Prenatal Testing for SOX9 Gene Mutations: Campomelic Dysplasia

Disorder also known as: CD; campomelic dwarfism; campomelic syndrome with autosomal sex reversal; CMPS; acampomelic campomelic dysplasia; ACD

Clinical Features:
Newborns and Children: Campomelic dysplasia (CD) is a rare, often lethal skeletal dysplasia characterized by angular bowing and shortening of the long bones, severe respiratory distress, and XY sex reversal. It is caused by chromosome abnormalities or mutations affecting expression of the SOX9 gene located on chromosome 17q24.3-q25.1. Approximately 75% of patients with CD that have a 46,XY karyotype exhibit partial or complete sex reversal, ranging from ambiguous genitalia to normal female external genitalia.[1] In addition to bowing of the long bones, skeletal features of CD include club feet, a bell-shaped and underdeveloped thorax, eleven pairs of ribs, and hypoplastic scalpulae. CD is also associated with micrognathia and Pierre-Robin malformation. Many infants die shortly after birth from respiratory compromise. Children who survive the neonatal period often develop hearing loss, developmental delay, short stature and progressive kyphoscoliosis.[2] A small subgroup of patients with CD lack significant bowing of the limbs and are described as having acampomelic campomelic dysplasia (ACD). Patients with ACD have other characteristic features of campomelic dysplasia, and may exhibit mild campomelia on careful radiographic study.

Prenatal Ultrasound Findings: A 46,XY karyotype in a fetus with female or ambiguous genitalia on ultrasound accompanied by limb shortening and/or bowing is strongly suggestive of CD; however, CD should be considered in any fetus with shortening of the long bones with or without limb bowing. In the first and second trimester, 46,XX and 46,XY fetuses with CD may exhibit an increased nuchal translucency and/or cystic hygroma accompanied by shortening of the long bones of the lower extremities, with or without accompanying limb bowing.[3] Scapular hypoplasia is extremely difficult to detect in utero, and other characteristic facial features such as micrognathia may be difficult to identify by ultrasound in the first or second trimester of pregnancy. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial mutation can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Inheritance Pattern/Genetics:
Autosomal dominant, typically de novo. Germline and somatic mosaicism have been reported.[4-6]

Test Methods:

Using genomic DNA, analysis is performed by bi-directional sequencing of the coding region (exons 1-3) and the flanking splice sites of the SOX9 gene. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of the SOX9 gene. For known familial mutations, the relevant portion of the SOX9 gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination is performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

Test Sensitivity:

SOX9 is the only gene known to be associated with campomelic dysplasia. Of patients with a clinical diagnosis of CD or ACD that have a normal karyotype, an estimated 90-95% have mutations in the SOX9 gene that are identifiable by sequencing.[7] Additionally, an estimated 5% have deletions of the SOX9 gene that would be missed by sequencing but would be detected by ExonArrayDx. Of note, SOX9 mutations have not been identified in patients with isolated XY sex reversal in the absence of skeletal malformations.[8] The sensitivity of SOX9 testing in pregnancies with ultrasound anomalies suggestive of campomelic dysplasia is not currently known.

References:

1. Mansour et al., (1995) J Med Genet 32:415-420.
2. Mansour et al., (2002) J Med Genet 39:597-602;.
3. Massardier et al., (2008) Fetal Diagn Ther 24:452-457.
4. Wagner et al., (Cell) 79:1111-1120.
5. Cameron et al., (1996) Hum Mol Genet 5(10):1625-1630.
6. Smyk et al., (2007) Am J Med Genet 143A(8):866-870.
7. Pop et al., (2004) J Med Genet 41:e47.
8. Meyer et al., (1997) Hum Mol Genet 6(1):91-98.
9. Pop et al. (2005) Hum Genet 117:43-53.
10. Huang et al., (1999) Am J Med Genet 87:349 353.
11. Moog et al., (2001) Am J Med Genet 104:239-245.
12. Pfeifer et al., (1999) Am J Hum Genet 65(1):111-124.
13. Leipoldt et al., (2007) Clin Genet 71(1):67-75.
14. Schafer et al., (1996) Annals of the New York Academy of Sciences 785:137-149.