Prenatal Testing for CHD7 Gene Variants: 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:
CHARGE syndrome is inherited in an autosomal dominant pattern.

Test Methods:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding region (exons 2-38) and the flanking splice sites of the CHD7 gene. For known variants, bi-directional sequencing of the relevant portion of the gene will be analyzed in duplicate. Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

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.[2-3] 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.

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 43:306-14.
4. Lalani et al (2006) Am J Hum Genet 78:303-14.