

The University of Chicago Genetic Services Laboratories



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CHD7 analysis for CHARGE Syndrome

CHARGE syndrome:

Coloboma
Heart defect
Atresia of the choanae
Retardation of growth and development
Genital and urinary anomalies
Ear anomalies and deafness

Clinical Features:

The above acronym was given to this syndrome for its cardinal clinical features. Blake et al (1998) suggested the following criteria, which are more widely accepted. Clinical diagnosis of CHARGE syndrome requires **4 major signs** or **3 major signs along with 3 minor signs** [1]:

Major signs:

Coloboma
Choanal atresia
Characteristic ear abnormalities
Cranial nerve dysfunction

Minor signs:

Genital hypoplasia
Developmental delay
Orofacial cleft
Growth deficiency
Cardiovascular malformations
Tracheoesophageal fistula
Distinctive facial features

Many other features have been seen in patients with the clinical diagnosis of CHARGE syndrome. These include: semicircular canal defects, thymic/parathyroid hypoplasia, facial palsy, swallowing difficulties, characteristic hands, spine abnormalities, omphalocele, and renal anomalies. Patients with CHARGE syndrome have variable expression and presentation of these features.

Inheritance:

CHARGE syndrome is an autosomal dominant condition that occurs in 1 in 12,000 live births. Most cases appear to be *de novo*. Recurrence risk for unaffected parents of an isolated case is 1-2%. However, due to the variability in expression, parents of affected individuals may be carriers. Recurrence risk for affected individuals and carrier parents is 50%.

Molecular Genetics:

Microdeletions, identifiable by FISH analysis, and mutations of the *CHD7* gene have recently been identified in patients with CHARGE syndrome [2]. In this study, 10 of 17 affected individuals without microdeletions were found to have heterozygous mutations in *CHD7*. This gene is a member of the chromodomain helicase DNA-binding (CHD) genes. These proteins are thought to play pivotal roles in early embryonic development and *CHD7* is ubiquitously expressed in several fetal and adult tissues, including those affected in CHARGE syndrome [2]. *CHD7* has 38 exons and is 188kb. Several different mutations have been identified in the *CHD7* gene including nonsense mutations, missense mutations and splicing mutations. No phenotypic difference has been reported between mutation or deletion patients. Detectable mutations or deletions in the *CHD7* gene account for approximately 65% of patients with CHARGE syndrome. Up to 10% of patients are found to have a microdeletion [2], while approximately 53-65% are found to have a heterozygous mutation in *CHD7* [2,3].

Additional Resources:

The CHARGE Syndrome Foundation Marion Norbury: (Executive Director)

Email: marion@chargesyndrome.org

www.chargesyndrome.org

Test methods:

We offer deletion analysis by FISH for *CHD7* and mutation analysis of all 38 exons and intron/exon boundaries by full gene sequencing. Sample submission paperwork and instructions are included with this packet.

Please, send a completed CHARGE Clinical Questionnaire with each sample.

Deletion analysis (FISH)

Sample specifications: 3 to10 cc of blood in a green top (sodium heparin) tube
Cost: \$325
CPT codes: 88230, 88271, 88291, 88273
Turn-around time: 10-12 days

Mutation analysis (sequencing)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$2400
CPT codes: 83891, 83898 x 9, 83904 x 9, 83912
Turn-around time: 10 weeks

Note: We cannot bill insurance for CHD7 sequencing.

Testing for a known mutation in additional family members

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$390
CPT codes: 83891, 83898 x 2, 83894, 83912
Turn-around time: 3-4 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost: \$590
CPT codes: 83891, 83898 x 2, 83894, 83912, 99051
Turn-around time: 1-2 weeks

Results:

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

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ABMG Certified Molecular Geneticist

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References:

1. Blake et al., CHARGE Association: An Update and Review for the Primary Pediatrician (1998) *Clinical Pediatrics*, 37: 159-174.
2. Vissers et al., Mutations in a new member of the chromodomain gene family cause CHARGE syndrome (2004) *Nature Genetics*, 36: 955-57.
3. Jongmans M, et al., CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene (2005) *J Med Genet*. Oct 14 [Epub]

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