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

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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].

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

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

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