

Hematologically Important Mutations: X-Linked Chronic Granulomatous Disease - An Update

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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) for the protein gp91-*phox*. 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 123 mutations in the gp91-*phox* gene known to cause CGD (1). In these updated tables 68 newly identified mutations have been added (marked with * in the last column). Table 1 includes missense mutations, nonsense mutations, splice site mutations, deletions and insertions that have been precisely defined. 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 listed here with those in a X-CGD database which lists X91 CGD patients by accession number (2). The database contains additional biochemical, genetic and clinical information and is available at <http://www.helsinki.fi/science/signal/databases/>

x-cgdbase. Additional information about the mutations and about CGD in general can also be found in recent reviews (3-5) and in the cited literature. A table listing the mutations causing the autosomal recessive forms of CGD has been published separately (6).

We have used the standard notation for differentiating the various phenotypes of X-linked CGD, X91^o, X91⁻, and X91⁺, where the superscript denotes whether the level of gp91-*phox* protein is undetectable (o), diminished (-) or normal (+), as determined by immunoblot analysis and/or spectral analysis. The designation X91[?] indicates that the level of protein has not been determined. The nucleotides are numbered according to the cDNA sequence described in (7), where the start of translation is +1 and the A of the ATG start codon is 13.

Keywords: chronic granulomatous disease, mutation, NADPH oxidase, phagocyte, X-linked disease

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Table 1. Mutations in the gene for gp91-*phox* that cause X-linked CGD

cDNA Nucleotide (or Splice Site) Change	Mutation	Amino Acid Change	CGD Type	Accession Number	Reference	
-57 a-c (regulatory)	missense	NA	X91 ⁻	A0089	(8)	
-55 t-c (regulatory)	missense	NA	X91 ⁻	A0166	(8)	
13 A-G	missense	start codon lost	X91 ^o	A0242	(2)	*
23 G-A	nonsense	4 Trp→stop	X91 ^o	A0260	(4)	
24 G-A	nonsense	4 Trp→stop	X91 ^o	A0108	(2)	*
52 G	deletion	frameshift	X91 ^o	A0079	(2)	*
5' intron 1 gt-ct	splice site	del exon 1	X91 ^o	A0223	(2)	*
5' intron 1 gtaag-gtaaa	splice site	del exon 1	X91 ^o	A0003	(4)	
5' intron 1 gtaagt-gtaagc	splice site	ND	X91 ^o	A0134	(2)	*
3' intron 1 ag-aa	splice site	del exon 2	X91 ^o	A0224	(9)	
59 T	deletion	frameshift	X91 ^o	A0214	(10)	
60/61 G	deletion	frameshift	X91 ^o	A0215	(4)	
66 G-C	missense	18 Trp→Cys	X91 ⁻	A0083	(2)	*
70 G-C	missense	20 Gly→Arg	X91 ^o	A0136	(5)	
AACG after 79 G	insertion	frameshift	X91 ^o	A0298	(4)	
111 T-A	nonsense	33 Tyr→stop	X91 ^o	A0024	(4)	
130/133 T	deletion	frameshift	X91 ^o	A0018	(10)	
139 A-T	nonsense	43 Arg→stop	X91 ^o	A0261	(4)	
151/153 G	deletion	frameshift or splice	X91 ^o		(4)	
5' intron 2 g	deletion	del exons 2, 3	X91 ^o	A0216	(2)	*
5' intron 2 gt-tt	splice site	del exon 2	X91 ^o	A0138 A0154	(5)	
5' intron 2 gt-at	splice site	ND	X91 ^o	A0131	(2)	*
5' intron 2 gtaag-gtaaa	splice site	del exon 2	X91 ^o	A0225	(2)	*
3' intron 2 ag-gg	splice site	del exon 3	X91 ^o	A0105	(11)	
C after 169 G	insertion	frameshift	X91 ^o	A0160	(2)	*
170 C-A	missense	53 Ala→Asp	X91 ⁻	A0050	(4)	
172 A-G	missense	54 Arg→Gly	X91 ⁺	A0243	(2)	*
174 G-C	missense	54 Arg→Ser	X91 ⁺	A0133	(12,13)	
179 C-T	missense	56 Pro→Leu	X91 ⁻	A0244 A0304	(3,14)	
182 C-A	missense	57 Ala→Glu	X91 ⁺	A0069	(15)	
187 T-C	missense	59 Cys→Arg	X91 ^o	A0175	(2)	*
189 C-G	missense	59 Cys→Trp	X91 [?]	A0246	(2)	*
202 T-C	missense	64 Cys→Arg	X91 ^o	A0247	(2)	*
G after 207 G	insertion	frameshift	X91 ^o	A0196	(5)	
229 C-T	nonsense	73 Arg→stop	X91 ^o	A0008 A0188 A0262 A0263	(16,17)	
251/254 G	deletion	frameshift	X91 ^o	A0011	(4)	
263 C	deletion	frameshift	X91 ^o	A0110	(17)	
A after 263 C	insertion	frameshift	X91 ^o	A0127	(2)	*

Table 1. Mutations in the gene for *gp91-phox* that cause X-linked CGD

cDNA Nucleotide (or Splice Site) Change	Mutation	Amino Acid Change	CGD Type	Accession Number	Reference	
264 G→A (3' end of exon 3)	splice site	del exon 3	X91°	A0022 A0063 A0100 A0193	(4)	
5' intron 3 gtaag-gtaac	splice site	del exon 3	X91°	A0148	(2)	*
5' intron 3 gtaag-gtaaa	splice site	del exon 3	X91°	A0023	(9)	
2.1 kb after 274 A	insertion	frameshift	X91°	A0299	(2)	*
283 C→T	nonsense	91 Arg→stop	X91°	A0029 A0149 A0178	(4,5)	
307 A	deletion	frameshift	X91°	A0097	(4)	
314 A→G	missense	101 His→Arg	X91°	A0017 A0248	(4,16)	
330 G→A	nonsense	106 Trp→stop	X91°	A0015	(4)	
G after 332 T	insertion	frameshift	X91°	A0057	(4)	
338-339 CA	deletion	frameshift	X91°	A0210	(4)	
3' intron 4 ag-cg	splice site	del exon 5	X91°	A0232	(2)	*
366 A	deletion	frameshift	X91°	A0103	(2)	*
A after C 367	insertion	frameshift	X91°	A0007	(4)	
371 T→C	missense	120 Leu→Pro	X91°	A0249	(4)	
400 C→T	nonsense	130 Arg→stop	X91°	A0065 A0080 A0113	(4)	
454-455 CA del/T insert	del/insert	frameshift	X91°	A0111	(17)	*
A after 458 A	insertion	frameshift	X91°	A0139	(17)	
468 T→A	nonsense	152 Tyr→stop	X91°	A0124	(2)	*
478 G→A	missense	156 Ala→Thr	X91°	A0055 A0137 A0187	(16,17)	
481 C→T	nonsense	157 Arg→stop	X91°	A0074 A0095 A0098 A0152 A0177	(4,11,18)	
494 A→G	missense	161 Lys→Arg	X91°	A0179	(17)	
494-495 AG + 5' intron 5 gtaa deleted	splice site	del exon 5	X91°	A0181	(2)	*
495 G→T (end of exon 5)	splice site	del exon 5	X91°	A0233	(4)	
5' intron 5 gt-tt	splice site	del exon 5	X91°	A0115 A0234	(2,4)	
5' intron 5 gt-gc	splice site	ND	X91°	A0164	(11)	
5' intron 5 gta-gtt	splice site	del exon 5	X91°	A0009	(9)	
5' intron 5 gtaag-gtaaa	splice site	ND	X91°?	A0140	(2)	*
527/529 C	deletion	frameshift	X91°	A0217	(4)	
566 G	deletion	frameshift	X91°	A0218	(2)	*
567 C→A	nonsense	185 Cys→stop	X91°	A0182	(2)	*
619 G→T	nonsense	203 Glu→stop	X91°	A0278	(4)	
625 T→A	missense	205 Phe→Ile	X91°?	A0060	(19)	*
633 C→A	splice site (created)	del part exon 6	X91°	A0012	(9)	

Table 1. Mutations in the gene for gp91-*phox* that cause X-linked CGD

cDNA Nucleotide (or Splice Site) Change	Mutation	Amino Acid Change	CGD Type	Accession Number	Reference	
637 C-T	missense	209 His-Tyr	X91 ⁻	A0006	(16)	
637-638 CA	deletion	frameshift	X91 ^o	A0211	(2)	*
639 T-A	missense	209 His-Gln	X91 ^o	A0125	(17)	
655/660 TTC	deletion	215 or 216 Phe	X91 ^o	A0010 A0058 A0085	(14,19)	
677 A-G	missense	222 His-Arg	X91 ^o	A0250	(4)	
679-680 GG-TT	missense	223 Gly-Leu	X91 [?]	A0109	(2)	*
5' intron 6 gtgag-gtgaa	splice site	del exon 6	X91 [?]	A0235	(4)	
5' intron 6 del gtga	splice site	del exon 6	X91 ^o	A0051 A0052	(4)	
5' intron 6 gagt deleted	splice site	ND	X91 ^o	A0106	(2)	*
688 C-T	nonsense	226 Arg-stop	X91 ^o	A0132 A0150	(4,20)	
40 bp dupl. after 702 G	insertion	frameshift	X91 ^o	A0301	(21)	
711/716 AG	deletion	frameshift	X91 [?]	A0120 A0212	(4,17)	
728-732 ATAAT	deletion	frameshift	X91 ^o	A0117	(17)	
742 T-C	missense	244 Cys-Arg	X91 [?]	A0171	(17)	
743 G-C	missense	244 Cys-Ser	X91 ⁻	A0251	(3,16)	
743 G-A	missense	244 Cys-Tyr	X91 ⁻	A0252	(22)	
748 C-T	nonsense	246 Gln-stop	X91 ^o	A0186 A0122	(2)	*
752-753 AA del/T insert	del/insert	frameshift	X91 ^o	A0021	(2)	*
A after 754 A	insertion	frameshift	X91 ^o	A0002 (a)	(4,17,19)	
764 G-A	nonsense	251 Trp-stop	X91 ^o	A0285	(4)	
764/767 G	deletion	frameshift	X91 ^o	A0219 A0195	(2)	*
A after 772 A	insertion	frameshift	X91 ^o	A0128	(5)	
793-794 CA	deletion	frameshift	X91 ^o	A0001	(4)	
793 C-T	nonsense	261 Gln-stop	X91 ^o	A0020 A0286	(4)	
5' intron 7 gt-ga	splice site	del exon 7	X91 ^o	A0005	(9)	
5' intron 7 gt-gc	splice site	del exon 7	X91 ^o	A0236	(4)	
3' intron 7 ag-cg	splice site	del exon 8	X91 ^o	A0238	(2)	*
827 G-A	nonsense	272 Trp-stop	X91 ^o	A0099 A0287	(2)	*
828 G-A	nonsense	272 Trp-stop	X91 ^o	A0047	(4)	
880 C-T	nonsense	290 Arg-stop	X91 ^o	A0045 (b)	(4,11)	
5' intron 8 gt-tt	splice site	del exon 8	X91 ^o	A0239 A0303	(4)	
928/931 A	deletion	frameshift	X91 ^o	A0221	(4)	
928 A-T	nonsense	306 Lys-stop	X91 ^o	A0290	(4)	
937 G-A	missense	309 Glu-Lys	X91 ⁻	A0101	(5)	
947 T-G	missense	312 Met-Arg	X91 [?]		(4)	
948/957 GAA (or AAG)	deletion	313, 314 or 315 Lys	X91 ⁻	A0208 A0163	(5,22)	
960 G	deletion	frameshift	X91 ^o	A0222	(2)	*
975/977 G	deletion	frameshift	X91 ^o	A0118	(17)	
979 C-T	nonsense	323 Gln-stop	X91 ^o	A0067	(2)	*

Table 1. Mutations in the gene for *gp91-phox* that cause X-linked CGD

cDNA Nucleotide (or Splice Site) Change	Mutation	Amino Acid Change	CGD Type	Accession Number	Reference	
1009 T→C	missense	333 Ser→Pro	X91 [?]	A0200	(17)	
1018 G→T	nonsense	336 Glu→stop	X91 ^o	A0087 A0088	(17)	
1022 G→A	nonsense	337 Trp→stop	X91 ^o	A0292	(4)	
1024 C→T	missense	338 His→Tyr	X91 ⁻	A0014 A0084	(4)	
1028 C→A	missense	339 Pro→His	X91 ⁻	A0096 A0070	(2,23)	
1034 C→A	missense	341 Thr→Lys	X91 ⁺	A0255	(2)	*
1037 T→A	missense	342 Leu→Gln	X91 ^o	A0064 A0256	(4,19)	
1050 T	deletion	frameshift	X91 ^o	A0129 A0161	(2)	*
1074-1083 10 bp	deletion	frameshift	X91 ^o	A0207	(4)	
1087 G→A	missense	359 Gly→Arg	X91 ^o	A0056	(4)	
1117 T→C	missense	369 Cys→Arg	X91 ⁺	A0257	(4)	
1141 C→T	nonsense	377 Gln→stop	X91 ^o	A0293	(4)	
1151 G→A	nonsense	380 Trp→stop	X91 ^o	A0174 A0086	(17)	
1162-1163 AA + 5' intron 9 gt del	splice site	ND	X91 ^o	A0156	(17)	
1178 G→C	missense	389 Gly→Ala	X91 ⁻	A0004	(16)	
1181 C→T	missense	390 Pro→Leu	X91 ^o	A0258	(4)	
1192-1194 GCC del/ ATGTGATGAACACAT insert	del/insert	394 Ala del/ Met stop insert	X91 ^o	A0072	(24)	
1202-1203 AT	deletion	frameshift	X91 ^o	A0213	(4)	
1226 T→G	missense	405 Met→Arg	X91 [?]	A0142	(2)	*
1234 G→A	missense	408 Gly→Arg	X91 [?]	A0157	(2)	*
1235 G→A	missense	408 Gly→Glu	X91 ⁺	A0013 A0016 A0190	(2,4)	
G after 1249 G	insertion	frameshift	X91 [?]	A0144	(2)	*
1256 C→A	missense	415 Pro→His	X91 ⁺	A0048 A0076 A0107	(4,25)	
1256 C→T	missense	415 Pro→Leu	X91 [?]	A0112	(2)	*
1276 T→C	missense	422 Ser→Pro	X91 [?]	A0202	(2)	*
1321/1325 A	deletion	frameshift	X91 ^o	A0053	(4)	
1325-1326 AG del/T insert	del/insert	frameshift	X91 ^o	A0091	(2)	*
1327 A	deletion	frameshift	X91 [?]	A0081	(2)	*
1332 C→A	nonsense	440 Tyr→stop	X91 [?]	A0151	(17)	
1341 G→A	nonsense	443 Trp→stop	X91 ^o	A0168	(17)	
1362 C	deletion	frameshift	X91 [?]	A0192	(2)	*
1427 G	deletion	frameshift	X91 ^o	A0092	(2)	*
1440 C→A	nonsense	476 Tyr→stop	X91 ^o	A0071	(4,23)	
1461 G→A	nonsense	483 Trp→stop	X91 ^o	A0294	(2)	*
1467 G	deletion	frameshift	X91 [?]	A0165	(2)	*
T after 1467 G	insertion	frameshift	X91 ^o	A0184	(2)	*
5' intron 11 gt→at	splice site	del exon 11	X91 ^o	A0241	(2)	*

Table 1. Mutations in the gene for gp91-*phox* that cause X-linked CGD

cDNA Nucleotide (or Splice Site) Change	Mutation	Amino Acid Change	CGD Type	Accession Number	Reference	
3' intron 11 ag→gg	splice site	partial del exon 12 (del 10 AA)	X91 ⁺	A0078	(26)	
1475 C	deletion	frameshift	X91 ^o	A0114	(2)	*
1511 A→G	missense	500 Asp→Gly	X91 ⁺	A0019	(27)	
1531 C→T	nonsense	507 Gln→stop	X91 ^o	A0116	(17)	
1533-1537 AAAGA del/ CATCTGGG insert	del/insert	507-509 GlnLys Thr del/HisIle TrpAla insert	X91 ⁺	A0068	(28)	
1540-1541 TT	deletion	frameshift	X91 ^o	A0143	(2)	*
1560 G→T	missense	516 Trp→Cys	X91 [?]	A0094	(2)	*
1560 G→A	nonsense	516 Trp→stop	X91 [?]	A0295	(2)	*
1567 G→T	nonsense	519 Glu→stop	X91 ^o	A0059	(19)	*
1573 A→T	nonsense	521 Lys→stop	X91 ^o	A0025	(4)	
1613 T→A	missense	534 Val→Asp	X91 [?]	A0147	(2)	*
1621 T→C	missense	537 Cys→Arg	X91 ⁺	A0199	(2)	*
CCTT dupl. after 1637	insertion	frameshift	X91 ^o	A0183	(2)	*
1637 T→C	missense	542 Leu→Ser	X91 [?]	A0082	(2)	*
1657 C→T	nonsense	549 Gln→stop	X91 [?]	A0297	(2)	*
T after 1674 T	insertion	frameshift	X91 ^o	A0302	(2)	*
1694-1724 (31 nucleotides)	deletion	frameshift	X91 ^o	A0155	(2)	*
31 bp dupl. after 1702 A	insertion	frameshift (del last 6 AA)	X91 [?]	A0300	(22)	
1714 G→A	missense	568 Glu→Lys	X91 ⁺	A0259	(2)	*

(a) This mutation (A inserted after 754 A) is found in eight additional patients in the X-CGD database, with accession nos. A0061, A0062, A0121, A0126, A0146, A0162, A0170, and A0189.

(b) This mutation (880 C→T) is found in five additional patients (A0046, A0145, A0159, A0194 and A0198).

Acc. #, accession number in the X-CGD database (see text); * mutation added since last tabulation; ND, not determined; NA, not applicable; del, deletion; insert, insertion; dupl., duplication; bp, base pairs; AA, amino acids.

A / separating sequence numbers indicates a range within which the designated nucleotide(s) are deleted; e.g., 1321/1325 A indicates that a single A is deleted in a run of As from 1321 to 1325.

Table 2. Large deletions known to cause X-linked CGD

Approximate size of deletion (associated disease)	Affected exon(s)	CGD Type	Accession Number	Reference	
~5,000 kb (+DMD, RP, McLeod)	NA	X91°	A0030	(29)	
~4,000 kb (+ DMD, McLeod)	NA	X91°	A0031	(30)	
~800 kb (+ McLeod)	NA	X91°	A0032	(31)	
ND (+ RP, McLeod)	NA	X91°	A0033	(32)	
>27 kb	del exons 1-13	X91°	A0034 (c)	(4)	*
25 kb	del exons 1-7	X91°		(33)	*
>20 kb	del exons 1-10	X91°	A0039	(4)	
>15 kb	del exons 4-13	X91°	A0040	(4)	
~14 kb	del exons 4-9	X91°	A0026	(10)	
>13 kb	del exons 6-13	X91°	A0041	(34)	
>10 kb	del exons 8-13	X91°	A0042	(4)	
>6.5 kb	del exons 11-13	X91°	A0043	(4)	
~6 kb	del exons 12-13	X91°	A0044	(18)	
>5.3 kb	del exons 1-3	X91°	A0204	(2)	*
>4 kb	del exons 11-13	X91°	A0172	(17)	
~3.5 kb	del exons 6-7	X91°	A0028	(10)	
~3.2 kb	del exon 7	X91 [?]	A0205	(4)	
~3 kb	del exon 5	X91°	A0027	(10)	
~2.2 kb	del exon 5	X91°	A0206	(2)	*
~1 kb	intron 12 to 3'UT (~530 Thr-570 Phe)	X91°	A0203	(30)	

(c) There are at least nine additional entries in the X-CGD database with similar large deletions which result in the entire gene (13 exons) being deleted (A0035, A0036, A0037, A0038, A0066, A0119, A0167, A0169, A0201). DMD, Duchenne muscular dystrophy; RP, X-linked retinitis pigmentosa; McLeod, McLeod hemolytic anemia; 3'UT, 3' untranslated region.

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