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CLINICAL UTILITY GENE CARD

Clinical Utility Gene Card for: campomelic dysplasia

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Campomelic dysplasia (CD; campomelic dwarfism, campomelic syndrome, camptomelic dwarfism, camptomelic dysplasia. Includes acampomelic campomelic dysplasia (ACD))

1.2 OMIM# of the disease

114290.

1.3 Name of the analysed genes or DNA/chromosome segments

SOX9.

1.4 OMIM# of the gene(s)

608160.

1.5 Mutational spectrum

The majority of mutations are point mutations (missense, nonsense, splice site mutations), but also short insertions/deletions causing frameshifts.[1] Missense mutations cluster exclusively in the DNA-binding HMG domain,[1] but for two that have been found so far in the dimerization domain of SOX9.[2,3] Larger deletions covering SOX9[4,5] or located upstream of *SOX9*[5,6] have occasionally been described. A few percent of cases are due to inversions or translocations interrupting the 1-Mb regulatory domain of *SOX9*.[7–10] A single publication describes cases with brachydactyly and anonychia, a phenotype compatible with Cooks syndrome MIM 106995[11] due to microduplications of noncoding elements 5′ of *SOX9*. Missense mutations and translocations are overrepresented in CD cases without overt bending of the long bones (ACD).[10,12–14] Of note, individuals with translocation breakpoints or deletions located greater than 1 Mb upstream of *SOX9* only show isolated Pierre Robin sequence and none of the other clinical symptoms of CD/ACD.[15,16] Similarly, several duplications and a deletion of a region ~0.5 Mb upstream of *SOX9* have been reported, which only lead to isolated disorders of sexual development.[17–19]

1.6 Analytical methods

The main strategy for mutation screening consists in sequencing of the three *SOX9* exons and exon/intron boundaries, which allows for the detection of ~90% of mutations in CD/ACD cases. This may need to be followed by screening for large deletions by quantitative PCR or array CGH, and by cytogenetic analyses to detect translocations or larger inversions, which brings the detection rate to ~95%.

1.7 Analytical validation

The existence of a mutation is confirmed by sequencing a second, independent PCR product from the patient's sample.

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence if known to be variable between ethnic groups, please report)
1 in 40 000 to 1 in 80 000.

1.9 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☐	☒
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:
CD is due to *de novo* heterozygous mutations in *SOX9*, with recurrence risk of a few percent (estimate ~5%) due to germ line mosaicism in one of the parents. A predictive prenatal testing is thus only possible if a *SOX9* mutation has been identified in a previous pregnancy.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: False positives	C: False negative D: True negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A + C)
			Specificity:	D/(D + B)
Negative	C	D	Positive predictive value:	A/(A + B)
			Negative predictive value:	D/(C + D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
About 95%.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
100%.

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2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

About 95%.

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases, a general statement should be given, even if a quantification can only be made case by case.

100%.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive)
Nearly 100%. In rare instances such as far upstream translocations[8–10] or upstream deletions,[6] disease symptoms can be very mild so as to go unnoticed. As mentioned above, individuals with translocation breakpoints or deletions located greater than 1 Mb upstream of *SOX9* only show isolated Pierre Robin sequence and none of the other clinical symptoms of CD/ACD.[15,16]

2.6 Negative clinical predictive value
(probability not to develop the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
Not applicable.
Index case in that family had not been tested:
Not applicable.

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: The tested person is clinically affected
(To be answered if in 1.9 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	(continue with 3.1.4)	☐
Yes	☒	
	Clinically	☒
	Imaging	☒
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe)	

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Definitive diagnosis of CD is feasible in a majority of affected individuals based on radiological findings, such as bowing of the femora and tibiae, hypoplasia of the scapulae, widely spaced vertical ischia and hypoplastic pubes, and hypoplastic cervical vertebrae. However, the molecular test for *SOX9* and its regulatory domain is important for several reasons. Affected individuals with aberration of the regulatory domain and chromosome derangement tend to have better clinical outcomes. In addition, a subset of patients does not show the full skeletal manifestation, but a few skeletal changes only (eg, brachydactyly or Pierre Robin sequence).

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable. Only radiological and molecular assessments are relevant.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☒	
Yes	☐	
	Therapy (please describe)	There is no targeted therapy available.
	Prognosis (please describe)	Poor, most patients die in the perinatal period, but ~10% survive beyond 2 years of age.[14]
	Management (please describe)	Surgical closure of a cleft palate is recommended. In surviving individuals with a 46, XY karyotype and female genitalia, gonadectomy is recommended due to the increased risk of gonadoblastoma. Survivors usually need orthopedic surveillance and/or care, with surgical correction of club feet and control of hip luxation. Cervical fusion surgery is sometimes needed for cervical vertebral instability resulting from vertebral malformations. Surgery is often required in childhood for progressive cervico-thoracic kyphoscoliosis that compromises lung function.[20]

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.9 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
If the test result is positive (please describe)
If the test result is negative (please describe)

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done?
(please describe)

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.9 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
CD is due to *de novo* heterozygous *SOX9* mutations. Recurrence may occur due to germ line mosaicism in one parent, who may also show somatic mosaicism and may have partial manifestations. Recurrence risk for the next pregnancy cannot be determined exactly, but is estimated to be around 5%. In rare, usually milder cases, transmission of the mutation can be familial.[6,8,9,14]

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Standard molecular tests of family members in addition to analysis of the index patient will not help to clarify a possible risk for parental germinal mosaicism, as only somatic mosaicism in peripheral blood DNA samples can be tested for.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
As mentioned above, not applicable.

3.4 Prenatal diagnosis

(To be answered if in 1.9 'D' was marked)

Early genetic testing from chorionic villi is possible. Routine ultrasound readily reveals bowing and shortening of the femora. However, meticulous assessment is mandatory to identify more specific findings, such as hypoplastic scapulae. CD, unlike other severe skeletal dysplasias, frequently shows only mild femoral shortening and only mild or no bowing. Thus, 'ACD' tends to be overlooked, although its clinical presentation is, in most cases, as severe as that of classic cases.

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?

Yes.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

A positive genetic test outcome provides an unequivocal diagnosis of CD in patients whose clinical and radiological symptoms are not clearcut. This alleviates psychological stress due to uncertain diagnosis, makes additional genetic testing for other suspected skeletal disorders obsolete and allows to offer prenatal testing in a further pregnancy at risk of recurrence of $\sim$5% from germline mosaicism.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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