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

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## Keywords

chronic granulomatous disease; mutation; polymorphism; autosomal recessive; NADPH oxidase

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 (ΔGT) 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 ΔGT on both alleles of *NCF1* (20 homozygous, 2 compound heterozygous). The ΔGT-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 ΔGT. Recombination events between *NCF1* and these highly homologous pseudogenes lead to the incorporation of ΔGT 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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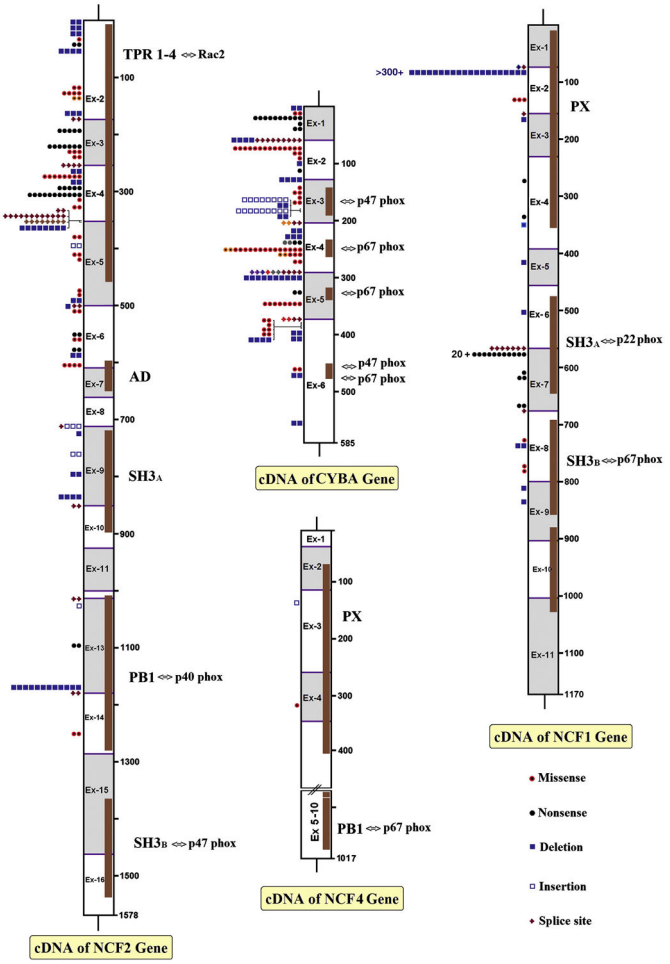


**Figure 1. Schematic overview of mutations in *NCF2, CYBA, NCF4* and *NCF1***

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 phosphatidyl-inositol-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.

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**Table 1**

Mutations in the p22-*phox* gene *CYBA*.

| Nucleotide change | Mutation | Amino acid or mRNA change | CGD type | Reference | Families (alleles)[a] | 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<br>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<br>p.Ile20SerfsX77 | A22° | [31,32] unpubl. | 5(9) | H0028<br>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<br>H0024<br>H0025<br>H0028<br>H0030<br>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<br>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<br>H0032<br>H0036<br>H0037 | |
| c.173delA [#] | Deletion | p.Lys58ArgfsX16 | A22° | [34] | 1(2) | H0041 | * |
| c.203+1G>T [e] | Splice site | del. exon 3<br>p.Ile43_Trp68delinsMet | A22° | [30] | 1(2) | H0016 | |
| c.204–2A>G [e] | Splice site | del. exon 4?<br>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<br>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<br>H0019<br>H0020 | |
| c.268C>G | Missense | p.Arg90Gly | A22° | unpubl. | 1(2) | | * |
| c.269G>A | Missense | p.Arg90Gln | A22° | [28,37] | 2(3) | H0001<br>H0006<br>H0007<br>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<br>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?<br>p.Gly69_Leu96del? | A22° | unpubl. | 1(1) [f] | | * |
| c.288–6_296del16 [e] | Splice site | del. exon5<br>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<br>p.Leu97ArgfsX68 | A22° | unpubl. | 1(2) | | * |
| c.295_301delGTGCCCG | Deletion | p.Val99ProfsX90 | A22° | [13,17,19] unpubl. | 5(10) [c] | H0040 | * |
| c.339C>A | Nonsense | p.Cys113X | A22° | [33] | 1(2) | | * |

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| Nucleotide change | Mutation | Amino acid or mRNA change | CGD type | Reference | Families (alleles)[a] | Accession number(s)[g] | |
|---|---|---|---|---|---|---|---|
| c.354C>A | Missense | p.Ser118Arg | A22° | [28,30] unpubl. | 4(8) | H0003<br>H0010<br>H0022 | |
| c.369+1G>C [e] | Splice site | del. exon 5<br>p.Leu97ArgfsX68 | A22° | [6,39] | 1(2) | H0002 | |
| c.369+1G>A [e] | Splice site | del exon 5<br>p.Leu97ArgfsX68 | A22° | [34] | 1(2) | H0045<br>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<br>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 *CYBA*

| | 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 | |

[a] Number of different families with patients with this mutation (number of alleles carrying this mutation).

[b] Not applicable.

[c] One patient presumed homozygous for this mutation.

[d] Unpublished data from the authors' laboratories.

[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/imt/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 [h] | |
|---|---|---|---|---|---|---|---|
| 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_63delAAGAAGGAC [a] | Deletion | p.Lys19_Asp21del | A67° | 4(4) | [41–43] unpubl. | M0004<br>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?<br>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<br>p.Ala59IlefsX2 | A67° | 2(4) | [13,48] | M0010<br>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?<br>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_501delTGGAGTGTGTCTGG [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 | pVal267LeufsX8 | 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 *NCF2* | | | | | | | |
| | 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/imt/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?<br>p.Met1_Tyr24del? | A47° | 1(1) | [8] | N0031 | |
| c.72+3G>T [e] | Splice site | del. exon 1?<br>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]<br>p.Lys52MetX24 | A47° | 1(1) | [14] | N0068 | * |
| c.154–283_451+821 del2858 [e] | Deletion | del. exon 3_5<br>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<br>N0056<br>N0057<br>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<br>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]<br>p.Asp151_Ala227del | A47° | 4(7) unpubl. | [8, 14] | N0036<br>N0064<br>N0065<br>N0066<br>N0067 | |
| c.579G>A | Nonsense | p.Trp193X | A47° | 17(31) | [14,16,56] unpubl. | N0024<br>N0025<br>N0026<br>N0037<br>N0038<br>N0039<br>N0060<br>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<br>p.Trp193_Gly228del | A47° | 1(1) | [14] | N0062<br>N0063 | * |
| c.730G>A | Missense | p.Glu244Lys | A47° | 1(1) | unpubl. | | * |
| c.734_748del15 | 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 *NCF1* | | | | | | | |
| | 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/imt/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° | 1(1) | [59] | * |
| c.314G>A | Missense | p.Arg105Gln | A40$^{+}$ | 1(1) | [59] | * |

**Table 5**

Polymorphisms 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 6**

Polymorphisms 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 8**

Polymorphisms 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] |

[a]Positions 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.