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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: DiGeorge syndrome, velocardiofacial syndrome, Shprintzen syndrome, chromosome 22q11.2 deletion syndrome (22q11.2, *TBX1*)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), Shprintzen syndrome, Takao syndrome, Sedlackova syndrome, chromosome 22q11.2 deletion syndrome.

1.2 OMIM# of the disease

188400 (DGS), 192430 (VCFS).

1.3 Name of the analysed genes or DNA/chromosome segments

22q11.2, *TBX1*.

1.4 OMIM# of the gene(s)

602054 (*TBX1*).

1.5 Mutational spectrum

Deletions in 22q11.2:[1,2]
- 3 Mb (90% of cases)
- 1.5 Mb (7–8% of cases)
- Atypical smaller deletions.

Point mutations in *TBX1*.[3]

1.6 Analytical methods

FISH, MLPA, quantitative PCR, array CGH, sequencing.
Conventional cytogenetics usually normal except for rare cases resulting from unbalanced translocations.

1.7 Analytical validation

Parallel analysis of positive and negative controls, depending on the method.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

Prevalence at birth: 1:5000 (ranges from 1:4000 to 1:10 000 in the literature).[4–8]

1.9 If applicable, prevalence in the ethnic group of investigated person

None.

1.10 Diagnostic setting

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

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)

Depends on analytical method:
- Typical 3 and 1.5 Mb deletions: almost 100% for all methods.
- Atypical deletions: FISH: >95%.
  MLPA, array CGH: virtually 100%.
- Point mutations in *TBX1*: 0%, requires sequencing (research).[9,10]

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

Nearly 100%.

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2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
In such cases a general statement should be given, even if a quantification can only be carried out case by case.

95%. The DGS phenotype in a neonate can be mimicked by certain other chromosomal imbalances (eg, a deletion in 10p13-p14), monogenic conditions (eg, CHARGE syndrome) or disorders caused by teratogens (eg, retinoid or maternal diabetes).

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 carried out case by case.

Depends on the quality of clinical assessment due to highly variable expressivity of the disease.

As most apparently healthy carriers show at least minimal manifestations of the disease on careful examination, the clinical specificity is nearly 100%.

In familial cases, mosaics can be found in 'healthy' truly asymptomatic persons.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
100%, but high clinical variability.

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:
Practically 100%.
Index case in that family had not been tested:
Can only be clarified through analysis of the non-affected person.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: the tested person is clinically affected
(To be answered if in 1.10 '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
Not applicable.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable.

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

No ☐

Yes ☒

Therapy (please describe)	*Depends on clinical manifestations: calcium supplementation, tube feeding, speech therapy, velopharyngeal surgery, heart surgery*
Prognosis (please describe)	*Moderate*
Management (please describe)	*Highly dependent on age and phenotype: screening for renal and asymptomatic heart defects, immunologic check-up, calcium survey, prevention of infections, detection of hearing loss. Management of behavioural problems. Social support through patient organisations.*

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history
(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?
Yes.
If the test result is positive (please describe):
Yes, see 3.1.4.
If the test result is negative (please describe):
Depends on clinical manifestations.

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

3.3 Genetic risk assessment in family members of a diseased person
(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Yes, but only when the relatives are tested too.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Unaffected or only minimally affected relatives can be diagnosed by the test and may then profit from preventive measures (eg, calcium). If a deletion is detected in a parent, prenatal diagnosis is possible for further pregnancies.

3.4 Prenatal diagnosis
(To be answered if in 1.10 'D' was marked)

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)

Parents are given accurate information about the cause of the disease and recurrence risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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