

# Hematologically Important Mutations: The Autosomal Recessive Forms of Chronic Granulomatous Disease

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Mutations in the genes encoding the phagocyte NADPH oxidase components p47-*phox*, p67-*phox* and p22-*phox* cause the auto-somal recessive forms of chronic granulomatous disease (CGD). These three forms of the disease collectively account for approximately 35% of all CGD. The remaining 65% of cases are caused by mutations in the X-linked gene for gp91-*phox*; these mutations have been previously tabulated in this journal (1).

The protein p22-*phox* is one of two membrane-bound subunits of cytochrome *b*<sub>558</sub> (the other is gp91-*phox*) and mutations in the p22-*phox* gene (termed CYBA, located at 16q24) account for about 6% of CGD (Table 1). Approximately 5% of CGD cases are caused by mutations in the gene for p67-*phox* (NCF2, located at 1q25), a cytosolic component of the superoxide-generating NADPH oxidase system (Table 2). The most common form of autosomal recessive CGD is caused by mutations in the gene for p47-*phox* (NCF1, located at 7q11.23). Mutations at this locus account for nearly 25% of all CGD. Unlike the other autosomal recessive and X-linked forms of the disease, a single mutation accounts for the vast majority of cases of p47-*phox*-deficient CGD (Table 3). Of nearly 60 patients investigated worldwide, all but four are reported to be homozygous for the GT deletion listed (2-7). The four ex-

ceptions appear to be heterozygous for the GT deletion. In one of these patients the mutation on the second allele is a deletion of 502 G (4). Other mutations reported in abstract form (6,7) await confirmation following the recent discovery that p47-*phox* has one or more highly conserved pseudogenes (8). Additional information about these mutations, the individual patients and about CGD in general can be found in recent reviews (5,9,10) and in the cited literature.

In the following tables we have used the now standard notation for differentiating the various phenotypes of CGD (e.g., A22<sup>°</sup>, A22<sup>+</sup>, A67<sup>°</sup>, A67<sup>-</sup> and A47<sup>°</sup>). 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. The cDNA nucleotide numbering system we have used 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; and for p47-*phox* (GenBank accession nos.

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**Table 1.** Mutations in the Gene for p22-phox

| cDNA Nucleotide Change    | Mutation    | Amino Acid Change | CGD Type         | Reference |
|---------------------------|-------------|-------------------|------------------|-----------|
| >10 kb                    | deletion    | NA                | A22°             | (11)      |
| 158 A → T                 | missense    | 53 Glu → Val      | A22°             | (12)      |
| G between 166 C and 172 A | insertion   | frameshift        | A22°             | (12)      |
| 244 C                     | deletion    | frameshift        | A22°             | (11)      |
| 269 G → A                 | missense    | 90 Arg → Gln      | A22°             | (11, 13)  |
| 281 A → G                 | missense    | 94 His → Argh     | A22°             | (13)      |
| 5' intron 4 gt → at       | splice site | del. exon 4       | A22°             | (13)      |
| 354 C → A                 | missense    | 118 Ser → Arg     | A22°             | (11)      |
| 5' intron 5 gt → ct       | splice site | del. exon 5       | A22°             | (5)       |
| 467 C → A                 | missense    | 156 Pro → Gln     | A22 <sup>+</sup> | (14)      |

**Table 2.** Mutations in the Gene for p67-phox

| cDNA Nucleotide Change                    | Mutation    | Amino Acid Change | CGD Type           | Reference |
|---|-------------|-------------------|--------------------|-----------|
| 170–172 AGA or 171–173 GAA or 172–174 AAG | deletion    | 58 Lys            | A67 <sup>-</sup> * | (15, 16)  |
| 233 G → A                                 | missense    | 78 Gly → Glu      | A67°               | (17)      |
| 5' intron 3 gt → gc                       | splice site | del. exon 3       | A67°               | (18)      |
| AG after 397 A (or 399 G)                 | insertion   | frameshift        | A67°               | (19)      |
| 5' intron 9 gt → at                       | splice site | del. exon 8 and 9 | A67°               | (20)      |

\* Patient is heterozygous for this mutation and an undefined deletion of 11–13 kb in the other allele.

**Table 3.** Mutations in the Gene for p47-phox

| cDNA Nucleotide Change | Mutation | Amino Acid Change | CGD Type | Reference |
|------------------------|----------|-------------------|----------|-----------|
| 73–74 GT or 75–76 GT   | deletion | frameshift        | A47°     | (2–4)     |
| 502 G                  | deletion | frameshift        | A47°     | (4)       |

M25665 and M26193) subtract 12 from the GenBank numbering.

**Keywords:** chronic granulomatous disease, mutation, phagocytes, neutrophils, autosomal recessive, NADPH oxidase, p67-phox, p47-phox, p22-phox

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