CHARGE Syndrome

CHARGE syndrome is a complex genetic syndrome with pattern of birth defects that are often life threatening. CHARGE is an acronym representing the major characteristics common to the disorder: coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities. Less common (minor) characteristics include kidney abnormalities; immune system problems; scoliosis or kyphosis; and limb abnormalities such as polydactyly or oligodactyly, clubfoot, and abnormalities of the long bones of the arms and legs. Affected individuals usually have more than one major characteristic or a combination of major and minor characteristics.

A clinical diagnosis of CHARGE syndrome is established or suspected based on the presence of at least two major and several minor characteristics. Due to clinical variability among patients, CHD7 testing is recommended to aid in diagnosis; however, a negative result does not exclude the diagnosis of CHARGE syndrome. The characteristics of this syndrome overlap with other disorders, including 22q11.2 deletion syndrome, Kabuki syndrome, and VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities).

Tests to Consider

CHARGE Syndrome, CHD7 Sequencing 2012609
Method: Polymerase Chain Reaction/Sequencing
Genetic testing to confirm a diagnosis of CHARGE syndrome

CHARGE Syndrome (CHD7) Sequencing, Fetal 2012717
Method: Polymerase Chain Reaction/Sequencing
Prenatal test for a fetus with ultrasound findings suggestive of CHARGE syndrome

Disease Overview

Incidence
~1/10,0001

Symptoms

CHARGE is an acronym for the major features of the condition:

- Coloboma
- Heart defects
- Choanal atresia
- Restricted growth and delayed development
- Genital abnormalities
- Ear anomalies

Diagnostic Criteria

Diagnosis is based primarily on clinical findings and temporal bone imaging.

Clinical criteria for CHARGE syndrome are four major characteristics, or three major and three minor characteristics.

Clinical criteria for possible/probable CHARGE syndrome are two major and several minor characteristics.
### Major Characteristics

- Ocular coloboma
- Choanal atresia or stenosis
- Cranial nerve dysfunction or anomaly
- Abnormalities of the inner, middle, or external ear characteristic of CHARGE syndrome

### Minor Characteristics

- Genital hypoplasia
- Developmental delay
- Cardiovascular malformation
- Growth deficiency
- Orofacial cleft
- Tracheoesophageal fistula
- Characteristic facial features

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### Genetics

**Gene**

*CHD7*

**Inheritance**

Autosomal dominant

- Usually de novo
- Rare parent-to-child transmission has been reported

**Penetrance**

100%; severity of the condition is highly variable

**Variants**

- Most variants are sequence variants
- Partial or full deletions of *CHD7* are rare

### Test Interpretation

**Sensitivity/Specificity**

- Clinical sensitivity:
  - ~90% in individuals or fetuses fulfilling clinical criteria for CHARGE syndrome
  - 65-70% for typical and suspected cases combined
- Analytical sensitivity/specificity: >99%

**Results**

- **Positive**
  - One copy of a pathogenic variant detected: confirms a diagnosis of CHARGE syndrome
- **Negative**
  - No pathogenic variant detected: likelihood of CHARGE syndrome is reduced, but not excluded
- **Inconclusive**
  - Variant of uncertain clinical significance detected; unclear if variant is benign or disease causing
Limitations

- Diagnostic errors can occur due to:
  - Rare sequence variants or repeat element insertions
  - Primer- or probe-site variants
- Not detected:
  - Large deletions and duplications
  - Deep intronic and regulatory region variants

References


