

CHD7 Gene Analysis in CHARGE Syndrome

Disorder also known as:

Coloboma, Heart Anomaly, Choanal Atresia, Retardation, Genital and Ear Anomalies.

Clinical Features:

CHARGE syndrome refers to a specific set of birth defects, including coloboma of the eye, heart defects, choanal atresia, mental and growth retardation and ear anomalies or hearing loss. Congenital anomalies, which when seen together are quite specific to CHARGE syndrome, include coloboma of the iris, retina, choroid and/or optic disc with or without microphthalmos; choanal atresia or stenosis; and hypoplastic semi-circular canals. Cranial nerve dysfunction is a minor sign and includes anosmia, neurosensory deafness, facial palsy and swallowing difficulties. Ear abnormalities involving the helices, middle ear and inner ear are very common and were seen in 90% of affected individuals in one study.¹ Affected patients may also have genital abnormalities (hypogonadotropic hypogonadism), pre- and post-natal growth deficiency, hypotonia, and characteristic hands (broad palms with “hockey-stick” palmar crease, short fingers and small/unusual thumbs). The characteristic facial appearance includes square face with broad prominent forehead, arched eyebrows, large eyes with or without ptosis, prominent nasal bridge and columella, flat midface, small mouth and facial asymmetry. CHARGE syndrome encompasses additional nonspecific features such as mental retardation, skeletal abnormalities, hypodontia, orofacial clefting, tracheoesophageal fistula, and urinary tract and renal anomalies.

Inheritance Pattern/Genetics:

Autosomal dominant

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively.

Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

In addition, prenatal analysis of the entire CHD7 gene is also available for fetal specimens, when fetal ultrasound abnormalities are suggestive of CHARGE syndrome.

Test Sensitivity:

Sequence analysis of the CHD7 coding region detects variants in approximately 60%-65% of individuals diagnosed with CHARGE syndrome on the basis of clinical features.²⁻⁴ Gross deletions in the CHD7 gene are rare, but have been identified. The sensitivity of CHD7 analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown.

Published variants in CHD7 are distributed throughout the gene. Loss-of-function variants, including frameshift, nonsense, and splice-site variants are common. The majority of variants have arisen de novo, although parent-to-child transmissions as well as germline mosaicism have been reported. The empiric recurrence risk for gonadal mosaicism is 1-2%. Advanced paternal age has been associated with sporadic cases of CHARGE syndrome.

References:

1. Stromland et al., (2005) *Am J Med Genet* 133A:331-339.
2. Vissers et al., (2004) *Nat Genet* 36:955-957.
3. Jongmans et al., (2006) *J Med Genet* 43:306-314.
4. Lalani et al., (2006) *Am J Hum Genet* 78:303-314.
5. <https://www.ncbi.nlm.nih.gov/pubmed/27061523>