

Hematologically Important Mutations: X-Linked Chronic Granulomatous Disease

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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 cytochrome *b*₅₅₈ (the other is p22-*phox*) and is an essential component of the phagocyte NADPH oxidase system. Here we have tabulated the 123 mutations in the gp91-*phox* gene known to cause CGD. Table 1 includes missense mutations, nonsense mutations, splice site mutations, deletions and insertions that have been precisely defined. In Table 2 we have listed larger mutations affecting the gp91-*phox* gene, some of which also cause other diseases. Additional information about these mutations and about CGD in general can be found in recent reviews (1-3) and in the cited literature. A future

table will list the mutations causing the autosomal recessive forms of CGD.

We have used the now 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 protein has not been determined. The nucleotides are numbered according to the cDNA sequence described in (4), 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, gp91-*phox*

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

cDNA Nucleotide Change	Mutation	Amino Acid Change	CGD Type	Reference
-57 a→c (regulatory)	missense	NA	X91 ⁻	(5)
-55 t→c (regulatory)	missense	NA	X91 ⁻	(5)
23 G→A	nonsense	4 Trp→stop	X91 [°]	(2)
5' intron 1 gtaag→gtaaa	splice site	del. exon 2	X91 [°]	(2)
3' intron 1 ag→aa	splice site	del. exon 2	X91 [°]	(6)
59 T	deletion	frameshift	X91 [°]	(7)
60/61 G*	deletion	frameshift	X91 [°]	(2)

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cDNA Nucleotide Change	Mutation	Amino Acid Change	CGD Type	Reference
70 G→C	missense	20 Gly→Arg	X91°	(3)
AACG after 79 G	insertion	frameshift	X91°	(2)
111 T→A	nonsense	33 Tyr→stop	X91°	(2)
130/133 T	deletion	frameshift	X91°	(7)
139 A→T	nonsense	43 Arg→stop	X91°	(2)
151/153 G	deletion	frameshift or splice	X91 [?]	(2)
5' intron 2 gt→tt	splice site	del. exon 2	X91°	(3)
3' intron 2 ag→gg	splice site	del. exon 3	X91°	(8)
170 C→A	missense	53 Ala→Asp	X91 ⁻	(2)
174 G→C	missense	54 Arg→Ser	X91 ⁺	(9,10)
179 C→T	missense	56 Pro→Leu	X91 ⁻	(1,11)
182 C→A	missense	57 Ala→Glu	X91 ⁺	(12)
G after 207 G	insertion	frameshift	X91°	(3)
229 C→T	nonsense	73 Arg→stop	X91°	(13,14)
251/254 G	deletion	frameshift	X91°	(2)
263 C	deletion	frameshift	X91°	(14)
264 G→A (3' end of exon 3)	splice site	del. exon 3	X91°	(2)
5' intron 3 gtaag→gtaaa	splice site	del. exon 3	X91°	(6)
283 C→T	nonsense	91 Arg→stop	X91°	(2,3)
307 A	deletion	frameshift	X91°	(2)
314 A→G	missense	101 His→Arg	X91°	(2,13)
330 G→A	nonsense	106 Trp→stop	X91°	(2)
G after 332 T	insertion	frameshift	X91°	(2)
338-339 CA	deletion	frameshift	X91 [?]	(2)
A after C 367	insertion	frameshift	X91°	(2)
371 T→C	missense	120 Leu→Pro	X91°	(2)
400 C→T	nonsense	130 Arg→stop	X91°	(2)
454 C→stop	nonsense	148 Gln→stop	X91 [?]	(14)
A after 458 A	insertion	frameshift	X91°	(14)
478 G→A	missense	156 Ala→Thr	X91 ⁻	(13,14)
481 C→T	nonsense	157 Arg→stop	X91°	(2,8,15)
494 A→G	missense	161 Lys→Arg	X91 ⁻	(14)
495 G→T	missense or splice site	161 Lys→Asn or del. exon 5	X91°	(2)
5' intron 5 gt→tt	splice site	del. exon 5	X91°	(2)
5' intron 5 gt→gc	splice site	ND	X91 [?]	(8)
5' intron 5 gta→ggt	splice site	del. exon 5	X91°	(6)
527/529 C	deletion	frameshift	X91°	(2)
619 G→T	nonsense	203 Glu→stop	X91°	(2)
633 C→A	splice site	partial del. exon 6	X91°	(6)
637 C→T	missense	209 His→Tyr	X91°	(13)
639 T→A	missense	209 His→Gln	X91°	(14)
655/660 TTC	deletion	215 or 216 Phe	X91°	(11)
677 A→G	missense	222 His→Arg	X91°	(2)

cDNA Nucleotide Change	Mutation	Amino Acid Change	CGD Type	Reference
5' intron 6 gtgag→gtgaa	splice site	del. exon 6	X91 [?]	(2)
5' intron 6 del. gtga	splice site	del. exon 6	X91 [°]	(2)
688 C→T	nonsense	226 Arg→stop	X91 [°]	(2,16)
40 bp dupl. after 702 G	insertion	frameshift	X91 [°]	(17)
711/716 AG	deletion	frameshift	X91 [?]	(2,14)
728-732 ATAAT	deletion	frameshift	X91 [°]	(14)
742 T→C	missense	244 Cys→Arg	X91 [?]	(14)
743 G→C	missense	244 Cys→Ser	X91 ⁻	(1,13)
743 G→A	missense	244 Cys→Tyr	X91 ⁻	(18)
A after 754 A	insertion	frameshift	X91 [°]	(2,14)
764 G→A	nonsense	251 Trp→stop	X91 [°]	(2)
A after 772 A	insertion	frameshift	X91 [°]	(3)
793-794 CA	deletion	frameshift	X91 [°]	(2)
793 C→T	nonsense	261 Gln→stop	X91 [°]	(2)
5' intron 7 gt→ga	splice site	del. exon 7	X91 [°]	(6)
5' intron 7 gt→gc	splice site	del. exon 7	X91 [°]	(2)
828 G→A	nonsense	272 Trp→stop	X91 [°]	(2)
880 C→T	nonsense	290 Arg→stop	X91 [°]	(2,8)
5' intron 8 gt→tt	splice site	del. exon 8?	X91 [°]	(2)
928/931 A	deletion	frameshift	X91 [°]	(2)
928 A→T	nonsense	306 Lys→stop	X91 [°]	(2)
937 G→A	missense	309 Glu→Lys	X91 ⁻	(3)
947 T→G	missense	312 Met→Arg	X91 [?]	(2)
948/956 GAA	deletion	313, 314 or 315 Lys	X91 ⁻	(3,18)
975/977 G	deletion	frameshift	X91 [?]	(14)
1009 T→C	missense	333 Ser→Pro	X91 [?]	(14)
1018 G→T	nonsense	336 Glu→stop	X91 [°]	(14)
1022 G→A	nonsense	337 Trp→stop	X91 [°]	(2)
1024 C→T	missense	338 His→Tyr	X91 [°]	(2)
1028 C→A	missense	339 Pro→His	X91 [°]	(19)
1037 T→A	missense	342 Leu→Gln	X91 [°]	(2)
1074-1083 10 bp	deletion	frameshift	X91 [°]	(2)
1087 G→A	missense	359 Gly→Arg	X91 [?]	(2)
1117 T→C	missense	369 Cys→Arg	X91 ⁺	(2)
1141 C→T	nonsense	377 Gln→stop	X91 [°]	(2)
1151 G→A	nonsense	380 Trp→stop	X91 [°]	(14)
5' intron 9 del. Agtgc	splice site	ND	X91 [°]	(14)
1178 G→C	missense	389 Gly→Ala	X91 ⁻	(13)
1181 C→T	missense	390 Pro→Leu	X91 [°]	(2)
1192-1194 GCC del./15 bp insert.	del./insert.	394 Ala del./ Met stop insert.	X91 [°]	(20)
1202-3 AT	deletion	frameshift	X91 [°]	(2)
1235 G→A	missense	408 Gly→Glu	X91 ⁺	(2)

cDNA Nucleotide Change	Mutation	Amino Acid Change	CGD Type	Reference
1256 C→A	missense	415 Pro→His	X91 ⁺	(2,21)
1321/1325 A	deletion	frameshift	X91 [°]	(2)
1332 C→A	nonsense	440 Tyr→stop	X91 [?]	(14)
1341 G→A	nonsense	443 Trp→stop	X91 [°]	(14)
1440 C→A	nonsense	476 Tyr→stop	X91 [°]	(2,19)
3' intron 11 ag→gg	splice site	partial del. exon 12 (del. 10 AA)	X91 ⁺	(22)
1511 A→G	missense	500 Asp→Gly	X91 ⁺	(23)
1531 C→T	nonsense	507 Gln→stop	X91 [°]	(14)
1533-1537 AAAGA del./CATCTGGG insert.	del./insert.	507-509 GlnLysThr del./HisIleTrpAla insert.	X91 ⁺	(24)
1573 A→T	nonsense	521 Lys→stop	X91 [°]	(2)
31 bp dupl. after 1702 A	insertion	frameshift (del. last 6 AA)	X91 ⁻	(18)

ND, not determined; NA, not applicable; del., deletion; dupl., duplication; AA, amino acids.

*A slash (/) 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 (and associated disease)	Affected exon(s)	CGD Type	Reference
~5,000 kb (+DMD, RP, McLeod)	NA	X91 [°]	(25)
~4,000 kb (+ DMD, McLeod)	NA	X91 [°]	(26)
~800 kb (+ McLeod)	NA	X91 [°]	(27)
ND (+ RP, McLeod)	NA	X91 [°]	(28)
>27 kb	del. exons 1-13	X91 [°]	(2)
>27 kb	del. exons 1-13	X91 [°]	(2)
>27 kb	del. exons 1-13	X91 [°]	(2)
>27 kb	del. exons 1-13	X91 [°]	(2)
>20 kb	del. exons 1-10	X91 [°]	(2)
>15 kb	del. exons 4-13	X91 [°]	(2)
~14 kb	del. exons 4-9	X91 [°]	(7)
>13 kb	del. exons 6-13	X91 [°]	(29)
>10 kb	del. exons 8-13	X91 [°]	(2)
>6.5 kb	del. exons 11-13	X91 [°]	(2)
~6 kb	del. exons 12-13	X91 [°]	(15)
>4 kb	del. exons 11-13	X91 [°]	(14)
~3.5 kb	del. exons 6-7	X91 [°]	(7)
~3.2 kb	del. exon 7	X91 [?]	(2)
~3 kb	del. exon 5	X91 [°]	(7)
~1 kb	intron 12 to 3' UT (~530 Thr-570 Phe)	X91 [°]	(26)

DMD, Duchenne muscular dystrophy; RP, X-linked retinitis pigmentosa; McLeod, McLeod hemolytic anemia; 3' UT, 3' untranslated region.

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