.	
c.1598_1600delGAG	Deletion	p.Gly533del	X91 [−]		[28]	2(2) *
					unpubl.	
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	[1,12,19,41]	2(2)
				A0545	unpubl.	
c.1611_1612delTG	Deletion	p.Cys537TrpfsX3	X91 ^o		[23]	1(1) *
c.1618delG	Deletion	p.Glu540LysfsX7	X91 ^o	A0537	[97]	2(3) *
					unpubl.	
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	[1,19,24]	3(5)
				A0348	unpubl.	
				A0556		
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.Gly560GluX17	X91 ^o	A0307	[77,80,98]	3(3) *
c.1682−1712del31	Deletion	p.Val561AspfsX6	X91 ^o	A0155	[1,12,19]	2(2)
					unpubl.	
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 mosaicism 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	X91°	A0035	[1,11,19]	1(1)	
>27 kb	del exons 1_13 ^a	X91°	A0034	[1,11,12,20,23,29,54]	30*(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)	

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