

CYBB *ProGenotyper*[®] Test

Test Name: CYBB *ProGenotyper*[®] Test

Alternative Names: Cytochrome b-245, Beta Polypeptide; CGD; X-CGD; Chronic Granulomatous Disease; GP91-PHOX, and NOX2

Test Code: 30029

CPT Code: 83890, 83891 x 13, 83898 x 13, 83904 x 26, 83912

Clinical Utility: Chronic granulomatous disease is a genetically heterogeneous immunodeficiency disorder resulting from an inability of phagocytes to kill microbes that they have ingested. The disorder presents most often with pneumonia, infectious dermatitis, osteomyelitis, and recurrent or severe abscess formation beneath the skin and in the organs of the mononuclear phagocyte system. The impairment in microbial killing is caused by defects in the NADPH oxidase enzyme complex which generates the microbicidal respiratory burst. Pneumonia or sepsis due to *Aspergillus* or *Burkholderia cepacia* infection are the most common causes of death in CGD patients.

Background: In chronic granulomatous disease, about 65-75% of cases are due to mutation in the X-linked CYBB gene (cytochrome b-245, beta polypeptide), coding for the gp91 (phox) catalytic subunit of NADPH oxidase (cytochrome b558). The phagocytes in these patients lack NADPH oxidase activity. The detection of mutations (insertions/deletions, nonsense or missense mutations, or splice-site mutations) in this gene can assist in the diagnosis of chronic granulomatous disease in the patient, as well as detection of carrier status in female relatives and for prenatal diagnosis. *De novo* mutations occur in about 10% of these cases. A wide spectrum of mutations has been described in CYBB, with no predominant genotype. More than 350 mutations in CYBB are known and all are unique to individual families. These changes can be present in any of the exons.

Frequency: 1: 200,000-250,000 live births in USA.

Physical Manifestations:

- Liver abscess; common first presentation (especially with *Staphylococcus aureus*)
- Infections with catalase-positive organisms, especially deep seated abscesses, osteomyelitis, and chronic granulomata
- Mucous membrane infections, conjunctivitis, rhinitis, stomatitis, chronic or recurrent pneumonias, chronic cough, osteomyelitis
- Skin manifestations: eczematoid dermatitis, impetigo, recurrent skin furunculosis, subcutaneous abscesses
- Early manifestations: chronic and recurrent pyogenic infections during first 2 years of life, lymphadenopathy, recurrent enlargement of lymph nodes of neck.
- Later manifestations: gastrointestinal symptoms: hepatomegaly/hepatosplenomegaly, esophageal outlet, pyloric, and/or urethral obstruction, persistent diarrhea-granulomatous colitis, perianal abscesses or rectal fistulous tracts

Related Tests: *Neutrophil Oxidative Burst Test* (403002)

Specimen Requirements:

- 2mL whole blood (EDTA)
- Ship **overnight** at ambient temperature

Units and Normal Reference Range:

All 13 exons and intron/exon boundaries in CYBB are sequenced and compared to reference sequence NG_009065.1. Results are reported as no mutation detected, heterozygous (HET) mutation (carriers), homozygous (HOMO) mutation, or unknown (UKN) mutation. A mutation that has not previously been reported in the literature is considered unknown.

Method:

1. Patient DNA is extracted from whole blood.
2. Regions of the CYBB gene are amplified by PCR from the genomic DNA and the products of each fragment are purified.
3. Cycle sequencing is performed with one or two sequencing primers per CYBB fragment.
4. These products are purified and run on the ABI3130 or 3730 Genetic Analyzer.
5. The resulting sequence is compared to the reference sequence.

References:

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7. Rae J, Newburger PE, Dinauer MC et al. 1998. X-Linked chronic granulomatous disease: mutations in the CYBB gene encoding the gp91-phox component of respiratory-burst oxidase. *Am J Hum Genet*. 62(6):1320-31.
8. Winkelstein JA, Marino MC, Johnston RB, Jr., et al. 2000. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)* 79:155-69.

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