THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

CHARGE Syndrome: Mutation Analysis of *CHD7*

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:

Comprehensive sequence coverage of the coding regions and splice junctions of the *CHD7* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

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

CHD7 mutation analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
	81407
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Blake KD, Davenport SL, Hall BD et al. CHARGE association: an update and review for the primary pediatrician. Clin Pediatr (Phila) 1998: 37: 159-173.
2. Vissers LE, van Ravenswaaij CM, Admiraal R et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 2004: 36: 955-957.
3. Jongmans MC, Admiraal RJ, van der Donk KP et al. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. J Med Genet 2006: 43: 306-314.

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