CHARGE Syndrome Genetic Testing

Introduction

CHARGE syndrome genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD7 Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>CHD7 Sequencing</td>
<td>81407</td>
</tr>
<tr>
<td>CHD7 Deletion/Duplication Analysis</td>
<td>81479</td>
</tr>
</tbody>
</table>

What is CHARGE Syndrome

Definition

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

Incidence and Prevalence

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 patients have been identified, additional symptoms have been added to this list and include cleft lip and/or palate, developmental delay, hearing loss, cranial nerve dysfunction, and characteristic dysmorphic facial features.¹,² The clinical presentation is highly variable.³

Cause

CHARGE syndrome is caused by mutations in the CHD7 gene. This gene plays a role in guidance of neural crest cell migration.⁴ Approximately 90% of patients with typical CHARGE syndrome presentations have mutations in the CHD7 gene.¹,² Overall, 65-
70% of individuals with typical or atypical CHARGE syndrome will have CHD7 mutations.  

**Inheritance**

CHARGE syndrome is considered an autosomal dominant disorder, as single CHD7 mutations are considered causative. 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

If the parent of an affected child is also affected or has the same CHD7 mutation as the child, the recurrence risk is 50%. If neither parent is affected, there is a 1-2% risk of recurrence, mostly likely due to germline mosaicism.²

**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 2001) 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)*

<table>
<thead>
<tr>
<th>Criteria Set</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake⁵ ⁶</td>
<td>Coloboma or microphthalmia</td>
<td>Cardiac defect</td>
</tr>
<tr>
<td></td>
<td>Choanal atresia or stenosis</td>
<td>Genital hypoplasia or delayed puberty</td>
</tr>
<tr>
<td></td>
<td>External ear anomaly/ middle ear malformation/ mixed sensorineural deafness</td>
<td>Cleft lip and/or palate</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve dysfunction</td>
<td>Developmental delay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Characteristic facial features</td>
</tr>
<tr>
<td>Verloes⁷</td>
<td>Ocular coloboma</td>
<td>Cardiac or esophageal malformation</td>
</tr>
<tr>
<td></td>
<td>Choanal atresia</td>
<td>Malformation of the middle or external ear</td>
</tr>
</tbody>
</table>
### Criteria Set

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoplastic semicircular canals of the inner ear</td>
<td>Rhombencephalic dysfunction including sensorineural deafness</td>
</tr>
<tr>
<td></td>
<td>Hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency)</td>
</tr>
<tr>
<td></td>
<td>Mental retardation</td>
</tr>
</tbody>
</table>

### Treatment

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. Other recommended evaluation and surveillance include the following:

- 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

Survival is decreased in individuals with CHARGE syndrome who have:

- Cyanotic heart defects
- Bilateral choanal atresia
- Tracheoesophageal fistula
- Central nervous system malformations

### Test Information

#### Introduction

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

---

© 2020 eviCore healthcare. All Rights Reserved.
400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924
www.eviCore.com
CHD7 Sequence Analysis

- Sequence analysis looks for point mutations and small deletions or duplications (several nucleotides) across the entire coding region of the CHD7 gene.
- 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.\(^2,3\)

CHD7 Deletion/Duplication Analysis

- Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis
- These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes
- CHD7 gene deletions have been reported, but are considered rare.\(^2\)
  - Approximately 5% of mutations identified in CHD7 are whole or partial gene deletions.\(^2,3\)

CHD7 Known Familial Mutation Analysis

- Analysis for known familial mutations is typically performed by Sanger sequencing
- Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing
- Most cases of CHARGE syndrome are de novo; however, parent to child transmission has been reported.\(^1,2\)

Guidelines and Evidences

Introduction

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

Peer Reviewed Literature

van Ravenswaaij-Arts and Martin, 2017

In a review of the etiology and diagnosis of CHARGE syndrome, van Ravenswaaij-Arts and Martin state:\(^8\)

- “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.”
CHARGE Syndrome

- "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, among 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 state:

- "[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."

- "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.

**Lalani et al., 2012**

An expert authored review updated in 2012 states:²

- “The diagnosis of CHARGE syndrome is based on clinical findings and temporal bone imaging.”
- “Sequence analysis of the CHD7 coding region detects pathogenic variants in most individuals with typical CHARGE syndrome (i.e., having the four major characteristics or three major and three minor characteristics). Overall, CHD7 analysis in individuals with either typical CHARGE syndrome or a milder phenotype (i.e., fewer major characteristics) detects pathogenic variants in about 65%-70% of cases.”
- “Neonates require immediate evaluation of the airway, feeding, heart, and hearing.”
- “Special attention to potential airway problems associated with anesthesia.”
- “Regular ophthalmologic and audiologic evaluations; testing for hypogonadotropic hypogonadism if puberty has not occurred by age 13-14 years.”

**Bergman et al., 2011**

In addressing molecular testing for CHARGE syndrome, Bergman and colleagues suggest 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, 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.


