CHARGE Syndrome (*CHD7*)

Indications for Ordering

Confirms a clinical diagnosis or suspected diagnosis of CHARGE syndrome

Test Description

Bidirectional sequencing of entire coding region and intron/exon borders of the *CHD7* gene

Tests to Consider

CHARGE Syndrome, *CHD7* Sequencing 2012609
- Genetic testing to confirm a diagnosis of CHARGE syndrome

CHARGE Syndrome (*CHD7*) Sequencing, Fetal 2012717
- Prenatal test for a fetus with ultrasound findings suggestive of CHARGE syndrome

Disease Overview

Incidence – ~1/10,000

Symptoms
- CHARGE is an acronym for the major features of the condition
  - **C**oloboma
  - **H**eart defects
  - Choanal **a**tresia
  - **R**estricted growth and delayed development
  - **G**enital abnormalities
  - **E**ar anomalies
- Condition is highly variable

Diagnostic criteria
- Diagnosis is based primarily on clinical findings and temporal bone imaging
- Clinical criteria for CHARGE syndrome
  - Four major characteristics, or three major and three minor characteristics
- Clinical criteria for possible/probable CHARGE syndrome
  - 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

Genetics

Gene – *CHD7*

Inheritance – autosomal dominant

Penetrance – 100%, though severity of the condition is highly variable

De novo variants
- Almost always de novo
- Rare parent-to-child transmission has been reported

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
- 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 still possible

Limitations
- Diagnostic errors can occur due to
  - Rare sequence variations
  - Primer- or probe-site variants
- Not detected
  - Large deletions and duplications
  - Regulatory region variants
  - Deep intronic variants

References

- Bergman JE, Janssen N, et al. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. J Med Genet. 2011;48:334-342
- Janssen N, Bergman JE, et al. Mutation update on the CHD7 gene involved in CHARGE syndrome. Hum Mutat. 2012;33:1149-1160