

Test Specific Guidelines

CHARGE Syndrome Genetic Testing

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Introduction

CHARGE syndrome genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

<u>Procedure addressed by this guideline</u>	<u>Procedure code</u>
<u>CHD7 Deletion/Duplication Analysis</u>	<u>81479</u>
<u>CHD7 Known Familial Mutation Analysis</u>	<u>81403</u>
<u>CHD7 Sequencing</u>	<u>81407</u>

What Is CHARGE Syndrome?

Definition

CHARGE syndrome is a clinically variable syndrome involving multiple congenital anomalies of diverse organ systems.¹

Incidence

CHARGE syndrome occurs in approximately 1/10,000 newborns with an estimated range of 1/8,500 – 1/15,000.¹⁻³ The disorder is pan-ethnic.³

Symptoms

CHARGE was the acronym initially used to describe an association of eye colobomas, heart defects, choanal atresia, growth retardation, genital anomalies, and ear malformations.¹ As more individuals have been identified, additional symptoms have been added to this list and include cleft lip and/or palate, developmental delay, hearing loss, cranial nerve anomalies, vestibular defects, hypothyroidism, tracheoesophageal anomalies, brain anomalies, seizures, renal anomalies, and characteristic dysmorphic facial features.^{1,2} The clinical presentation is highly variable.^{2,3}

Inheritance

CHARGE syndrome is considered an autosomal dominant disorder. Although some cases of parent to child transmission have been reported, most cases of CHARGE syndrome are simplex (the only case in the family) and CHD7 mutations, if identified, are de novo.^{1,2}

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

If neither parent is affected, there is a 1-2% risk of recurrence, mostly likely due to germline mosaicism.²

Cause

CHARGE syndrome is caused by mutations in the CHD7 gene. This gene plays a role in guidance of neural crest cell migration.⁴ Sequencing the CHD7 gene will find a causative mutation in over 90% of individuals meeting clinical diagnostic criteria for typical presentations of CHARGE syndrome and 60-70% of all individuals with suspected CHARGE syndrome.¹⁻³ Approximately 5% of mutations identified in CHD7 are whole or partial gene deletions.^{2,3}

Diagnosis

Two common sets of clinical diagnostic criteria for CHARGE syndrome have been described.¹ The Blake criteria (first published in 1998 and updated in 2009) set out major and minor diagnostic criteria to be used in diagnosing typical CHARGE syndrome.^{5,6} The Verloes criteria provide a means of diagnosing typical CHARGE syndrome as well as minor presentations termed partial CHARGE and atypical CHARGE.⁷ (See Table) Verloes also includes criteria for partial CHARGE (criteria: 2 major and 1 minor) and atypical CHARGE (criteria: 2 major and 0 minor or 1 major and 3 minor).⁷

Clinical Diagnostic Criteria for Typical CHARGE Syndrome (Adapted from Bergman Et al. 2011)¹

<u>Criteria Set</u>	<u>Major Criteria</u>	<u>Minor Criteria</u>
<u>Blake^{5,6}</u> <u>(4 Major or 3 Major and 3 Minor)</u>	<u>Coloboma or microphthalmia</u>	<u>Cardiac defect</u>
	<u>Choanal atresia or stenosis</u>	<u>Tracheo-esophageal defects</u>

Criteria Set	Major Criteria	Minor Criteria
	<u>External ear anomaly/ middle ear malformation/ mixed sensorineural deafness</u>	<u>Genital hypoplasia or delayed puberty</u>
		<u>Cleft lip and/or palate</u>
	<u>Cranial nerve dysfunction</u>	<u>Developmental delay</u>
		<u>Growth retardation</u>
<u>Verloes⁷</u> <u>(3 major or 2 Major and 2 Minor)</u>	<u>Ocular coloboma</u>	<u>Cardiac or esophageal malformation</u>
	<u>Choanal atresia</u>	<u>Malformation of the middle or external ear</u>
	<u>Hypoplastic semicircular canals of the inner ear</u>	<u>Rhombencephalic dysfunction including sensorineural deafness</u>
		<u>Hypothalamo- hypophyseal dysfunction (gonadotropin or growth hormone deficiency)</u>
		<u>Mental retardation</u>

Management

Treatment of CHARGE syndrome is based on the variable clinical manifestations. Airway management and cardiac assessment are essential in the newborn period, as is addressing feeding difficulties.² Other recommended evaluation and surveillance include the following:²

- Ophthalmologic assessment
- Audiologic assessment
- Endocrine evaluation if puberty is delayed
- Imaging to assess middle and inner ear defects
- Cranial nerve assessment / swallowing studies
- Gastrointestinal assessment for esophageal atresia or trachea-esophageal fistula
- Renal ultrasound

Survival

“Life expectancy highly depends on the severity of manifestations; mortality can be high in the first few years when severe birth defects (particularly complex heart defects) are present and often complicated by airway and feeding issues. In childhood, adolescence, and adulthood, decreased life expectancy is likely related to a combination of residual heart defects, infections, aspiration or choking, respiratory issues including obstructive and central apnea, and possibly seizures. Despite these complications, the life expectancy for many individuals can be normal.”²

Test Information

Introduction

Testing for CHARGE syndrome may include known familial mutation analysis, next generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidences

Introduction

The following section includes relevant guidelines and evidence pertaining to CHARGE syndrome testing.

Selected Relevant Publications

van Ravenswaaij-Arts et al., 2020

An expert authored review updated in 2020 stated:²

- **"With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of heterozygous CHD7 pathogenic variants has broadened to encompass CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype ."**
- **"CHD7 disorder, refers to the entire phenotypic spectrum that can be associated with heterozygous CHD7 pathogenic variants and emphasizes both the need to evaluate an individual found to have a CHD7 pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and the importance of counseling families that the finding of a CHD7 pathogenic variant is not equivalent to a diagnosis of CHARGE syndrome."**
- **"The diagnosis of CHD7 disorder is established in a proband with suggestive clinical and imaging findings and a heterozygous pathogenic variant in or deletion of CHD7 identified by molecular genetic testing."**
- **"Sequence analysis of CHD7 is performed to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications and/or chromosomal microarray (CMA) to detect whole-gene deletions."**
- **"Because CHD7 disorder typically includes multiple congenital anomalies, it is also reasonable to pursue chromosomal microarray testing first, unless classic features of CHD7 disorder (e.g., the CHARGE syndrome phenotype) are apparent."**
- **"Management of the manifestations of CHD7 disorder can be complex and require a multidisciplinary approach involving clinicians, therapists, and educators ."**

- “Requires routine follow up of manifestations identified in infancy/childhood, as well as ongoing monitoring of growth, development, educational progress, behavior, and possible endocrine issues.”
- “Because of the increased risk of post-anesthesia airway complications, procedures requiring anesthesia should be minimized and combined whenever possible.”

van Ravenswaaij-Arts and Martin, 2017

In a review of the etiology and diagnosis of CHARGE syndrome, van Ravenswaaij-Arts and Martin stated:⁸

- “In clinically typical individuals with CHARGE syndrome, the tests of first choice are CHD7 Sanger sequencing and chromosomal microarray to screen for deletions and/or MLPA to test for exonic-deletions.”
- “CHD7 pathogenic variants have been described in very mildly affected individuals, for example, individuals with isolated hypogonadotropic hypogonadism [HH] due to CHD7 missense variants.”
- “It is recommended that individuals with HH and a CHD7 variant be clinically screened for CHARGE syndrome features such as balance problems and deafness, amongst [sic] others.”
- “One to two percent of individuals who test positive have an intragenic or whole CHD7 gene deletion that can be detected by microarray analysis, although for small exonic deletions, MLPA is preferred.”
- “Most individuals with CHARGE syndrome are sporadic, but recurrence has been documented (Jongmans et al., 2008). Parent-child transmission with a recurrence risk of 50% is predominantly seen in milder presentations of the syndrome, although intrafamilial variability is high and a mildly affected parent does not exclude a more severely affected child. If the pathogenic CHD7 variant of a proband cannot be detected in the parents, there remains a 2% recurrence risk due to germline mosaicism.”

Hefner and Fassi, 2017

In a review of genetic counseling issues in CHARGE syndrome (abbreviated CS in this publication), Hefner and Fassi stated:⁹

- “[Genetic counseling] is particularly important in CS, as it is extremely complex and variable in its presentation and in its natural history.”
- “Despite the identification of pathogenic CHD7 variants in the majority of cases, the diagnosis of CS remains clinical...with genetic testing being particularly helpful in borderline clinical cases.”

- “As CS can affect any organ system in the body, the features overlap with countless other syndromes. The top candidates in the differential diagnosis of CS are 22q11.2 deletion syndrome (22q) and Kabuki syndrome (KS). VACTERL association also has a good deal of overlap, but typically does not have significant dysmorphic features.”
- “CMA is often performed initially for fetuses or infants with multiple anomalies. This is reasonable as 22q is far more common than CS and CMA can identify other rare microdeletions or microduplications with overlapping features.”
- “If CMA is nondiagnostic, CHD7 genetic testing (sequencing and deletion/duplication analysis) is recommended in the presence of any major feature of CS with multiple anomalies. If CHD7 analysis is nondiagnostic, whole exome sequencing (WES) may be considered.”
- “Every individual with CS has his or her own unique set of medical and developmental issues. Medical management of CS involves comprehensive monitoring of multiple organ systems by a multitude of specialists.”
- “Appropriate therapies will involve not only traditional therapies (occupational, physical, speech, and language therapies, etc) but require the expertise of DB [deafblind] specialists. DB specialists are professionals expert in the unique needs of children with multiple sensory impairments.”
- Genetic counseling should include information on prognosis including mortality, morbidity, and sensory, motor and intellectual expectations.

Bergman et al., 2011

In addressing molecular testing for CHARGE syndrome, Bergman and colleagues suggested that CHD7 testing, including sequencing and deletion analysis, should be considered in individuals with:¹

- 3 cardinal features
- 2 cardinal features and 1 supportive feature
- 2 cardinal features if imaging shows semicircular canal abnormalities
- 1 cardinal feature and 1 supportive feature if imaging shows semicircular canal abnormalities

Criteria

Introduction

Requests for CHARGE syndrome testing are reviewed using the following

criteria.**CHD7 Known Familial Mutation Analysis**

- **Genetic Counseling**
 - **Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing**
 - **No previous genetic testing of CHD7 that would detect the familial mutation, AND**
- **Diagnostic Testing for Symptomatic Individuals**
 - **Known family mutation in CHD7 in 1st degree biologic relative, OR**
- **Prenatal Testing for At Risk Pregnancies**
 - **CHD7 mutation identified in a previous child or either parent, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

CHD7 Sequencing

- **Genetic Counseling**
 - **Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing**
 - **No previous CHD7 sequencing, and**
 - **No known CHD7 mutation in the family, and**
 - **Chromosomal microarray, if performed, was negative, AND**
- **Diagnostic Testing for Symptomatic Individuals**
 - **The member is suspected to have CHARGE syndrome, but the diagnosis is in question because member meets only one of the following using the Blake or Verloes criteria:⁵⁻⁷**
 - **2 major criteria and 1 minor criterion, or**
 - **2 major criteria and 0 minor criteria, or**
 - **1 major criterion and 3 minor criteria, AND**
- **Molecular test results will impact medical management, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy.**

CHD7 Deletion/Duplication Analysis

- Genetic Counseling
 - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
 - No previous CHD7 deletion/duplication testing, and
 - Previous CHD7 sequencing was performed and was negative, and
 - No known CHD7 mutation in the family, and
- Diagnostic Testing for Symptomatic Individuals
 - The member meets the above criteria for CHD7 sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

This guideline cites the following references.

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2. van Ravenswaaij-Arts CM, Hefner M, Blake K, et al. CHD7 Disorder. 2006 Oct 2 [Updated 2020 Sep 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1117/>
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5. Blake KD, Davenport SL, Hall BD, et al. CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila).* 1998;37(3):159-173.

6. Amiel J, Attiee-Bitach T, Marianowski R, et al. Temporal bone anomaly proposed as a major criteria for diagnosis of CHARGE syndrome. *Am J Med Genet.* 2001;99:124–127.
7. Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A.* 2005;133A(3):306-308.
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