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Hematologically Important Mutations: The Autosomal Recessive Forms of Chronic Granulomatous Disease (Second Update)

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Keywords

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Mutations in the genes encoding four of the phagocyte NADPH oxidase components, p22-phox, p47-phox, p67-phox and 40-phox, cause the autosomal recessive forms of chronic granulomatous disease (CGD). These four forms of the disease collectively account for approximately one-third of all CGD cases. Many new mutations have been identified in these four genes since publication of the first updated version of the tables with these mutations (1). The remaining two-thirds of cases are caused by mutations in the X-linked gene for gp91-phox, CYBB; these mutations have been tabulated previously in this journal (2). The incidence of CGD as a whole is between 1 in 200,000 and 1 in 250,000 individuals.

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The protein p22-*phox* is one of two membrane-bound subunits of cytochrome *b*₅₅₈ (the other is gp91-*phox*), and mutations in the p22-*phox* gene (*CYBA*, located at 16q24, OMIM *608508) account for about 6% of CGD (Table 1). Also about 6% of CGD cases are caused by mutations in the gene for p67-*phox* (*NCF2*, 1q25, OMIM *608515), a cytosolic component of the superoxide-generating NADPH oxidase system (Table 2). The most common form of autosomal recessive CGD (about 20% of all cases) is caused by mutations in the gene for p47-*phox* (*NCF1*, 7q11.23, OMIM *608512), a second cytosolic component of the enzyme (Table 3). Only one patient has been described with mutations in *NCF4* (22q13.1, OMIM *601488), the gene encoding p40-*phox*, the third cytosolic NADPH oxidase component (Table 4). The type, position and number of the mutations in these four genes is depicted in figure 1. Tables 5-8 list apparently benign polymorphisms that have been identified in the *CYBA*, *NCF2*, *NCF1* and *NCF4* genes, respectively. It is important to realize that SNPs and other sequence variants available on the internet are not necessarily functionally neutral.

Unlike the other autosomal recessive and X-linked forms of the disease, in which there is a large heterogeneity among mutations, a single defect accounts for the vast majority of cases of p47-*phox*-deficiency. Of ~250 patients investigated worldwide at the DNA level, all but 53 patients in 42 families appear to be homozygous for a dinucleotide (GT) deletion (GT) at the start of exon 2 (3-19). Of the 42 families with exceptions, 20 had patients who were compound heterozygotes for the GT deletion and one additional mutation, and the others had patients with mutations other than GT on both alleles of *NCF1* (20 homozygous, 2 compound heterozygous). The GT-bearing allele of *NCF1* is therefore the most common CGD-causing allele in the population, carried by approximately 1 in 250 individuals. The reason for this predominance is that most normal individuals have two p47-*phox* pseudogenes, each of which co-localizes with the functional gene to 7q11.23 and carries GT. Recombination events between *NCF1* and these highly homologous pseudogenes lead to the incorporation of GT into *NCF1* (7, 20).

Additional information about the tabulated mutations and about CGD in general can be found in recent reviews (21-25) and in the cited literature. In the following tables we have used the standard notation for differentiating the various phenotypes of CGD (e.g., A22°, A22+, A67°, A67+, A67-, A47°, A40° and A40+). In this nomenclature the first letter refers to the mode of inheritance (autosomal recessive), the numeral indicates the *phox* component affected, and the superscript symbol indicates whether the protein is absent (°), diminished (-) or normal (+), based on immunoblot analysis. When this information is unavailable, that has been indicated as (?). The respective proteins can be non-functional, exert residual activity, or in case of (-) be fully functional. Online Mendelian Inheritance in Man (OMIM) numbers for A22, A67, A47 CGD are #233690, #233710, and #233700, respectively. Mutations added since the last updated versions of Tables 1-3 were published (1) are marked with an asterisk in the right hand column. 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 sequences; for p22-*phox* (GenBank accession nos. M21186 and J03774) subtract 28 from the GenBank sequence number to make the initiator A +1; for p67-*phox* (accession no. M32011) subtract 67 from

the GenBank numbering; for p47-*phox* (GenBank accession nos. M25665 and M26193) subtract 12 from the GenBank numbering, and for p40-*phox* (accession no. NM_000631) subtract 184 from the GenBank numbering. The notation of the mutations and polymorphisms follows the recommendations of the Human Genome Variation Society (26) (see also www.hgvs.org/mutnomen). Where possible we have cross-referenced the mutations listed here with those in three CGD databases that list CGD patients by accession number. These databases contain additional biochemical, genetic and clinical information and are available at <http://www.uta.fi/imt/bioinfo/CYBAbase/> (or NCF1base/, or NCF2base/). In addition, information can also be found in the HGMD database at <http://www.hgdm.cf.ac.uk/ac.search.php>. The consequences of the mutations for protein composition have been checked with the Mutalyzer program (www.lovd.nl/mutalyzer) (27).

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Figure 1. Schematic overview of mutations in *NCF2*, *CYBA*, *NCF4* and *NCF1*

For each cDNA, the exon positions and the corresponding protein domains have been depicted. For some of the protein domains, their interaction with other proteins has been indicated. The PX domains interact with phosphatidylinositol-phosphates. The type of mutations (explained in the right hand corner), their position and number of mutated alleles are indicated. Splice site mutations are given at the exon borders.

Table 1

Mutations in the p22-phox gene CYBA.

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Reference	Families (alleles) ^d	Accession number(s) ^g
g. del>10 kb	Deletion	NA ^b	A22°	[28]	1(2)	
c.2T>A	Missense	p.Met1Lys	A22 [?]	unpubl. ^d	1(2) ^c	*
c.7C>T	Nonsense	p.Gln3X	A22°	[29] unpubl.	5(10)	H0023 H0026
c.26G>A	Nonsense	p.Trp9X	A22°	[30]	1(1)	H0017
c.27G>A	Nonsense	p.Trp9X	A22°	[31]	1(2)	H0027
c.58+4_-7delAGTG ^e	Splice site	ins. 79 bp in intron 1 p.Ile20SerfsX77	A22°	[31,32] unpubl.	5(9)	H0028 H0039
g.exon2_3del	Deletion	p.Ile20ArgfsX6	A22°	[30]	1(2)	
g.exon2_5del	Deletion	p.Ile20SerfsX68	A22°	unpubl.	1(2) ^c	*
c.70G>A	Missense	p.Gly24Arg	A22°	[16,29-31,33] unpubl.	9(14)	H0021 H0024 H0025 H0028 H0030 H0034
c.71G>A	Missense	p.Gly24Glu	A22°	[16]	1(2)	*
c.74G>T	Missense	p.Gly25Val	A22°	[30]	1(1)	H0017
c.77delT	Deletion	p.Ile26ThrfsX48	A22°	unpubl.	1(1)	*
c.107G>A	Nonsense	p.Trp36X	A22°	[30]	1(1)	H0021
g.exon3_5del	Deletion	p.Ile43MetfsX68	A22°	[34]	1(2)	*
g.exon3_6del	Deletion	NA	A22°	[33]	1(2)	*
c.152T>A	Missense	p.Leu51Gln	A22°	unpubl.	1(1)	*
c.155T>C	Missense	p.Leu52Pro	A22°	[30]	1(2)	H0014
c.158A>T	Missense	p.Glu53Val	A22°	[35]	1(1)	H0005
c.164C>G	Missense	p.Pro55Arg	A22°	[16]	1(2)	*
c.166dupC	Insertion	p.Arg56ProfsX157	A22°	[30,33] unpubl.	5(8)	H0019 H0020
c.171delG	Deletion	p.Lys58ArgfsX16	A22°	unpubl.	1(2)	*

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Reference	Families (alleles) ^a	Accession number(s) ^g
c.171dupG	Insertion	p.Lys58GlufsX155	A22°	[16,35] unpubl.	5(9)	H0005 H0032 H0036 H0037
c.173delA #	Deletion	p.Lys58ArgfsX16	A22°	[34]	1(2)	H0041
c.203+1G>T ^e	Splice site	del. exon 3 p.Ile43_Trp68delinsMet	A22°	[30]	1(2)	H0016
c.204-2A>G ^e	Splice site	del. exon 4? p.Gly69_Leu96del?	A22°	[36]	1(2)	*
c.223delG #	Deletion	p.Ala75ProfsX3	A22°	[34]	1(2)	H0042
c.246delC	Deletion	p.Phe83LeufsX108	A22°	[28,30]	2(3)	H0001 H0015
c.261C>G	Nonsense	p.Tyr87X	A22°	unpubl.	1(2)	*
c.261C>A	Nonsense	p.Tyr87X	A22°	unpubl.	1(2)	*
c.268C>T	Missense	p.Arg90Trp	A22°	[30] unpubl.	8(14)	H0018 H0019 H0020
c.268C>G	Missense	p.Arg90Gly	A22°	unpubl.	1(2)	*
c.269G>A	Missense	p.Arg90Gln	A22°	[28,37]	2(3)	H0001 H0006 H0007 H0008
c.269G>C	Missense	p.Arg90Pro	A22°	unpubl.	1(2)	*
c.281A>G	Missense	p.His94Arg	A22°	[37]	1(2)	H0012
c.287+1G>A ^e	Splice site	del. exon 4 p.Gly69_Leu96del	A22°	[37] unpubl.	2(4)	H0009 H0035
c.287+1G>T ^e	Splice site	del. exon 4 p.Gly69_Leu96del	A22°	unpubl.	1(2)	*
c.287+2T>C ^e	Splice site	del. exon 4? p.Gly69_Leu96del?	A22°	unpubl.	1(1) ^f	*
c.288-6_296del16 ^e	Splice site	del. exon5 p.Leu97ArgfsX68	A22°	unpubl.	1(1)	*
c.288-15_308del36 ^e	Splice site	intron4ins179/exon5del21	A22°	[38]	1(2)	H0038
c.288G>T	Splice site	del. exon 5 p.Leu97ArgfsX68	A22°	unpubl.	1(2)	*
c.295_301delGTGCCCCG	Deletion	p.Val99ProfsX90	A22°	[13,17,19] unpubl.	5(10) ^c	H0040
c.339C>A	Nonsense	p.Cys113X	A22°	[33]	1(2)	*

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Reference	Families (alleles) ^d	Accession number(s) ^g
c.354C>A	Missense	p.Ser118Arg	A22°	[28,30] unpubl.	4(8)	H0003 H0010 H0022
c.369+1G>C ^e	Splice site	del. exon 5 p.Leu97ArgfsX68	A22°	[6,39]	1(2)	H0002
c.369+1G>A ^e	Splice site	del exon 5 p.Leu97ArgfsX68	A22°	[34]	1(2)	H0045 H0046
c.370G>T	Missense	p.Ala124Ser	A22°	[17]	1(2)	*
c.371C>T	Missense	p.Ala124Val	A22°	[31]	1(1)	H0030
c.373G>A	Missense	p.Ala125Thr	A22°	[34]	1(2)	H0047
c.385G>A	Missense	p.Glu129Lys	A22?	unpubl.	1(2)	*
c.385_388delGAGC	Deletion	p.Glu129SerfsX61	A22°	[34]	2(4)	H0043 H0044
c.399delC	Deletion	p.Ile134SerfsX57	A22?	unpubl.	1(2) ^c	*
c.408delC	Deletion	p.Lys137SerfsX54 [#]	A22°	[33]	1(2)	
c.467C>A	Missense	p.Pro156Gln	A22+	[40]	1(2)	H0011
c.472_484del	Deletion	p.Pro160AlafsX27	A22?	[1]	1(2) ^c	H0031
c.571_604del	Deletion	p.Thr191ProfsX	A22°	[31]	1(2)	
Mutations in <i>CYBA</i>						
Number of different alleles			Total number of alleles			
Deletions	16 alleles		(29.1%)	42 alleles		(24.3%)
Nonsense mutations	7 alleles		(12.7%)	20 alleles		(11.6%)
Splice site mutations	11 alleles		(20.0%)	29 alleles		(16.8%)
Missense mutations	19 alleles		(34.6%)	65 alleles		(37.5%)
Insertions	2 alleles		(3.6%)	17 alleles		(9.8%)
Total 55 different allelic mutations			Total 87 families with 173 identified alleles in the 96 patients			

^aNumber of different families with patients with this mutation (number of alleles carrying this mutation).

^bNot applicable.

^cOne patient presumed homozygous for this mutation.

^dUnpublished data from the authors' laboratories.

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^e Position of introns in *CYBA*: intron 1 c.58_59; intron 2 c.128_129; intron 3 c.203_204; intron 4 c.287_288; intron 5 c.369_370.

^f Patient is heterozygous for this mutation and for an unidentified mutation in the other allele.

^g Accession number in database at <http://www.uta.fi/fimt/bioinfo/CYBAbase/>.

* New mutations since ref. [1].

Corrected after consultation of the authors.

Table 2

Mutations in the p67-*phox* gene *NCF-2*.

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference	Accession number ^b
c.-547-?_174+?del ^g	Deletion	p.Met1_Lys58del	A67°	1(2)	Unpubl.	*
c-274-?_174 + ?del~400 ^g	Deletion	p.Met1_Lys58del	A67°	1(2)	Unpubl.	*
c-274-?_174 + ?del~400 ^g	Deletion	p.Met1_Lys58del	A67°	1(2)	Unpubl.	*
c.1A>G	Missense	p.Met1Val	A67°	1(1)	Unpubl.	*
c.29G>A	Nonsense	p.Trp10X	A67°	1(2)	Unpubl.	*
c.55_63delAAAGGAGAC ^a	Deletion	p.Lys19_Asp21del	A67°	4(4)	[41-43] unpubl.	M0004 M0015
c.125A>G	Missense	p.Asn42Ser	A67°	1(2)	Unpubl.	*
c.130G>C	Missense	p.Gly44Arg	A67°	2(4) ^b	[1,43]	
c.130G>T	Missense	p.Gly44Cys	A67°	1(2)	Unpubl.	*
c.172_174delAAG	Deletion	p.Lys58del	A67°	2(3) ^c	[44,45] unpubl.	M0009
c.175-1G>A ^g	Splice site	del. exon 3? p.Ala59IlefsX2?	A67°	1(2)	Unpubl.	*
c.196C>T	Nonsense	p.Arg66X	A67°	3(5)	[42]	
c.229C>T	Nonsense	p.Arg77X	A67°	4(7)	[46], unpubl.	*
c.230G>A	Missense	p.Arg77Gln	A67°	3(3)	[42], unpubl.	M0016
c.233G>A	Missense	p.Gly78Glu	A67°	1(2)	[47]	M0002
c.257+2T>C ^g	Splice site	del. exon3 p.Ala59IlefsX2	A67°	2(4)	[13,48]	M0010 M0020
c.258-?_366 + ?del~1100 ^g	Deletion	p.Tyr87CysfsX22	A67°	1(2)	Unpubl.	*
c.279C>G ^d	Missense	p.Asp93Glu	A67°	4(8)	[46], unpubl.	*
c.287_289delAAG	Deletion	p.Glu96del	A67°	1(2)	Unpubl.	*
c.298C>T	Nonsense	p.Gln100X	A67°	5(5)	[42], unpubl.	M0016
c.304C>T	Nonsense	p.Arg102X	A67°	6(11) ^b	[16,41,46,48] unpubl.	M0001
c.305G>C	Missense	p.Arg102Pro	A67°	1(1)	Unpubl.	*
c.323A>T	Missense	p.Asp108Val	A67°	1(2)	[43]	*
c.364_366+2delGAGGT ^g	Splice site	del. exon 4? p.Tyr87CysfsX2?	A67°	1(2)	[17]	*

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference	Accession number ^h
c.366-1G>A ^g	Splice site	del. exon 3, 4 p.Ala59_Glu122del	A67°	8(12)	[17,41–43] unpubl.	M0011 M0018
c.366+1G>C ^{e, g}	Splice site	del. exon 4? p.Tyr87CysfsX22?	A67°	4(8)	Unpubl.	*
c.366+2401_502–527 del1380 ^g	Deletion	del. exon 5 p.Val123_Trp167del	A67°	4(8)	[50]	*
c.383C>T	Missense	p.Ala128Val	A67°	1(2)	[42]	M0013
c.398_399dupAG	Insertion	p.Lys134ArgfsX12	A67°	1(2)	[51]	M0006
c.409T>A	Missense	p.Trp137Arg	A67–	1(2)	Unpubl.	*
c.419C>G	Missense	p.Ala140Asp	A67°	1(1)	Unpubl.	*
c.[479A>T; 481A>G]	Dbl. missense	p.AspLys160_161 ValGlu	A67°	1(1), ^f	[52]	M0012
c.482delA	Deletion	p.Lys161ArgfsX16	A67?	1(2) ^b	Unpubl.	*
c.488_501delTTGGAGTGTCTCTGG ^g	Deletion/splice site	del. exon 5 p.Val123_Trp167del	A67°	1(1)	Unpubl.	*
c.502–1G>T ^g	Splice site	del. exon 6? p.Lys168_Thr203del?	A67°	1(2)	Unpubl.	*
c.505C>G	Missense	p.Gln169Glu	A67?	1(2)	Unpubl.	*
c.550C>T	Nonsense	p.Arg184X	A67?	1(2)	Unpubl.	*
c.551G>C	Missense	p.Arg184Pro	A67°	1(2)	Unpubl.	*
c.576C>T	Nonsense	p.Gln192X	A67?	1(2) ^b	[53]	*
c.586_588delAAG	Deletion	p.Lys196del	A67+	1(2)	Unpubl.	*
c.605C>T	Missense	p.Ala202Val	A67–	2(4)	[46] unpubl.	*
c.714-?_924+?dup~1100 ^g	Insertion	p.Glu309GlyfsX15	A67°	2(3), ^f	[54] unpubl.	*
c.714–1G>T ^g	Splice site	del. exon 9? p.Ala239ArgfsX59?	A67°	1(1)	Unpubl.	*
c.728delA	Deletion	p.Glu243GlyfsX28	A67°	1(1)	[41]	*
c.767_768dupAA	Insertion	p.Glu257LysfsX15	A67°	1(2)	Unpubl.	*
c.799_800delGT	Deletion	p.Val267LeufsX8	A67°	1(2)	[17]	*
c.835_836delAC	Deletion	p.Thr279GlyfsX16	A67°	2(4) ^b	[42] unpubl.	M0017
c.855+1G>A ^g	Splice site	del. exon 8, 9 p.Ala224_Gln285del	A67°	1(2)	[55]	M0007
c.1026G>A ^g	Splice site	del. exon 12 p.Gln335SerfsX38	A67°	2(2)	[49]	*

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference	Accession number ^h
c.1034dupA	Insertion	p.Leu346AlafsX36	A67 [?]	1(1)	Unpubl.	*
c.1099C>T	Nonsense	p.Gln367X	A67 [?]	1(2) ^b	Unpubl.	*
c.1171_1175delAAGCT	Deletion	p.Lys391GlufsX9	A67 [°]	6(12)	[16,19,41]	M0005
c.1179-2A>T ^g	Splice site	del. exon 14? p.Ser393ArgfsX54?	A67 [°]	1(2)	Unpubl.	*
c.1256A>T	Missense	p.Asn419Ile	A67 [°]	1(2)	[13]	M0019
Mutations in <i>NCF2</i>						
Number of different alleles			Total number of alleles			
Deletions	14 alleles		(25.9%)	48 alleles		(28.1%)
Nonsense mutations	8 alleles		(14.8%)	36 alleles		(21.0%)
Splice site mutations	11 alleles		(20.4%)	38 alleles		(22.2%)
Missense mutations	17 alleles		(31.5%)	41 alleles		(24.0%)
Insertions	4 alleles		(7.4%)	8 alleles		(4.7%)
Total 54 different allelic mutations			Total 83 families with 171 identified alleles in the 95 patients			

^a Always in combination with c.1183C>T (polymorphism, rs13306575) on the same allele.

^b One patient presumed homozygous for this mutation.

^c One patient is heterozygous for this mutation and for an undefined deletion of 11-13 kb in the other allele [44,45].

^d Always in combination with c.366+1G>C on the same allele.

^e Always in combination with c.279C>G on the same allele.

^f One patient is heterozygous for this mutation and for an unidentified mutation in the other allele [54].

^g Positions of introns in *NCF2*: intron 1 c.-510_-274 in 5' UTR; intron 2 c.174_175; intron 3 c.257_258; intron 4 c.366_367; intron 5 c.501_502; intron 6 c.609_610; intron 7 c.669_670; intron 8 c.713_714; intron 9 c.855_856; intron 10 c.924_925; intron 11 c.1000_1001; intron 12 c.1026_1027; intron 13 c.1178_1179; intron 14 c.1290_1291; intron 15 c.1468_1469.

^h Accession number in database at <http://www.uta.fi/mt/bioinfo/NCF2base/>.

Table 3

Mutations in the *p47-phox* gene *NCF1*.

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference	Accession number(s) ^a
c.72+1G>A ^e	Splice site	del. exon 1? p.Met1_Tyr24del?	A47°	1(1)	[8]	N0031
c.72+3G>T ^e	Splice site	del. exon 1? p.Met1_Tyr24del?	A47°	1(1)	[8]	N0032
c.75_76delGT	Deletion	p.Tyr26HisfsX26	A47°	>300 homozygous, 20 heterozygous ^b	[3–19] unpubl.	N0004–7,9–23, 27–29, 31–35, 40–63, 69,70
c.125G>A	Missense	p.Arg42Gln	A47°	3(3)	[8] unpubl.	N0034N0035
c.153+1G>A ^e	Splice site	c.153+1_+73ins ^c p.Lys52MetX24	A47°	1(1)	[14]	N0068
c.154–283_451+821 del2858 ^e	Deletion	del. exon 3_5 p.Lys52ThrfsX82	A47°	1(1)	[14]	N0061
c.271C>T	Nonsense	p.Gln91X	A47°	1(1)	[14]	N0027
c.333T>A	Nonsense	p.Cys111X	A47°	1(1)	[9,14]	N0028 N0056 N0057 N0058
c.353_354delCC insAA	Deletion/insertion	p.Phe118X	A47°	1(1)	[10,14]	N0059
c.417_451+650 del685 ^e	Deletion	del. exon 5 p.Thr133HisfsX66	A47°	1(1)	unpubl.	
c.502delG	Deletion	p.Glu168ArgfsX19	A47°	1(1)	[5]	N0002
c.574G>A ^e	Splice site	del. exon 6+7 ^d p.Asp151_Ala227del	A47°	4(7) unpubl.	[8, 14]	N0036 N0064 N0065 N0066 N0067
c.579G>A	Nonsense	p.Trp193X	A47°	17(31)	[14,16,56] unpubl.	N0024 N0025 N0026 N0037 N0038 N0039 N0060 N0068
c.604C>T	Nonsense	p.Arg202X	A47°	1(1)	[17]	
c.612G>A	Nonsense	p.Trp204X	A47 [?]	1(2) ^f	[57]	
c.678T>>G	Nonsense	p.Tyr226X	A47°	1(2)	[17]	

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference	Accession number(s) ^a
c.682+1G>C ^e	Splice site	del. exon 7 p.Trp193_Gly228del	A47°	1(1)	[14]	N0062 N0063
c.730G>A	Missense	p.Glu244Lys	A47°	1(1)	unpubl.	*
c.734_748del115	Deletion	p.Val245_Glu249del	A47°	1(2)	unpubl.	*
c.784G>A	Missense	p.Gly262Ser	A47°	1(1)	[8]	N0033
c.789G>C	Missense	p.Trp263Cys	A47°	1(1)	unpubl.	*
c.811delG	Deletion	p.Val271SerfsX105	A47°	1(1)	[8]	
c.838delC	Deletion	p.Leu280CysfsX96	A47°	1(1)	[18]	*
Mutations in <i>NCF1</i>						
Number of different alleles			Total number of alleles			
Deletions	7 alleles		(30.4%)	7 alleles		(11.1%)
Nonsense mutations	6 alleles		(26.1%)	38 alleles		(60.3%)
Splice site mutations	5 alleles		(21.7%)	11 alleles		(17.5%)
Missense mutations	4 alleles		(17.4%)	6 alleles		(9.5%)
Deletion/insertions	1 allele		(4.4%)	1 allele		(1.6%)
Total 23 different allelic mutations (including delta-GT)			Total 42 families with 6 (other than delta-GT) in 3 identified alleles the 53 patients			

^a Accession number in database at <http://www.uta.fi/mt/bioinfo/NCF1base/>.

^b One patient is a compound heterozygote for this mutation and for an undefined chromosomal microdeletion on the other allele [58].

^c Activation of cryptic donor splice site in intron 2, leading to incorporation of 73 nucleotides from the 5' side of intron 2 into mRNA, including the mutated G>A at position +1 of intron 2. At the protein level, this mutation predicts incorporation of 24 aberrant amino acids after His51, followed by a stop codon at position 76 [14].

^d In addition, these patients show evidence of mRNA for p47^{phox} from which the last 22 bp at the 3' region of exon 6 has been skipped (r.552_574del), as well as mRNA in which intron 6 has been included and in which the mutated exon 6 is expressed (r.[intron6+1_exon6-1ins; 574 g>a]) [14].

^e Positions of introns in *NCF1*: intron 1 c.72_73; intron 2 c.153_154; intron 3 c. 229_230; intron 4 c.395_396; intron 5 c.451_452; intron 6 c.574_575; intron 7 c.682_683; intron 8 c.801_802; intron 9 c.905_906; intron 10 c.1051_1052.

^f Patient presumed to be homozygous for the mutation.

Table 4

Mutations in the p40-*phox* gene *NCF4*.

Nucleotide change	Mutation	Amino acid or mRNA change	CGD type	Families (alleles)	Reference
c.143_152dup10	Insertion	p.Lys52ArgfsX79	A40 ^o	1 (1)	[59] *
c.314G>A	Missense	p.Arg105Gln	A40 ⁺	1 (1)	[59] *

Table 5Polymorphisms in the p22-*phox* gene *CYBA*.

Polymorphic nucleotide	Amino acid change	Reference
c.59–37A/G	NA	[30]
c.36A/G	p.Glu12Glu	[60]
c.179A/C	p.Lys60Thr	[30]
c.214C/T	p.His72Tyr	[28,60]
c.288–138ins50	NA	[13]
c.381T/C	p.Arg127Arg	[60]
c.403G/A	p.Glu135Lys	[30]
c.480G/A	p.Pro160Pro	[30,37,60]
c.512A/G	p.Glu171Gly	[60]
c.521C/T	p.Ala174Val	[28,30,31,60]
c.579G/T	p.Glu193Asp	[60]
c.612A/G (+24 of 3' UT region)	NA	[37,60]

Table 6Polymorphisms in the p67-*phox* gene *NCF2*.

Polymorphic nucleotide	Amino acid change	Reference
c.-185G/A	NA	[41,42]
c.-181G/A	NA	[41,42]
c.-24C/T	NA	[41,42]
c.235A/G	p.Met79Val	[41]
c.542A/G	p.Lys181Arg	[41,42,51]
c.606G/A	p.Ala202Ala	[42]
c.895C/T	p.Leu299Leu	[41,47,51]
c.925-21G/A	NA	[41]
c.983G/A	p.Arg328Lys	[41,47,51]
c.1105G/A	p.Gly369Arg	[42]
c.1167C/A	p.His389Gln	[41,42]
c.1183C/T	p.Arg395Trp	[41-43]

Table 7

Polymorphisms in the p47-*phox* gene *NCF1*.

Polymorphic nucleotide ^a	Amino acid change	Reference
c.66G/C	p.Glu22His	Unpubl.
c.73G/A	p.Val25Met	Unpubl.
c.345C/T	p.Leu115Leu	[8]
c.468C/T	p.Ile156Ile	Unpubl.
c.558A/G	p.Val186Val	Unpubl.
c.621G/A	p.Ala206Ala	Unpubl.
c.825C/T	p.Phe275Phe	Unpubl.
c.849A/G	p.Ser283Ser	Unpubl.
c.936C/T	p.His312His	Unpubl.

^a Identification of polymorphic sites in *NCF1* is complicated by the p47-*phox* pseudogenes, which contain several differences from the functional gene; the referenced polymorphism was identified after amplification of *NCF1* with primers that do not bind to the pseudogenes [8]. More synonymous polymorphisms can be expected to be introduced into *NCF1* by recombination with the pseudogenes [20].

Table 8Polymorphisms in the p40-*phox* gene *NCF4*.

Polymorphic nucleotide ^a	Amino acid change	Reference
c.32+1258G/T	N.A.	[61]
c.33-1101T/C	N.A.	[61]
c.33-728T/C	N.A.	[61]
c.118-360G/A	N.A.	[61]
c.342+202G/C	N.A.	[61]
c.342+342G/T	N.A.	[61]
c.342+1326G/A	N.A.	[61]
c.343-1378A/G	N.A.	[61]
c.343-339A/G	N.A.	[61]
c.528+16G/A	N.A.	[61]
c.627+711G/A	N.A.	[61]
c.627+1040G/T	N.A.	[61]
c.628-1193G/A	N.A.	[61]
c.758+57A/T	N.A.	[61]

^aPositions of introns in *NCF4*: intron 1 c.32_33; intron 2 c.117_118; intron 3 c.271_272; intron 4 c.342_343; intron 5 c.470_471; intron 6 c.528_529; intron 7 c.627_628; intron 8 c.758_759; intron 9 c.824_825.