

Genetic testing of the SOX9 Gene in Campomelic Dysplasia

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

Clinical Features:

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 scapulae.

CD is also associated with distinctive facial features including micrognathia, midfacial hypoplasia, a long philtrum, depressed nasal bridge, hypertelorism, and Pierre Robin cleft palate. Macrocephaly, congenital heart defects, absence of the olfactory bulbs, renal malformations, and pancreatic abnormalities have also been reported. Many infants die shortly after birth from respiratory compromise due to cervical spine instability, laryngotracheomalacia, hypoplastic lungs, and/or narrow airways. 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 typical features of campomelic dysplasia, and in some cases radiographs may reveal mild campomelia.

Chromosome rearrangements and missense mutations in the DNA binding domain of SOX9 are typically associated with a less severe phenotype and a longer survival.^{11,2} In fact, patients with ACD and/or long-term survival are more likely to have a genomic rearrangement than to have a mutation within the SOX9 coding region.^{12,13} Only an estimated 10% of patients with ACD have a mutation within the SOX9 coding region detectable by sequencing.¹³ Conversely, 9 out of 15 (60%) patients reported with a chromosome abnormality affecting the SOX9 region had ACD. No other significant genotype-phenotype correlations have been established, and patients with identical mutations have been reported to be discordant for the presence or absence of sex reversal.^{14,7}

Inheritance Pattern/Genetics:

Autosomal dominant, predominantly due to de novo mutations. Germline and somatic mosaicism have been reported.³⁻⁵

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

For pregnancies with ultrasound anomalies suggestive of campomelic dysplasia, SOX9 sequencing and ExonArrayDx deletion/duplication testing are performed concurrently to facilitate the fastest turn-around-time with the highest sensitivity.

Test Sensitivity:

SOX9 is the only gene known to be associated with campomelic dysplasia. An estimated 5% of patients with CD have large deletions, translocations, or inversions that encompass SOX9 or have breakpoints surrounding the SOX9 locus on chromosome 17q. These genomic rearrangements are typically detectable on routine karyotype analysis or whole genome array CGH. 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.⁶ Additionally, an estimated 5% have deletions of the SOX9 gene that would be missed by sequencing but would be detected by ExonArrayDx or other methods of deletion analysis.⁶ The sensitivity of SOX9 testing in pregnancies with ultrasound anomalies suggestive of campomelic dysplasia is currently not 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. Wagner et al., (Cell) 79:1111-1120.

4. Cameron et al., (1996) Hum Mol Genet 5(10):1625-1630.
5. Smyk et al., (2007) Am J Med Genet 143A(8):866-870.
6. Pop et al., (2004) J Med Genet 41:e47.
7. Meyer et al., (1997) Hum Mol Genet 6(1):91-98;.
8. Pop et al. (2005) Hum Genet 117:43-53.
9. Huang et al., (1999) Am J Med Genet 87:349-353.
10. Refai et al., (2010) Am J Med Genet A 152A:422-426.
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.