European Journal of Human Genetics (2011) 19; doi:10.1038/ejhg.2010.193

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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Deletion 22q13 syndrome

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European Journal of Human Genetics (2011) **19,** doi:10.1038/ejhg.2010.193; published online 8 December 2010

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Phelan-McDermid syndrome/22q13 deletion syndrome/chromosome 22q13.3 deletion syndrome/telomeric 22q13 monosomy syndrome.

1.2 OMIM# of the disease
606232.

1.3 Name of the analysed genes or DNA/chromosome segments
SHANK3, 22q13.3.

1.4 OMIM# of the gene(s)
602306.

1.5 Mutational spectrum
Phelan-McDermid syndrome can result from simple 22q13 deletions, ring chromosomes and unbalanced translocations.[1–5] The deletions are extremely variable in size, ranging from 95 kb to 9 Mb. The gene responsible for the core neurological features is *SHANK3*, which has been found to be mutated in patients with autism spectrum disorders and intellectual disability.[6–9]

55% *de novo* deletion 22q13.3 of the paternally derived chromosome
20% *de novo* deletion 22q13.3 of the maternally derived chromosome
10% paternal structural rearrangement
10% maternal structural rearrangement
4% *de novo* unbalanced rearrangement
<1% mutations within *SHANK3* gene (only a small number of studies have sequenced *SHANK3*, so the frequency may be underestimated).[6–10] Deletions of 22q13, not including the *SHANK3* gene, have been reported in two unrelated individuals with Phelan-McDermid syndrome.[11]

1.6 Analytical methods
Chromosome analysis, FISH, array CGH, MLPA and DNA sequencing.

Conventional cytogenetics is usually normal except for cases resulting from unbalanced translocations (24%). Small terminal or interstitial deletions of 22q13 will not be detected by FISH unless this region of chromosome 22 is targeted by probes specific for *SHANK3* or other loci within the deleted region.

1.7 Analytical validation
Parallel analysis of positive and negative controls, depending on analytical method.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
Unknown due to underdiagnosis.

1.9 If applicable, prevalence in the ethnic group of investigated person
Not applicable.

1.10 Diagnostic setting

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

Comment:
In 20% of cases, deletion 22q13 results from a structural rearrangement in one of the parents. Study of the parents allows determination of whether additional family members are at risk of being balanced carriers. Detection of an inherited rearrangement may also influence the family's interest in prenatal diagnosis.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives B: false positives	C: False negatives D: true negatives
	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)
Nearly 100%.

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

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.

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Nearly 100%. This may vary in the presence of mosaicism for the deletion of chromosome 22.

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.

Nearly 100%.

2.5 Positive clinical predictive value
(life-time risk of developing the disease if the test is positive)

Nearly 100%.

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:
Nearly 100%.

Index case in that family had not been tested:
Nearly 100%. Family members who do not have clinical symptoms will not develop the disorder.

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)	Physical therapy, occupational therapy, and adaptive sports to improve strength, balance and coordination; behavioural therapy; speech therapy and introduction of assistive technology to improve communication; medication for hyperactivity, anxiety and self-stimulatory behaviour; other medical issues should be addressed by standard methods.	
Prognosis (please describe)	Early interventions programs can improve outcomes. However, despite aggressive therapies, developmental delay and impaired speech will persist throughout lifetime. No life-shortening conditions have been identified.	
Management (please describe)	Assessment for renal abnormalities and brain imaging studies (increased risk of arachnoid cysts) are recommended after the diagnosis is made. Management of behavioural issues through behaviour modification programs with positive reinforcement. Medication for hyperactivity and self-stimulatory behaviour. Management of medical problems by routine methods. Family support through patient organizations.	

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?

If the test result is **positive** (please describe):
Not applicable.

If the test result is **negative** (please describe):
Not applicable.

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)?
Not applicable.

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. Establishing whether the deletion is *de novo* or secondary to a chromosomal rearrangement in one of the parents will influence the need for genetic testing in other family members.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes. Knowing whether the deletion is *de novo* or secondary to a familial translocation has direct consequences for the genetic counselling of relatives.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes. Prenatal testing is an option for family members who are carriers of a balanced rearrangement.

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 diagnosis?
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 genetic test is necessary to make a positive diagnosis. A diagnosis of 22q13 deletion has immediate consequences to the index patient, by facilitating care by experienced specialists. Parents are given accurate information about the cause of the disease and recurrence risk. Knowledge of the results of the genetic test may resolve feeling of guilt in the parents. Additional genetic testing is

useful to relatives in the presence of a structural abnormality that might be inherited.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by EuroGentest, an EU-FP6 supported NoE, contract number 512148 (EuroGentest Unit 3: 'Clinical genetics, community genetics and public health', Workpackage 3.2).

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