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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Aarskog–Scott syndrome (faciogenital dysplasia)

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Aarskog–Scott syndrome (AAS), faciodigitogenital syndrome, *FGDY*, faciogenital dysplasia.

1.2 OMIM# of the disease

305400.

1.3 Name of the analysed genes or DNA/chromosome segments

FGD1.

1.4 OMIM# of the gene(s)

300546.

1.5 Mutational spectrum

Missense, nonsense, deletions and insertions are reported in addition to gross rearrangements. No mutational hotspots or common mutations are seen; the majority of mutations are unique within families. To the best of our knowledge, incorporating information from published articles, unpublished data and congress reports, 56 mutations have been characterised with the following mutational spectrum: 29 missense mutations, 16 frameshift mutations, 5 nonsense mutations, 3 splice site mutations, 1 in-frame deletion and 2 gross deletions.[1–4] No evident genotype–phenotype correlation is apparent from comparison of patients with different mutations.[1,5]

1.6 Analytical methods

Various methods have been used for detection of point mutations (denaturing high-performance liquid chromatography, sequencing, and so on). MLPA (multiplex ligation-dependent probe amplification) kits for detection of deletions/duplications of one or more exons of the *FGD1* gene are commercially available.

1.7 Analytical validation

This is undertaken by analysis of independent control samples for the presumed pathogenic mutation found in affected individuals, comparison to data base entries and journal data, and testing of other affected/unaffected relatives in the family to see if the mutation segregates only with disease and avoid possible polymorphisms (mainly in cases of novel missense mutations).

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

A total of 29 molecularly proven cases have been published worldwide,[1] but the number of clinically diagnosed cases is much larger. The majority of patients published before the advent of molecular tests have not been restudied for mutations. Experience in Leuven and in Manchester (JP Fryns and J Clayton-Smith: personal communications) indicates 2–3 new patients with a proven mutation in the *FGD1* gene per year, the same as for Angelman and Prader–Willi syndrome, with a population prevalence of AAS probably lower or equal to 1/25 000.

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

Not applicable. Almost all individuals in whom mutations have been sought are of Caucasian origin. However, clinical experience suggests that this condition occurs in many different ethnic groups.

1.10 Diagnostic setting

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

Comment: Predictive testing – not applicable. As AAS is not a late onset disease and the signs are usually present in childhood, the genetic test, even in young children, are to be considered diagnostic and not predictive. Prenatal testing – see further (3.4) for considerations about the prenatal diagnosis.

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)

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2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
100%.

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

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
Approximately 22%.[1] 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. Failure to detect a mutation in most patients referred for *FGD1* analysis is likely to be largely attributable to the clinical and genetic heterogeneity of AAS, and the fact that the clinical features overlap with those of several other disorders (including Noonan's syndrome, SHORT syndrome, pseudohypoparathyroidism and Robinow syndrome). To reach the highest mutation detection rate, only affected individuals who fully met the classical diagnostic criteria should be considered for testing.[1] This approach will, however, limit the probability of detecting a mutation in less typical patients, who may represent broader clinical subtypes of AAS. It is already acknowledged that some patients with pathogenic mutations do not have all the typical clinical features.[6–8]

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 of developing the disease if the test is positive)
Not applicable; see comment to the point 1.10 'D' about predictive tests.

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 (due to genetic heterogeneity).
Index case in that family had not been tested:
Not applicable.

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)	There are no specific therapies for AAS. Some features (hypospadias, inguinal or umbilical hernias, cryptorchidism and unusually severe craniofacial features) may need surgical intervention. Radiological and orthopaedic surveys of the cervical spine should be carried out, as compression of nerve roots may be a consequence of cervical vertebral defects (hypoplasia of the first cervical vertebra, unfused posterior arch, synostosis, anomaly of the odontoid).[9] The effect of growth hormone treatment on height gain has been reported only in preliminary studies and needs confirmation.[10] In the case of neurodevelopmental symptoms, generally mild learning problems and attention deficit and hyperactivity disorder, a neuropsychiatric opinion may be useful.[11,12]
	Prognosis (please describe)	Due to the clinical and genetic heterogeneity, the identification of a *FGD1* mutation in an AAS patient will not lead to a different prognosis, when compared with patients in whom a mutation was not found. However, the molecular test is essential to confirm clinical diagnosis and for accurate genetic counselling of the families concerned.
	Management (please describe)	Multidisciplinary clinical follow-up (neuropsychiatrics,paediatrics, orthopaedic). A positive genetic test will impact on genetic counselling by permitting carrier detection, diagnosis in individuals with milder manifestations and the provision of an accurate recurrence risk for the families concerned.

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?

A positive test (finding of a *FGD1* mutation) will confirm the diagnosis of AAS and genetic counselling. It is useful, in particular, for carrier detection in females who may not manifest significant clinical signs. The assessment of recurrence risk for future pregnancies will be possible. A negative test will not completely rule out the possibility of AAS.

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?

Not applicable; see comment to the point 1.10 'B'.

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?

Prenatal diagnosis for pregnancies at increased risk is possible when the disease-causing mutation in the family has been identified. However, in practice, prenatal testing is unlikely to be requested frequently, as even in male patients, physical signs can be mild and the broad variability of clinical expression in an individual family makes prediction of the phenotype difficult.[13]

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).

The result of an *FGD1* genetic test may have no immediate medical consequences for the affected individual and their families, but having a positive molecular genetic diagnosis will influence genetic counselling and may influence reproductive decisions. It is likely that relatives will consider genetic counselling and carrier testing to assess their own risks.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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