



## Chronic Granulomatous Disease

Synonym: CGD

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Created: August 9, 2012; Updated: April 21, 2022.

### Summary

#### Clinical characteristics

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) resulting from impaired killing of bacteria and fungi. CGD is characterized by severe recurrent bacterial and fungal infections and dysregulated inflammatory responses resulting in granuloma formation and other inflammatory disorders such as colitis. Infections typically involve the lung (pneumonia), lymph nodes (lymphadenitis), liver (abscess), bone (osteomyelitis), and skin (abscesses or cellulitis). Granulomas typically involve the genitourinary system (bladder) and gastrointestinal tract (often the pylorus initially, and later the esophagus, jejunum, ileum, cecum, rectum, and perirectal area). Some males with X-linked CGD have McLeod neuroacanthocytosis syndrome as the result of a contiguous gene deletion. While CGD may present anytime from infancy to late adulthood, the vast majority of affected individuals are diagnosed before age five years. Use of antimicrobial prophylaxis and therapy has greatly improved overall survival.

#### Diagnosis/testing

The diagnosis of CGD is established in a proband with suggestive findings by identification of pathogenic variant(s) in one of six genes that encode or permit assembly of the subunits of phagocyte NADPH oxidase: biallelic pathogenic variants in *CYBA*, *CYBC1*, *NCF1*, *NCF2*, and *NCF4* cause autosomal recessive CGD; pathogenic variants of *CYBB* cause X-linked CGD.

#### Management

*Treatment of manifestations:* A definitive microbiologic diagnosis is essential to proper treatment of infections. Newer azole drugs (voriconazole, posaconazole, isavuconazole) have expanded therapeutic options for fungal infections. Long courses of antimicrobials are often needed for adequate treatment. Abscesses may require

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percutaneous drainage or excisional surgery. Simultaneous administration of antimicrobials and corticosteroids can help resolve the associated heightened inflammatory response, including colitis.

*Prevention of primary manifestations:* Lifelong daily antibacterial and antifungal prophylaxis is recommended; immunomodulatory therapy with interferon gamma (IFN-gamma) is part of the prophylactic regimen in many centers.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only known cure for CGD and is associated with excellent overall and event-free survival, especially when performed with matched donors at a younger age.

*Surveillance:* Screening labs every 3-4 months in a healthy individual with CGD can aid in early detection and treatment of asymptomatic or minimally symptomatic infections and noninfectious complications such as colitis, pulmonary granulomas, and pulmonary fibrosis.

*Agents/circumstances to avoid:* (1) Decayed organic matter (e.g., mulching, gardening, leaf raking, house demolition) as inhalation of fungal spores can result in fulminant pneumonitis; (2) live bacterial vaccines including *bacille Calmette-Guérin* (BCG) vaccination and *Salmonella typhi* vaccination; (3) persons with CGD and McLeod neuroacanthocytosis syndrome: blood transfusions that are Kell antigen positive.

*Evaluation of relatives at risk:* Early diagnosis of relatives at risk allows for prompt initiation of antimicrobial prophylaxis and other treatment.

*Pregnancy management:* The major concern during the pregnancy of a woman known to have CGD is use of prophylactic antimicrobials: trimethoprim, a folic acid antagonist, is discontinued during pregnancy because of the high risk for birth defects. Although sulfamethoxazole is not known to increase the risk of birth defects in humans, it is typically administered in conjunction with trimethoprim. Data regarding teratogenicity of itraconazole are limited.

## Genetic counseling

CGD associated with a pathogenic variant in *CYBB* is inherited in an X-linked manner. CGD associated with biallelic pathogenic variants in *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4* is inherited in an autosomal recessive manner.

- **X-linked CGD.** If the mother of an affected male is heterozygous for a *CYBB* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant will be heterozygous. Heterozygous females are typically not affected with CGD but are at substantial risk for inflammatory conditions. Once the *CYBB* pathogenic variant has been identified in an affected family member, molecular genetic heterozygote detection for at-risk female relatives is possible.
- **Autosomal recessive CGD.** If both parents are known to be heterozygous for an autosomal recessive CGD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the CGD-causing pathogenic variants have been identified in an affected family member, molecular genetic carrier testing for at-risk relatives is possible.

Once the CGD-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible. (Other prenatal testing options may be available if the pathogenic variant[s] in the family are not known.)

## Diagnosis

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) resulting from impaired killing of bacteria and fungi. CGD is caused by pathogenic variants in one of six genes that encode or permit assembly of the subunits of phagocyte NADPH oxidase.

## Suggestive Findings

Chronic granulomatous disease (CGD) **should be suspected** in individuals (usually children) with the following clinical features, laboratory findings, and family history.

## Clinical Features

- Growth restriction in childhood
- Infections of lung (pneumonia), lymph nodes (lymphadenitis), liver (abscess), bone (osteomyelitis), and skin (abscesses or cellulitis), especially spontaneously occurring severe or recurrent bacterial infections. Microbiologic confirmation of the cause of infection helps confirm the likelihood of CGD, since the spectrum of infection in CGD is distinct and narrow (see Table 2).
- Granuloma formation, especially genitourinary (bladder) and gastrointestinal (often pyloric initially, and later esophageal, jejunal, ileal, cecal, rectal, and perirectal)
- Colitis, manifesting as frequent stooling and fistulae or fissures. This may be the sole finding in some individuals.
- Abnormal wound healing caused by excessive granulation, which may cause the wound to dehisce and gape, leading to healing by secondary intention

## Laboratory Findings

Clinical tests that rely on direct measurement of neutrophil superoxide production via the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex to establish the diagnosis of CGD include the following.

**Dihydrorhodamine (DHR) test** uses flow cytometry to measure the oxidation of dihydrorhodamine 123 to rhodamine 123 in phorbol myristate acetate (PMA)-stimulated neutrophils, a marker for cellular NADPH oxidase activity [Vowells et al 1996]. In this test the generation of hydrogen peroxide oxidizes the dye, leading to the emission of fluorescence. Mean fluorescence intensity of the activated cells correlates directly with (and thus serves as a reliable surrogate for) superoxide production [Kuhns et al 2010]. Routine DHR testing of peripheral blood does not detect *NCF4*-related CGD.

The DHR test can distinguish the following forms of CGD:

- Complete forms (i.e., those with absent-to-greatly diminished production of superoxide) commonly observed in males with X-linked CGD
- Hypomorphic (variant) forms of CGD characterized by reduced protein expression/function and residual superoxide production (observed in some autosomal recessive CGD and protein-positive X-linked CGD)
- Mosaic forms (i.e., those with two discrete populations of phagocytes: some oxidase-positive and some oxidase-negative) commonly observed in females who are heterozygous for X-linked CGD

Note: Although the pattern of oxidase-positive and oxidase-negative phagocytes can suggest X-linked inheritance of CGD or autosomal recessive inheritance of CGD, the results are not definitive in establishing the molecular cause or mode of inheritance.

The DHR is superior to other tests for CGD, and is widely available to ordering clinicians.

**Nitroblue tetrazolium (NBT) test**, the oldest and most recognized diagnostic test for CGD, relies on light microscopy to provide a mostly qualitative determination of phagocyte NADPH oxidase activity. When stimulated in vitro, normal phagocytes produce superoxide that reduces yellow NBT to blue/black formazan, forming a precipitate in cells [Baehner & Nathan 1967]. The NBT test is typically performed on a microscope slide, which is read manually to distinguish reducing (blue-black) from non-reducing (unstained) cells:

- **Neutrophils in individuals without CGD.** More than 95% of cells produce superoxide that reduces NBT to formazan.
- **Neutrophils in individuals with CGD.** Production of superoxide is absent or greatly diminished, leaving cells not reducing NBT to formazan.
- **Females who are heterozygous for X-linked CGD** (who have two populations of leukocytes). Superoxide is typically produced in 20%-80% of cells [Elloumi & Holland 2014] (range: 0.001%-97%).

Note: Because the NBT test is semi-quantitative and evaluates only a limited number of cells, it may be falsely interpreted as normal in: (1) females who are heterozygous for X-linked CGD, especially those with skewed (non-random) X-chromosome inactivation (see X-Linked CGD: Heterozygous Females); and (2) persons with hypomorphic (variant) forms of CGD characterized by partial protein expression/function and residual superoxide production (observed in autosomal recessive CGD and protein-positive X-linked CGD).

## Family History

Family history is consistent with **autosomal recessive inheritance** (e.g., affected sibs and/or parental consanguinity) or with **X-linked inheritance** (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of CGD is **established** in a proband with suggestive findings by identification of pathogenic (or likely pathogenic) variant(s) in one of six genes that encode or permit assembly of the subunits of phagocyte NADPH oxidase (see Table 1).

- *CYBA*, *CYBC1*, *NCF1*, *NCF2*, and *NCF4* are the genes in which biallelic pathogenic variants cause autosomal recessive chronic granulomatous disease (AR-CGD).
- *CYBB* is the gene in which a hemizygous or heterozygous pathogenic variant causes X-linked chronic granulomatous disease (X-linked CGD).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas comprehensive genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings and/or abnormal results on the DHR test are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical findings in whom the diagnosis of CGD has not been considered are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

## Option 1

A **chronic granulomatous disease multigene panel** that includes the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequence-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

## Special Consideration in a Male with Suspected CGD and Other Medical Issues

Large deletions in Xp21.1 have been reported in some with X-CGD, which may affect genes lying in close proximity to *CYBB* at Xp21.1 (see Genetically Related Disorders, **Contiguous-gene rearrangements**). Therefore, individuals with suspected X-CGD and clinical manifestations of McLeod syndrome, retinitis pigmentosa, Duchenne muscular dystrophy, and/or ornithine transcarbamylase deficiency should have a chromosome microarray analysis (CMA). If a large deletion is found within *CYBB*, a CMA may be indicated.

**Table 1.** Molecular Genetic Testing Used in Chronic Granulomatous Disease (CGD)

Gene <sup>1, 2</sup>	MOI	Proportion of CGD Attributed to Pathogenic Variants in Gene <sup>3</sup>	Proportion of Pathogenic Variants <sup>4</sup> Detectable by Method	
			Sequence analysis <sup>5</sup>	Gene-targeted deletion/duplication analysis <sup>6</sup>
<i>CYBA</i>	AR	7%	~85% <sup>7</sup>	~15% <sup>7</sup>
<i>CYBB</i>	XL	~66%	~85% <sup>8</sup>	~15% <sup>8, 9</sup>
<i>CYBC1</i>	AR	Few persons	All <sup>7, 10</sup>	Unknown <sup>11</sup>
<i>NCF1</i>	AR	20%	~75% <sup>7</sup>	~25% <sup>7, 12</sup>
<i>NCF2</i>	AR	7%	~85% <sup>7</sup>	~15% <sup>7</sup>

Table 1. continued from previous page.

Gene <sup>1, 2</sup>	MOI	Proportion of CGD Attributed to Pathogenic Variants in Gene <sup>3</sup>	Proportion of Pathogenic Variants <sup>4</sup> Detectable by Method	
			Sequence analysis <sup>5</sup>	Gene-targeted deletion/duplication analysis <sup>6</sup>
<i>NCF4</i>	AR	<1%	90% <sup>7, 13</sup>	10% <sup>7, 13</sup>

AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. Roos et al [2021a], Roos et al [2021b]

4. See Molecular Genetics for information on variants detected in this gene.

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (see Genetically Related Disorders, **Contiguous-gene rearrangements**) may not be detected by these methods.

7. Roos et al [2021a]

8. Roos et al [2021b]

9. If a contiguous gene deletion involving multiple genes at Xp21.1 is suspected based on clinical findings, or if a large deletion is found within *CYBB*, a chromosome microarray analysis (CMA) to detect a microdeletion may be warranted.

10. Thomas et al [2019]

11. No data on detection rate of gene-targeted deletion/duplication analysis are available.

12. Rawat et al [2021]

13. van de Geer et al [2018]

## Clinical Characteristics

### Clinical Description

Chronic granulomatous disease (CGD) is characterized by severe recurrent bacterial and fungal infections and dysregulated inflammatory responses resulting in granuloma formation and other inflammatory disorders such as colitis.

**Age at diagnosis.** While CGD may present anytime from infancy to late adulthood, the vast majority of affected individuals are diagnosed before age five years. The median age of diagnosis was 2.5 to three years in several series [Jones et al 2008, Martire et al 2008]. More recently, increased numbers of affected individuals have been diagnosed in adolescence or adulthood [Wolach et al 2017, Gao et al 2019, El-Mokhtar et al 2021, Noh et al 2021, Rawat et al 2021]. This delay in diagnosis may be attributed to the following:

- Effective treatment of CGD-related infections with antimicrobials not available in the past
- Recognition of milder cases of autosomal recessive CGD that may have gone undiagnosed without currently available tests and/or awareness of milder disease manifestations
- Overall improvement in food handling and sanitation

**Presentation.** Infections and granulomatous lesions are usually the first manifestations of CGD, with the most frequent sites being the lung, lymph nodes, liver, bone, and skin. The types of infection seen most often include pneumonia, lymphadenitis, abscess, osteomyelitis, and cellulitis. Other pulmonary complications include empyema and hilar adenopathy. The most common sites for abscesses are the perianal and perirectal areas as well as the liver.

Although the frequency of infections in persons with CGD has decreased with the routine administration of antibacterial and antifungal prophylaxis, infections still occur at a frequency of 0.3/year.

In North America, the majority of infections in CGD are caused by *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species [Marciano et al 2015] (Table 2). In other parts of the world, important causes of infection are *Salmonella*, *bacille Calmette-Guérin* (BCG), and tuberculosis [Winkelstein et al 2000, van den Berg et al 2009].

**Table 2.** Infections in CGD: Common Pathogens and Sites of Involvement

	Pathogen	Presentation
<b>Bacterial infections</b>	<i>Staphylococcus aureus</i>	Soft-tissue infection; lymphadenitis; liver abscess; osteomyelitis; pneumonia; sepsis
	<i>Burkholderia</i> species: <sup>1</sup> <ul style="list-style-type: none"> <li>• <i>B cepacia</i> <sup>2</sup></li> <li>• <i>B gladioli</i></li> <li>• <i>B pseudomallei</i></li> </ul>	Pneumonia; sepsis
	<i>Serratia marcescens</i> <sup>3</sup>	More common: <ul style="list-style-type: none"> <li>• Osteomyelitis</li> <li>• Soft-tissue infection</li> </ul> Less common: <ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Sepsis</li> </ul>
	<i>Nocardia</i> species: <sup>4, 5</sup> <ul style="list-style-type: none"> <li>• <i>N asteroides</i></li> <li>• <i>N nova</i></li> <li>• <i>N otitidiscaviarum</i></li> <li>• <i>N farcinica</i></li> </ul>	Pneumonia; osteomyelitis; brain abscess
	<i>Granulibacter bethesdensis</i> <sup>6</sup>	Necrotizing lymphadenitis; sepsis; meningitis
	<i>Chromobacterium violaceum</i> <sup>7</sup>	Sepsis
	<i>Francisella philomiragia</i> <sup>8</sup>	Sepsis
<b>Fungal infections</b> <sup>9</sup>	<i>Aspergillus</i> species: <ul style="list-style-type: none"> <li>• <i>A fumigatus</i></li> <li>• <i>A nidulans</i></li> <li>• <i>A viridinutans</i></li> <li>• <i>A flavus</i></li> <li>• <i>A terreus</i></li> <li>• <i>A niger</i></li> </ul>	Pneumonia; osteomyelitis; brain abscess; lymphadenitis
	<i>Paecilomyces</i> species: <ul style="list-style-type: none"> <li>• <i>P variotti</i></li> <li>• <i>P lilacinus</i></li> </ul>	Pneumonia; soft-tissue infection; osteomyelitis

Table 2. continued from previous page.

	Pathogen	Presentation
	Other molds: <ul style="list-style-type: none"> <li>• <i>Geosmitha argillacea</i><sup>10</sup></li> <li>• <i>Cephalosporum species</i></li> <li>• <i>Chaetomium strumarium</i></li> <li>• <i>Phialophora richardsiae</i></li> <li>• <i>Scedosporium apiospermum</i></li> <li>• <i>Exophiala species</i></li> <li>• <i>Cladosporium species</i></li> <li>• <i>Zygomycete species</i></li> <li>• <i>Acremonium species</i></li> <li>• <i>Neosartorya udagawae</i></li> <li>• <i>Phellinus species</i><sup>11</sup></li> </ul>	Pneumonia; soft-tissue infection
<b>Yeast infections</b>	Candida <ul style="list-style-type: none"> <li>• <i>C albicans</i></li> <li>• <i>C glabrata</i></li> <li>• <i>C lusitaniae</i></li> </ul>	Sepsis; soft-tissue infection; liver abscess
	Trichosporon <ul style="list-style-type: none"> <li>• <i>T beigelii</i></li> <li>• <i>T inkin</i></li> </ul> <i>Arthrographis kalrae</i>	Pneumonia; soft-tissue infection

1. Greenberg et al [2009]

2. *B cepacia* is also a cause of pneumonia in [cystic fibrosis](#).

3. Galluzzo et al [2008], Friend et al [2009]

4. Dorman et al [2002]

5. Outside of CGD, *Nocardia* infections occur predominantly in the setting of high-dose corticosteroids.

6. Greenberg et al [2006]

7. Sirinavin et al [2005]

8. Mailman & Schmidt [2005]

9. Beauté et al [2011], Blumental et al [2011]

10. De Ravin et al [2011]

11. De Ravin et al [2014], Ramesh et al [2014], Shigemura et al [2015]

## Bacterial Infections

Widespread prophylaxis has limited staphylococcal infections primarily to the skin, lymph nodes, liver, and (rarely) lung [Marciano et al 2015].

*Burkholderia cepacia* complex infection is common in individuals with CGD and can occasionally cause sepsis.

Outside of CGD, *Nocardia* infections occur predominantly in the setting of high-dose corticosteroids.

Mycobacterial diseases in CGD are mostly limited to regional and disseminated BCG infections and tuberculosis. Persons with CGD are less susceptible to nontuberculous infections than persons with defects in T-cell or interferon gamma/IL-12 pathways: in persons with CGD, BCG infection may cause severe localized disease such as draining skin lesions at sites of BCG vaccination [Lee et al 2008], whereas in persons with severe combined immunodeficiency or defects in the IFN-gamma receptor pathway, BCG infection typically causes disseminated disease.

Uncommon bacterial infections that are virtually pathognomonic for CGD include the following:



- *Granulibacter bethesdensis*, which causes necrotizing lymphadenitis, sepsis, and meningitis [Greenberg et al 2006]
- *Chromobacterium violaceum*, which is found in brackish waters such as the Gulf of Mexico and causes sepsis [Sirinavin et al 2005]
- *Francisella philomiragia*, which is also found in brackish waters such as the Chesapeake Bay and is a cause of sepsis [Mailman & Schmidt 2005]

Bacteremia is relatively uncommon except with certain gram-negative organisms.

## Fungal Infections

Invasive fungal infections, which have the highest prevalence in CGD among all primary immunodeficiencies, remain the leading cause of mortality in CGD. They occur most commonly in the first two decades of life and can be the first presentation of disease [Marciano et al 2015]; about 30% of individuals with CGD will develop fungal infections [Beauté et al 2011, Marciano et al 2015].

Fungal infections are typically acquired through inhalation of spores or hyphae resulting in pneumonia that can spread locally to the ribs and spine or metastatically to the brain. Presentation may be insidious or manifest as failure to thrive and malaise. Other common presenting signs and symptoms include cough, fever, and chest pain.

*Aspergillus* species are the most common cause of invasive fungal infections, typically in the lung.

- *Aspergillus fumigatus* is the most common of the *Aspergillus* species to cause infection in CGD. Although angioinvasion is common in neutropenic settings, it does not occur in CGD.
- *Aspergillus nidulans* infection is almost exclusive to CGD and causes more severe and refractory disease with local and distant spread [Segal et al 1998, Beauté et al 2011].

*Paecilomyces lilacinus* and *Paecilomyces variotti* cause pneumonia and osteomyelitis in CGD almost exclusively.

Mucormycosis has been reported in CGD but appears to occur only in the setting of significant immunosuppression [Vinh et al 2009].

The overall frequency and mortality of invasive fungal infections have been significantly reduced with the use of itraconazole as antifungal prophylaxis and the use of other azoles (voriconazole and posaconazole) as therapy. However, when they occur, fungal infections develop at an older age and may require longer duration of therapy. Fungal infections cause more mortality than other infections in CGD [Marciano et al 2015]. An increased frequency of infection with *Aspergillus nidulans* and other opportunistic fungi may be associated with itraconazole prophylaxis [Blumental et al 2011].

Yeast infections are not nearly as common as bacterial and fungal infections in persons with CGD; mucocutaneous candidiasis is not encountered.

Note: The endemic dimorphic mold infections histoplasmosis, blastomycosis, and coccidioidomycosis do not occur in CGD [Holland 2010]. A single case of sporotrichosis in CGD has been reported [Trotter et al 2014].

## Inflammatory and Other Manifestations

Formation of granulomata and dysregulated inflammation in CGD contribute to morbidity and can cause multiple symptoms. The genitourinary and gastrointestinal tracts are most commonly affected.

**Genitourinary manifestations** include bladder granulomata associated with ureteral obstruction and urinary tract infections. Other manifestations include pseudotumors of the bladder and eosinophilic cystitis.

### Gastrointestinal manifestations

- Pyloric edema leads to functional gastric outlet obstruction and can be an initial presentation of CGD.
- Esophageal, jejunal, ileal, cecal, rectal, and perirectal granulomata similar to those in Crohn disease have also been described. Symptomatic inflammatory bowel disease affects up to 50% of individuals and can be the presenting finding [Marciano et al 2004].
- Other gastrointestinal symptoms indicative of CGD colitis include abdominal pain, diarrhea, strictures, and fistulae. Significant colitis leading to bowel obstruction, fistulae, and strictures can be an important cause of growth restriction [Marciano et al 2004].

**Liver involvement** is a significant cause of morbidity in CGD, with abscesses occurring in up to 35% of affected individuals. Liver abscesses have been difficult to cure without surgery and carry a significant risk for recurrence, but not relapse [Hussain et al 2007].

Other common liver abnormalities include liver enzyme elevation, persistent elevations in alkaline phosphatase, and drug-induced hepatitis.

High rates of portal venopathy are associated with splenomegaly and nodular regenerative hyperplasia. Portal hypertension and thrombocytopenia are associated with intrahepatic disease and important risk factors for mortality [Hussain et al 2007, Feld et al 2008].

**Hyperinflammation** is seen, especially in response to infectious agents. The exact etiology of dysregulated inflammation in CGD is unclear. Heightened inflammatory response has been described in chronic colitis [Marciano et al 2004], granulomatous cystitis [Kontras et al 1971], pulmonary infections with *Nocardia* [Freeman et al 2011], and staphylococcal liver abscesses [Yamazaki-Nakashimada et al 2006, Leiding et al 2012].

Fungi elicit an exuberant inflammatory response regardless of whether the fungi are alive or dead [Morgenstern et al 1997] as in "mulch pneumonitis," a syndrome caused by inhalation of aerosolized decayed organic matter (e.g., hay, dead leaves) [Siddiqui et al 2007]. Acute fulminant pneumonitis (similar to that seen in hypersensitivity pneumonitis) ensues.

Prolonged and dysregulated inflammation in CGD can overlap clinically with the syndrome of **hemophagocytic lymphohistiocytosis** (HLH). HLH is caused by an ineffective and unrestrained inflammatory response by T lymphocytes, NK cells, and macrophages leading to fever, hepatosplenomegaly, cytopenias, and hemophagocytosis in the bone marrow and other tissues. Persons with CGD can develop prolonged fever and most of the clinical features of HLH.

**Growth restriction** is common in CGD and slow growth can be a common presenting finding [Marciano et al 2004] that can be compounded by colitis. Growth may improve in late adolescence and many affected individuals may attain appropriate adult height and weight, albeit on the lower end of the spectrum.

**Chronic respiratory disease** can result from recurrent infection. Bronchiectasis, obliterative bronchiolitis, and chronic fibrosis may occur but are not as common as in some other primary immunodeficiencies.

**Ophthalmic manifestations** include chorioretinal lesions and granulomata with pigment clumping that are usually asymptomatic but often associated with recovery of bacterial DNA from retinal tissue samples [Wang et al 2013]. Inflammatory eye disease including keratitis and uveitis can occur as well.

**Oral manifestations** include gingivitis, stomatitis, aphthous ulceration, and gingival hypertrophy.

**Noninfectious skin manifestations** include photosensitivity, granulomatous lesions, vasculitis, and excessive inflammation at drainage and surgical wounds, leading to dehiscence.

**Autoimmune disorders** are common. Autoimmune diseases reported in individuals with CGD include idiopathic thrombocytopenic purpura, juvenile idiopathic arthritis, autoimmune pulmonary disease, myasthenia

gravis, IgA nephropathy, antiphospholipid syndrome, and recurrent pericardial effusion [Winkelstein et al 2000, De Ravin et al 2008].

**Malignancies** have been reported in CGD, and may be more common in autosomal recessive CGD than in X-linked CGD, raising the possibility that the increased incidence of malignancy may be due to other cosegregating autosomal recessive traits [Aguilera et al 2009, Geramizadeh et al 2010, Lugo Reyes et al 2011].

The histopathologic patterns of malignancy have significant overlap with certain chronic inflammatory conditions. However, the largest series of affected individuals to date reported no malignancies [Winkelstein et al 2000, van den Berg et al 2009]. Smaller, more recent studies corroborate a low overall incidence of malignancy [Köker et al 2013, Raptaki et al 2013, Baba et al 2014, Al-Zadjali et al 2015].

## Survival in CGD

Survival in CGD has improved greatly, and is now approximately 90% at age ten years [Jones et al 2008, Martire et al 2008, Kuhns et al 2010, Marciano et al 2015, Wolach et al 2017, Gao et al 2019, El-Mokhtar et al 2021, Noh et al 2021, Rawat et al 2021]. Overall rates of survival are lower among those with X-linked CGD than those with autosomal recessive CGD.

### Factors influencing survival

- **Residual superoxide production**, which correlates most directly with overall survival [Kuhns et al 2010] (See Genotype-Phenotype Correlations.)
  - Persons with *NCF1* pathogenic variants have relatively good overall survival (beyond age 40 years in >80%), which is similar to the survival rate in persons with *CYBB* pathogenic missense variants associated with residual superoxide production.
  - Persons with *CYBB* pathogenic variants that result in no superoxide production have a survival beyond age 40 years of approximately 55%.
- **Use of azoles for antifungal prophylaxis and therapy.** Several studies [Jones et al 2008, Kobayashi et al 2008, Martire et al 2008, Marciano et al 2015] report increased survival rates over the past 20 years:
  - 88%-97% at age 10 years
  - 73%-87% at age 20 years
  - 46%-55% at age 30 years

Note: Individuals diagnosed and treated before the use of azoles usually did not survive past age 30-40 years.

- **Access to care and expertise of caregivers**
- **Post-infectious complications** such as hepatic nodular regenerative hyperplasia and portal venopathy associated with liver abscess, which contribute to overall morbidity and mortality [Marciano et al 2004, Hussain et al 2007, Feld et al 2008]

Note: Inflammatory bowel disease does not influence mortality: overall survival rates of persons with CGD with and without colitis are similar [Marciano et al 2004, Kuhns et al 2010, Marciano et al 2015].

## X-Linked CGD: Heterozygous Females

Females who are heterozygous for a *CYBB* pathogenic variant are typically not affected with CGD, as the amount of gp91<sup>phox</sup> protein produced by their second (normal) *CYBB* allele allows adequate superoxide production and protection from CGD-related infections.

Neutrophils from heterozygous females express two populations that dihydrorhodamine (DHR) testing can detect: an abnormal DHR(-) population expressing the pathogenic variant and a brightly staining DHR (+) population expressing the normal allele. Skewed (non-random) X-chromosome inactivation can result in low %DHR+ neutrophil population because the *CYBB* disease-causing allele is primarily expressed.

When %DHR+ falls below 20%, heterozygous females are at risk for CGD-specific infections. The %DHR+ population can predict susceptibility to infections with CGD-specific pathogens but does not predict autoimmune symptoms of heterozygous females [Marciano et al 2018]. Heterozygous females are at substantial risk for inflammatory conditions.

Careful longitudinal evaluation of heterozygous females is recommended in order to detect inflammatory or infectious conditions if they occur over time.

Clinical evidence of CGD in heterozygous females:

- Cutaneous lesions resembling discoid lupus and recurrent aphthous stomatitis [Marciano et al 2018]
- Photosensitive skin rashes, alopecia, Raynaud's phenomenon, mouth ulcers, and joint pain [Marciano et al 2018]
- Chorioretinal lesions and granulomata with pigment clumping that are usually asymptomatic [Wang et al 2013]
- Crohn-like disease (colitis) [Marciano et al 2018]
- Systemic lupus erythematosus
- Infections

## Phenotype Correlations by Gene

***CYBB***. Historically, it has been recognized that pathogenic variants in *CYBB* (the cause of X-linked CGD) give rise to a more serious phenotype than pathogenic variants causing autosomal recessive (AR) forms of CGD. Compared to persons with AR-CGD, males with X-linked CGD are typically diagnosed earlier and have a significantly higher incidence of perirectal abscess, suppurative adenitis, gastric outlet obstruction, urinary obstruction, and higher mortality at a young age.

***CYBC1*** and ***NCF4*** are notable for severe and difficult-to-control inflammatory bowel disease, with relatively less common severe infections.

## Genotype-Phenotype Correlations

Hypomorphic (variant) CGD is characterized by partial protein expression/function and residual superoxide production (observed in AR-CGD and protein-positive X-linked CGD). Individuals with hypomorphic variants typically have a milder course and come to clinical attention later in life than those with absent protein expression [Bender et al 2009].

***CYBB***. Genotype-phenotype correlations in the X-linked gene *CYBB* (encoding gp91<sup>phox</sup>) include the following:

- All nonsense variants or deletions of *CYBB* in males are highly deleterious and associated with poorer outcomes.
- The phenotype caused by pathogenic variants in *CYBB* associated with residual superoxide production is characterized by better survival than with *CYBB* variants that cause no residual superoxide production.
  - Pathogenic missense variants that occur in the *CYBB* region encoding amino acids 1-309 are associated with residual superoxide production at a level sufficient for good overall survival. Exceptions are pathogenic variants in the nucleotides encoding histidine at residue 222, which do not support production of residual superoxide, and thus are more deleterious.

- *CYBB* regions encoding amino acid residues 310 and beyond affect the FAD- and NADPH-binding domains that are essential for superoxide function. Even when pathogenic variants in this region allow protein expression, the proteins are nonfunctional and associated with poorer overall outcomes in affected males [Kuhns et al 2010].

**CYBA.** Complete *CYBA* pathogenic variants (defined by the author as those variants resulting in absence of p22<sup>phox</sup> protein expression) lead to absent cytochrome b protein expression and thereby disable the formation of the cytochrome complex. These variants therefore behave like the most deleterious of the *CYBB* pathogenic variants.

No additional specific genotype-phenotype correlations have been identified for *CYBC1*, *NCF1*, *NCF2*, or *NCF4*.

## Nomenclature

When first characterized, chronic granulomatous disease was called "fatal granulomatous disease of childhood" [Bridges et al 1959].

## Prevalence

The retrospectively and voluntarily reported prevalence of CGD is approximately 1:200,000 live births in the United States [Winkelstein et al 2000].

Prevalence rates in other countries vary somewhat based on frequency of consanguinity [Wolach et al 2008, Fattahi et al 2011].

In regions with high rates of consanguineous marriages, the prevalence of recessive forms of CGD exceeds that of X-linked CGD.

## Genetically Related (Allelic) Disorders

*CYBA*, *CYBC1*, *NCF1*, *NCF2*, *NCF4*. No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in these five genes.

*CYBB* is one of several genes that can cause mendelian susceptibility to mycobacterial disease (MSMD) [Bustamante 2020]. *CYBB*-related MSMD (also known as immunodeficiency 34; OMIM 300645) consists of susceptibility to extrapulmonary mycobacterial disease due to BCG vaccination and is associated with impaired respiratory burst in macrophages with no dysfunction in monocytes and neutrophils [Bustamante et al 2011].

**Contiguous-gene rearrangements.** Other genes that lie in close proximity to *CYBB* at Xp21.1 and the disorders caused by their deletion include the following [Peng et al 2007] (see Note):

- *XK*, encoding the Kx blood group (telomeric) associated with [McLeod neuroacanthocytosis syndrome](#) (deletion of *XK*). This is a multisystem disorder with central nervous system, neuromuscular, cardiovascular, and hematologic manifestations in males.
- *RPGR*, encoding retinitis pigmentosa GTPase regulator (telomeric) associated with [RPGR-related retinitis pigmentosa](#)
- *DMD*, encoding the protein dystrophin (telomeric) associated with [Duchenne muscular dystrophy](#)
- *OTC*, encoding ornithine transcarbamylase (centromeric) associated with [ornithine transcarbamylase deficiency](#) (*OTC*) leading to urea cycle defects

Note: Concurrent deletion of *XK* with *CYBB* is the most common; deletion of all five genes is exceedingly rare.

## Differential Diagnosis

The differential diagnosis of chronic granulomatous disease (CGD) mainly involves disorders with recurrent or unusual infections or disorders associated with granuloma formation and hyperinflammation (see Tables 3 and 4).

**Note:** Spontaneously occurring severe or recurrent bacterial infections should always prompt consideration of immune deficiency. Persons with recurrent soft-tissue infections or staphylococcal lymphadenitis should be evaluated for CGD. Presence of liver abscess or other deep-tissue abscesses is concerning for CGD as well as other immunodeficiencies.

**Table 3.** Disorders of Known Genetic Cause in the Differential Diagnosis of Chronic Granulomatous Disease

Gene(s)	Disorder	MOI	Immunologic Characteristics	Distinguishing Features
<i>CFTR</i>	Cystic fibrosis (CF)	AR	Pulmonary infections w/ <i>Burkholderia cepacia</i> complex	While persons w/CGD are prone to recurrent infection w/different strains of <i>Burkholderia cepacia</i> complex, those w/CF are often persistently infected w/the same strain <sup>1</sup> & these infections are typically limited to the lung & concurrent w/ significant bronchiectasis.
<i>G6PD</i>	Glucose 6-phosphate dehydrogenase (G6PD) deficiency (OMIM 300908)	XL	Neutrophil respiratory burst is affected, ↑ing host susceptibility to infections	G6PD deficiency is also assoc w/hemolytic anemia.
<i>GSS</i>	Glutathione synthetase (GS) deficiency (OMIM 266130)	AR		GS deficiency is also assoc w/5-oxoprolinuria & intellectual disability.
<i>STAT3</i>	<i>STAT3</i> loss-of-function hyper-IgE syndrome ( <i>STAT3</i> LOF HIES)	AD	Staphylococcal & <i>Aspergillus</i> infections are common.	<i>STAT3</i> LOF HIES is also assoc w/retained primary teeth, scoliosis, bone fractures following minimal trauma, joint hyperextensibility, & characteristic facial appearance (typically emerging in adolescence).

AD = autosomal dominant; AR = autosomal recessive; CGD = chronic granulomatous disease; MOI = mode of inheritance; XL = X-linked

1. Greenberg et al [2009]

**Table 4.** Other Conditions in the Differential Diagnosis of Chronic Granulomatous Disease

Disorder	Clinical Characteristics	Comment
Allergic bronchopulmonary aspergillosis (ABPA)	Pulmonary hypersensitivity reaction to <i>Aspergillus fumigatus</i> & other molds; most commonly seen in asthmatics & persons w/cystic fibrosis	Diagnosis of ABPA is based on history, ↑ serum concentration of IgE, blood eosinophilia, immediate skin reactivity to <i>Aspergillus fumigatus</i> antigens, presence of precipitating serum antibodies to <i>Aspergillus fumigatus</i> , & specific imaging results, none of which are characteristic of CGD. <sup>1</sup>
Crohn disease	May present w/weight loss, abdominal pain, diarrhea, & colitis	Significant colitis → bowel obstruction, fistulae, & strictures can occur in persons w/CGD & can be an important cause of growth restriction. <sup>2</sup>

CGD = chronic granulomatous disease

1. Greenberger [2002]

2. Marciano et al [2004]

**Other conditions associated with abnormal dihydrorhodamine (DHR) test results.** Other conditions that may affect the ability of the neutrophil to generate the respiratory burst that is detected in the DHR assay include myeloperoxidase deficiency (OMIM 254600) [Mauch et al 2007] and SAPHO (the syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis) [Daoussis et al 2019]. In these two conditions the DHR results are

abnormal, but superoxide production levels and NBT staining are normal. In addition, neither of these syndromes has infection profiles that overlap with CGD.

Recently, acetaminophen administration has been shown to affect the DHR assay and should be considered in the differential of a low DHR response [Almutairi et al 2020].

## Management

No clinical practice guidelines for chronic granulomatous disease (CGD) have been published.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with chronic granulomatous disease (CGD), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Recommended Evaluations Following Initial Diagnosis in Individuals with Chronic Granulomatous Disease (CGD)

System/Concern	Evaluation	Comment
<b>Infection</b>	Look for general evidence of infection w/: <ul style="list-style-type: none"> <li>• C-reactive protein;</li> <li>• Erythrocyte sedimentation rate.</li> </ul>	Sensitive but nonspecific markers of inflammation
	Endoscopy & colonoscopy if signs & symptoms of colitis are present	
	Imaging as it pertains to specific symptoms for diagnosis & mgmt of infection; see Affected Organs / Manifestations of CGD on Imaging.	Different imaging modalities can be used depending on the site affected. <ul style="list-style-type: none"> <li>• CT scan is often used due to relative ease &amp; sensitivity.</li> <li>• US &amp; MRI can be used instead in many instances.</li> <li>• PET using fluorine-18-fluoro-2-deoxy-D-glucose (FDG) uptake can help discriminate active from resolved infection.<sup>1</sup></li> </ul>
<b>Anemia</b>	CBC	Anemia is common either due to anemia of chronic disease or iron deficiency anemia. Poor iron absorption is common in CGD.
<b>Hypoalbuminemia / Liver dysfunction</b>	Complete metabolic profile including albumin	Hypoalbuminemia is found in 70% of persons w/GI involvement & 25% of those w/o GI involvement [Marciano et al 2004].
<b>Males w/X-linked CGD</b>	For males w/X-linked CGD & <b>McLeod neuroacanthocytosis syndrome</b> , early consideration of autologous blood banking (See also Genetically Related Disorders, <b>Contiguous-gene rearrangements</b> .)	<ul style="list-style-type: none"> <li>• Persons w/McLeod neuroacanthocytosis syndrome do not express the erythrocyte blood group Kell antigen (i.e., they are Kell negative).</li> <li>• If they require transfusion of blood products, Kell-positive blood products must be avoided to prevent a transfusion reaction.</li> <li>• Kell-negative blood products are rarely available.</li> </ul>
<b>Genetic counseling</b>	By genetics professionals <sup>2</sup>	To inform affected persons & families re nature, MOI, & implications of CGD to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
<b>Family support &amp; resources</b>	Assess need for: <ul style="list-style-type: none"> <li>• Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>• Social work involvement for parental support;</li> <li>• Home nursing referral.</li> </ul>	

CBC = complete blood count; MOI = mode of inheritance; PET = positron emission tomography; US = ultrasound

1. High FDG uptake is consistent with active inflammation [Güngör et al 2001].

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Affected Organs / Manifestations of CGD on Imaging

### Lungs/pneumonia [Godoy et al 2008]

- **Chest x-ray.** Consolidation, reticular nodular opacities, scarring
- **CT**
  - Consolidation, ground-glass opacity, tree-in-bud opacity, centrilobular or random nodules, septal thickening, air trapping, scarring
  - Empyema or abscess
  - Mediastinal or hilar adenopathy, honeycomb lung, pleural thickening in chronic cases
  - Contiguous spread to chest wall, associated osteomyelitis of ribs and vertebral bodies
- **PET** [Güngör et al 2001]. Increased uptake at areas of consolidation

### Lymph nodes / suppurative adenitis [Towbin & Chaves 2010]

- **CT.** Enhancing lymph node with central area of hypodensity and enhancing septations
- **US**
  - Swirling debris, thickened septa, and increased color Doppler flow
  - Calcifications if granuloma present
- **PET.** Increased uptake

### Liver/abscess [Garcia-Eulate et al 2006]

- Single to multiple small or large abscesses, sharply defined; variable enhancement but usually with small central area with poor enhancement
- Calcifications

**Musculoskeletal/osteomyelitis** [Galluzzo et al 2008]. Multifocal, occurring in ribs, vertebral bodies, small bones of hands and feet

**Genitourinary/cystitis** [Walther et al 1992]. Inflammatory pseudotumors of the bladder, appearing as focal wall thickening on US

### Gastrointestinal / obstruction and colitis [Marciano et al 2004, Laskey et al 2009]

- **Obstruction**
  - Esophagus: strictures, diverticula, dysmotility
  - Thickening of bowel wall, fistulae
  - Upper GI: gastric outlet obstruction with gastric dilatation, delayed gastric emptying, circumferential antral narrowing, thickened gastric folds
  - Gastric wall thickening on US, CT, or MRI



- **Colitis.** Bowel wall thickening, skip lesions, luminal narrowing, fistulae, cobblestone mucosal pattern

### Head and neck / sinusitis [Towbin & Chaves 2010]

- **MRI.** Fungal sinusitis hypointense on T<sub>1</sub>- and T<sub>2</sub>-weighted images, associated with bony destruction
- **CT.** Fungal sinusitis hyperdense

**Central nervous system / abscess** [Towbin & Chaves 2010]. Abscesses with typical appearance on MRI with ring-enhancing lesions

## Treatment of Manifestations

**Table 6.** Treatment of Manifestations in Individuals with Chronic Granulomatous Disease

Manifestation/Concern	Treatment	Considerations/Other
<b>Serious bacterial &amp; fungal infections</b>	A definitive microbiologic diagnosis is essential & may require biopsy, fine needle aspiration &/or percutaneous drainage of an abscess prior to start of any antimicrobial therapy.	Imaging is important in detecting & understanding the severity of infections. CT or MRI should be followed closely until resolution of infections (see Affected Organs / Manifestations of CGD on Imaging).
	Empiric antibiotics & antifungals used until pathogen identified & specific agent can be used	Long courses of antimicrobials are often needed for adequate treatment.
	Azole drugs (voriconazole, posaconazole, isavuconazole) have expanded therapeutic options for fungal infections in CGD.	
	Granulocyte infusion	<ul style="list-style-type: none"> <li>• The principle is that a small number of normal phagocytes complement the oxidative defect in CGD phagocytes by supplying diffusible hydrogen peroxide.</li> <li>• Adverse effects may incl fever, development of leukoagglutinins, &amp; (rarely) pulmonary leukostasis.</li> <li>• Alloimmunization is a major concern, as many w/ history of severe infections may also be considered for HSCT [Heim et al 2011].</li> <li>• The possibility of CMV transmission is also a cause for caution.</li> </ul>
<b>Liver abscess or other intra-abdominal abscess</b>	Percutaneous drainage or excisional surgery	Staphylococcal liver abscesses can be treated w/o surgery by a combination of drainage of liquid pus (if present), intravenous antimicrobials, & moderate-dose corticosteroids (1 mg/kg/d tapered over 1-2 mos) [Leiding et al 2012, Straughan et al 2018].
<b>Lymphadenitis</b>	Excisional surgery	
<b>Colitis</b>	Prednisone 1 mg/kg/d for 1-2 wks followed by slow taper to 0.1-0.25 mg/kg/d over 1-2 mos [Holland 2010]	Long-term complications can incl growth restriction, osteoporosis, & ↑ risk of infection.
	Metronidazole to reduce bowel flora	
	Salicylic acid derivatives, 6-mercaptopurine, & mesalamine	
	Successful BMT appears to cure CGD & related colitis [Kang et al 2011]. See Prevention of Primary Manifestations.	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
<b>Heightened inflammatory response</b>	Simultaneous administration of antimicrobials & corticosteroids can help resolve infections & extensive areas of inflammation that can occur w/:	
	<ul style="list-style-type: none"> <li>Chronic colitis [Marciano et al 2004];</li> <li>Granulomatous cystitis [Kontras et al 1971];</li> <li>Pulmonary infections w/<i>Nocardia</i> [Freeman et al 2011];</li> <li>Staphylococcal liver abscesses [Leiding et al 2012];</li> <li>Mulch pneumonitis (the exuberant inflammatory response to inhalation of mulch or other organic matter) [Siddiqui et al 2007].</li> </ul>	
	Simultaneous administration of antimicrobials, IVIg, & steroids aggressively treats the syndrome of secondary HLH in CGD [Squire et al 2020]	<ul style="list-style-type: none"> <li>Because the HLH-like syndrome in CGD represents a reaction to bacterial or fungal infection, such infections must be aggressively treated in affected persons on immunosuppressants for HLH.</li> <li>While the merit of immunosuppression in the setting of infection-triggered HLH in CGD is unclear, treatment of infection is essential.</li> </ul>

BMT = bone marrow transplantation; CMV = cytomegalovirus; HLH = hemophagocytic lymphohistiocytosis; HSCT = hematopoietic stem cell transplantation

## Prevention of Primary Manifestations

**Antibacterial prophylaxis.** No randomized prospective clinical trials of antibacterial prophylaxis in persons with CGD have been performed; however, several retrospective studies suggest that trimethoprim-sulfamethoxazole (TMP-SMX) is effective in preventing bacterial infections. Lifelong daily antibacterial prophylaxis with oral TMP-SMX is recommended at 5 mg/kg up to 320 mg administered in two divided doses. Note: In liquid TMP-SMX the concentration of TMP is 40 mg per 5 mL and sulfamethoxazole 200 mg per 5 mL; the therapeutic dose of TMP-SMX is determined by the TMP component.

Alternatives to TMP-SMX for individuals allergic to sulfonamides include trimethoprim as a single agent, dicloxacillin, cephalosporins, and fluroquinolones.

**Antifungal prophylaxis.** A randomized prospective blinded crossover trial of itraconazole prophylaxis in persons with CGD showed excellent protection. The use of azole antifungal drugs has markedly reduced the frequency and severity of fungal infections in CGD. Lifelong antifungal prophylaxis with itraconazole 5 mg/kg oral solution to a maximum of 200 mg once daily is recommended [Gallin et al 2003].

For those unable to tolerate itraconazole, posaconazole has been studied in the oncology setting and is likely to be effective in CGD as well [Segal et al 2005].

Of note, the primary prophylaxis used to prevent bacterial and fungal infections also has good activity against yeasts.

**Immunomodulatory therapy.** A randomized prospective blinded international clinical trial of interferon gamma (IFN-gamma) prophylaxis in persons with CGD showed a 70% reduction in infections in recipients. IFN-gamma has become part of the prophylactic regimen in most centers in the United States; however, opinions differ on its use as primary prophylaxis and in the treatment of acute infections. The exact mechanism of IFN-gamma in CGD is not known, adding to the debate over its utility.

Some practitioners use IFN-gamma only in the setting of acute infection, rather than as primary prophylaxis. The data for this are anecdotal and unimpressive. The authors typically discontinue IFN-gamma during acute infection, as its utility is unclear and the exacerbation of malaise and fever can confuse the clinical picture and alter decision making [Holland 2010].

Administration by injection, cost, and lack of familiarity with cytokine therapy all affect the use of IFN-gamma in CGD. The authors use IFN-gamma in addition to antimicrobials as prophylaxis [Holland 2010]. Dosing is based on body surface area (BSA). For BSA  $>0.5/m^2$  the dose is  $50 \mu g/m^2$  subcutaneously 3x/week; for BSA  $\leq 0.5/m^2$  the dose is  $1.5 \mu g/kg$  subcutaneously 3x/week. Fever, myalgias, and malaise are the most common side effects but can be alleviated with concurrent administration of acetaminophen.

**Hematopoietic stem cell transplantation (HSCT).** Allogeneic HSCT is the only known cure for CGD. Historically, HSCT has been associated with high morbidity and mortality and thus reluctantly offered. However, the use of non-myeloablative conditioning regimens has greatly decreased the risk of regimen-related toxicity as well as allowing for transplantation in the setting of active infection [Güngör et al 2014]. Recent reports show excellent overall survival and event-free survival, especially when HSCT is performed with matched donors and at a younger age [Chiesa et al 2020, Chandra et al 2021].

The issue of which individuals with CGD should undergo HSCT remains complex. While transplant-related mortality rates have fallen dramatically and successful cure has risen, issues of long-term risk, sterility, graft-versus-host disease, donor matching, expense, center experience, availability, and insurance coverage all strongly influence family and physician choices regarding transplantation. Levels of residual superoxide production have correlated well with overall survival [Kuhns et al 2010]; that is, individuals with very low superoxide production had worse long-term survival than those with higher levels of residual superoxide production, suggesting that this latter group could benefit more from transplantation. However, even within this group some individuals do relatively well for long periods.

Individuals with CGD may experience behavioral, emotional, and learning difficulties as a consequence of chronic disease, recurrent hospitalization, and limitations of activity. Older children and adolescents are especially likely to be noncompliant with respect to prophylaxis and risk avoidance, increasing their risk for CGD-related complications. The inflammatory bowel disease present in up to 50% of persons with X-linked CGD may result in discomfort and growth impairment, and may require colostomy or colectomy. Overall quality of life is reduced in children with CGD, whereas those with CGD who have undergone transplant report quality of life comparable to healthy children [Cole et al 2013]. Thus, with improved outcomes HSCT presents an increasingly reasonable alternative and the possibility of a normal life.

As HSCT has become safer, more reliable, and more available it is offered earlier [Chiesa et al 2020] and in some cases is the initial choice for the management of CGD.

The European Bone Marrow Transplantation (EBMT) / European Society of Immunodeficiencies Inborn Errors Working Party [Lankester et al 2021] recommends allogeneic bone marrow transplantation for CGD be considered as soon as possible after diagnosis, prior to onset of disease-related organ damage.

## Surveillance

Regular follow-up visits can aid in early detection and treatment of asymptomatic or minimally symptomatic infections and noninfectious complications such as colitis, pulmonary granulomas, and pulmonary fibrosis [Roesler et al 2005].

**Table 7.** Recommended Surveillance for Individuals with Chronic Granulomatous Disease

System/Concern	Evaluation	Frequency in Healthy Person w/CGD & No Evidence of Infection or Chronic Inflammatory Symptoms
<b>Early detection of minimally symptomatic infections &amp; noninfectious complications incl colitis, pulmonary granulomata, &amp; pulmonary fibrosis</b>	<ul style="list-style-type: none"> <li>• CRP &amp; ESR; significant ↑s should prompt eval for infection.</li> <li>• CBC &amp; albumin; presence of microcytic anemia &amp; hypoalbuminemia may indicate development of colitis.</li> <li>• Liver chemistries; transaminase &amp; alkaline phosphatase ↑ may indicate drug-related hepatotoxicity.</li> </ul>	Every 3-4 mos
<b>Early detection of inflammatory &amp;/or infectious conditions in females heterozygous for a <i>CYBB</i> pathogenic variant</b>	<ul style="list-style-type: none"> <li>• Annual eval by a health care professional w/an eye toward concerns of invasive infection or for auto-inflammatory manifestations</li> <li>• To follow (as needed): referral to appropriate specialist &amp; lab &amp;/or radiologic eval per individual findings</li> </ul>	Annually or if new concern arises

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

## Agents/Circumstances to Avoid

**Exposures.** Activities that expose the affected person to decayed organic matter (e.g., mulching, gardening, leaf raking, house demolition) are to be avoided as inhalation of fungal spores can result in fulminant pneumonitis leading to hypoxia and respiratory failure [Siddiqui et al 2007]. Therefore, the following should be avoided:

- Exposure to mulch
- Potting of plants or gardening
- Raking leaves or mowing lawns
- Swimming in stagnant water, brackish water, or ponds

**Live bacterial vaccines should be avoided, whereas there is no contraindication to live viral vaccines.**

- *Bacille Calmette-Guérin* (BCG) vaccination should be avoided.
- *Salmonella typhi* vaccination should be avoided.
- All other vaccines including live viral vaccines are recommended in individuals with CGD.

**Transfusion considerations.** Persons with CGD and [McLeod neuroacanthocytosis syndrome](#) lack red blood cell Kell antigens and thus should not receive blood transfusions that are Kell antigen positive.

## Evaluation of Relatives at Risk

**For early diagnosis and treatment.** It is appropriate to evaluate apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of antimicrobial prophylaxis and other treatment. Evaluations include the following:

- Molecular genetic testing if the CGD-related pathogenic variant(s) in the family are known
- Routine dihydrorhodamine (DHR) testing of peripheral blood, which will detect the CGD disease state (except for *NCF4*-related CGD), if the pathogenic variant(s) in the family are not known

**For hematopoietic stem cell donation.** Any relative who is a potential hematopoietic stem cell donor should undergo HLA testing to determine if they are a potential match to their relative with CGD. If the relative is a suitable donor, they should undergo DHR testing and/or familial pathogenic variant testing to ensure they are not affected by CGD or heterozygous for X-linked CGD. A heterozygous female relative with a pathogenic variant in *CYBB* who is a matched donor to a relative with CGD is less acceptable as an HSCT donor compared to an alternative matched related donor or a matched unrelated donor. If there is no other suitable donor, heterozygous females may be considered as donors [Lankester et al 2021].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

The major concern during the pregnancy of a woman known to have CGD is continued use of prophylactic antimicrobials:

- **Trimethoprim**, a folic acid antagonist, is usually avoided in pregnancy.
- **Sulfamethoxazole** is not known to increase the risk of birth defects in humans; however, it is typically administered in conjunction with trimethoprim for prophylaxis in affected non-pregnant women.
- Data regarding teratogenicity of **itraconazole** are limited. Although case reports of birth defects in infants born to women taking itraconazole during pregnancy have been published, this observation is not supported by larger case series. Given the lack of adequate data on the use of itraconazole during pregnancy, some practitioners suggest that it should be avoided during pregnancy until such data become available.

The authors' practice for women with CGD who are or are planning to become pregnant is to use antibacterial prophylaxis (e.g., penicillin- or cephalosporin-based therapies) for which more data on safety during pregnancy exist [Author, personal communication]. Although no antifungal prophylactic medications known to be completely safe during pregnancy are currently available, the risks and benefits of antifungal treatment must be weighed case by case. Interferon gamma is held during pregnancy and restarted after breastfeeding has ceased.

See [MotherToBaby](#) for further information on medication use during pregnancy.

## Therapies Under Investigation

**Gene therapy.** Gene addition therapy using a lentiviral vector to insert a functional copy of *CYBB* into hematopoietic stem cells is currently under investigation ([NCT02234934](#) and [NCT01855685](#)) as a one-time curative therapy for individuals with X-linked CGD [Kohn et al 2020].

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Chronic granulomatous disease (CGD) associated with a pathogenic variant in *CYBB* is inherited in an X-linked manner.

CGD associated with biallelic pathogenic variants in *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4* is inherited in an autosomal recessive manner.

Note: The mode of inheritance cannot be confirmed in a family unless the CGD-causing pathogenic variant(s) have been identified in an affected family member. Dihydrorhodamine (DHR) testing can suggest X-linked inheritance or autosomal recessive inheritance, but DHR results are not definitive in establishing a molecular cause or mode of inheritance.

## X-Linked Inheritance – Risk to Family Members

### Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *CYBB* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is presumed to be heterozygous for a *CYBB* pathogenic variant. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant identified in the proband cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be heterozygous, the affected male may have a *de novo* pathogenic variant (in which case the mother is not heterozygous), or the mother may have somatic/germline mosaicism.
- DHR testing of the mother is recommended to confirm her status, assess her risk of inflammatory or infectious conditions (see X-Linked CGD: Heterozygous Females), and facilitate reliable recurrence risk assessment. Genetic testing can also be performed to confirm that the mother is heterozygous for the same *CYBB* pathogenic variant as the proband.

### Parents of a female proband

- A female proband may have the disorder as the result of a *de novo* pathogenic variant [Gono et al 2008] or a *CYBB* pathogenic variant inherited from a parent [Lewis et al 2008]. Alternatively, a female proband may have somatic mosaicism for a *CYBB* pathogenic variant [Wolach et al 2005].
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *CYBB* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygotes. Heterozygous females are typically not affected with CGD but are at substantial risk for inflammatory conditions (see X-Linked CGD: Heterozygous Females).
- If the proband represents a simplex case and if the *CYBB* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of the mother, the risk to sibs is still greater than that of the general population because of the possibility of maternal germline mosaicism [Gono et al 2008].

**Sibs of a female proband.** The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has a *CYBB* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
- If the father of the proband has a *CYBB* pathogenic variant, he will transmit it to all his daughters and none of his sons.

- If the proband represents a simplex case and if the *CYBB* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is still greater than that of the general population because of the possibility of parental germline mosaicism.

**Offspring of a male proband.** Affected males transmit the *CYBB* pathogenic variant to all of their daughters none of their sons.

**Offspring of a female proband.** Women with a *CYBB* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *CYBB* pathogenic variant, the parent's family members may be at risk.

**Heterozygote detection.** Molecular genetic testing of at-risk female relatives requires prior identification of the *CYBB* pathogenic variant in an affected family member (see Note).

Although females who are heterozygous for X-linked CGD are typically not affected with CGD (see X-Linked CGD: Heterozygous Females), careful longitudinal evaluation of heterozygous females is recommended in order to prevent or treat inflammatory or infectious conditions if they occur, as well as to provide genetic counseling.

Note: Women who are heterozygous for X-linked CGD have circulating populations of oxidase-positive and oxidase-negative phagocytes, which can be resolved by DHR testing if the family-specific pathogenic variant has not been identified. (Note: Nitroblue tetrazolium testing is not reliable for heterozygote detection because it may be falsely interpreted as normal in females who are heterozygous for X-linked CGD).

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of a child with autosomal recessive CGD (AR-CGD) are typically heterozygous for a *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a CGD-causing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].  
Note: Because *NCF1* is flanked by two pseudogenes, *de novo* pathogenic variants can result from gene conversion during meiosis. Such pathogenic variants occur with a low but finite frequency in the general population [Brunson et al 2010] and may explain the rare occurrence of pseudodominant inheritance of CGD caused by *NCF1* pathogenic variants.
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

### Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive CGD-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.

- Heterozygotes (carriers) are usually asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with AR-CGD are obligate heterozygotes (carriers) for a pathogenic variant in *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4*.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent is heterozygous for a *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4* pathogenic variant, each sib of the proband's parents is at a 50% risk of being a carrier of the familial pathogenic variant.

**Carrier detection.** Molecular genetic carrier testing for at-risk relatives requires prior identification of the *CYBA*, *CYBC1*, *NCF1*, *NCF2*, or *NCF4* pathogenic variants in the family.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.
- Prior to pregnancy, affected women should be advised about changes in antimicrobial prophylaxis (see Pregnancy Management).

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the CGD-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing (PGT) are possible.

**Percutaneous umbilical blood sampling (PUBS).** If the familial pathogenic variant(s) are not known, prenatal diagnosis can be made by analysis of neutrophil oxidase production from umbilical vein samples obtained via PUBS from a fetus at 18-20 weeks gestation. However, this procedure is performed well into the second trimester and is associated with substantial risk [Newburger et al 1979, Ayatollahi & Geramizadeh 2006, Kulkarni et al 2017].

PGT has also been used to identify female HLA-matched sibs of a male with X-linked CGD. After successful in vitro fertilization, embryo transfer, and pregnancy outcome, the female sib served as a hematopoietic stem cell donor for the affected child [Reichenbach et al 2008].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.



## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **CGD Association of America**  
[www.cgdaa.org](http://www.cgdaa.org)
- **Chronic Granulomatous Disorder Society**  
United Kingdom  
**Phone:** 0800 987 8988  
**Email:** [hello@cgdsociety.org](mailto:hello@cgdsociety.org)  
[www.cgdsociety.org](http://www.cgdsociety.org)
- **ImmUnity Canada**  
Canada  
**Phone:** 250-381-7134; 877 -607-2476  
**Email:** [info@immunitycanada.org](mailto:info@immunitycanada.org)  
[immunitycanada.org](http://immunitycanada.org)
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**  
United Kingdom  
**Phone:** +44 01503 250 668  
**Fax:** +44 01503 250 668  
**Email:** [info@ipopi.org](mailto:info@ipopi.org)  
[ipopi.org](http://ipopi.org)
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**  
**Email:** [info@jmfworld.org](mailto:info@jmfworld.org)  
[info4pi.org](http://info4pi.org)
- **European Society for Immunodeficiencies (ESID) Registry**  
**Email:** [esid-registry@uniklinik-freiburg.de](mailto:esid-registry@uniklinik-freiburg.de)  
ESID Registry
- **United States Immunodeficiency Network (USIDNET) Registry**  
**Email:** [contact@usidnet.org](mailto:contact@usidnet.org)  
Enrolling Institutions

## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** Chronic Granulomatous Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CYBA	16q24.2	Cytochrome b-245 light chain	CYBA database CYBAbase: Mutation registry for autosomal recessive chronic granulomatous disease (CGD), deficiency of p22phox	CYBA	CYBA

Table A. continued from previous page.

<i>CYBB</i>	Xp21.1-p11.4	Cytochrome b-245 heavy chain	CYBB database CYBBbase: Mutation registry for X-linked chronic granulomatous disease (previously known as X-CDGbase)	CYBB	CYBB
<i>CYBC1</i>	17q25.3	Cytochrome b-245 chaperone 1		CYBC1	CYBC1
<i>NCF1</i>	7q11.23	Neutrophil cytosol factor 1	NCF1 database NCF1base: Mutation registry for autosomal recessive chronic granulomatous disease (CGD), deficiency of p47 <sup>phox</sup>	NCF1	NCF1
<i>NCF2</i>	1q25.3	Neutrophil cytosol factor 2	NCF2 database NCF2base: Mutation registry for autosomal recessive chronic granulomatous disease (CGD), deficiency of p67 <sup>phox</sup>	NCF2	NCF2
<i>NCF4</i>	22q12.3	Neutrophil cytosol factor 4		NCF4	NCF4

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Chronic Granulomatous Disease ([View All in OMIM](#))

233690	GRANULOMATOUS DISEASE, CHRONIC, AUTOSOMAL RECESSIVE, 4; CGD4
233700	GRANULOMATOUS DISEASE, CHRONIC, AUTOSOMAL RECESSIVE, 1; CGD1
233710	GRANULOMATOUS DISEASE, CHRONIC, AUTOSOMAL RECESSIVE, 2; CGD2
300481	CYTOCHROME b(-245), BETA SUBUNIT; CYBB
306400	GRANULOMATOUS DISEASE, CHRONIC, X-LINKED; CGDX
601488	NEUTROPHIL CYTOSOLIC FACTOR 4; NCF4
608508	CYTOCHROME b(-245), ALPHA SUBUNIT; CYBA
608512	NEUTROPHIL CYTOSOLIC FACTOR 1; NCF1
608515	NEUTROPHIL CYTOSOLIC FACTOR 2; NCF2
613960	GRANULOMATOUS DISEASE, CHRONIC, AUTOSOMAL RECESSIVE, 3; CGD3
618334	CYTOCHROME b(-254) CHAPERONE 1; CYBC1
618935	GRANULOMATOUS DISEASE, CHRONIC, AUTOSOMAL RECESSIVE, 5; CGD5

## Molecular Pathogenesis

Chronic granulomatous disease is a single phenotype caused by pathogenic variant(s) in one of six genes that encode proteins of NADPH oxidase. The genes and the official names of their protein products are listed in Table A. However, the protein components are generally known by the names of gp91<sup>phox</sup> (encoded by *CYBB*) and p22<sup>phox</sup> (*CYBA*), which are membrane bound; EROS (*CYBC1*), which is required for gp91<sup>phox</sup> and p22<sup>phox</sup> assembly; and p47<sup>phox</sup> (*NCF1*), p67<sup>phox</sup> (*NCF2*), and p40<sup>phox</sup> (*NCF4*), which are cytoplasmic.

**Mechanism of disease causation.** Pathogenic variants in any one of the six genes that encode the proteins of the NADPH oxidase lead to absent or significantly reduced production of their respective encoded proteins. The reduction in the protein component of the NADPH oxidase causes an inability to produce intracellular reactive

oxygen species. This loss in NADPH function allows for select microbes to evade host defense and cause infection.

**Gene-specific laboratory technical considerations.** The most common *NCF1* pathogenic variants deserve special mention as they are due to gene conversions and occur with highly homologous flanking pseudogenes at the *NCF1* locus. These are very difficult to discern in exome and genome studies and may require immunoblotting or gene copy number analysis in conjunction with dihydrorhodamine testing for firm diagnosis [Kuhns et al 2019].

## Chapter Notes

### Revision History

- 21 April 2022 (ha) Comprehensive update posted live
- 11 February 2016 (ha) Comprehensive update posted live
- 9 August 2012 (me) Review posted live
- 7 November 2011 (jl) Original submission

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