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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Arterial tortuosity syndrome

Juliette Albuisson*[,1,2,3], Pamela Moceri[4,5], Elisabeth Flori[6], Emre Belli[7], Céline Gronier[8] and Xavier Jeunemaitre[1,2,3]

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Arterial tortuosity syndrome (arterial tortuosity).

1.2 OMIM# of the disease

208050.

1.3 Name of the analysed genes or DNA/chromosome segments

SLC2A10, also named *GLUT10*, located in 20q13.12 chromosomal segment.

1.4 OMIM# of the gene(s)

606145.

1.5 Mutational spectrum

To date, <30 mutations have been described, approximately one-third of them are present in the public *SLC2A10* variants database (http://databases.lovd.nl/shared/genes/SLC2A10).

The mutation spectrum comprises transitions, transversions, large (exonic) deletions, small deletions and splice-site mutations.

Consequences:

frameshift, missense, nonsense, splice-site, haploinsufficiency by mRNA decay.

Comment:

The collection of variants in a shared database is of great importance, particularly in the case of very rare disorders like ATS, as it improves the diagnosis in laboratories by helping analysis and interpretation of these rare variants. All published and unpublished case with identified *SLC2A10* pathogenic variant(s) should be submitted in an open-access database.

1.6 Analytical methods

Sequencing of both strands is necessary. This can be completed if needed by a semi-quantitative technique seeking for partial or complete deletions of the gene, as described.[1] As this disorder is recessive and frequently caused by homozygous mutations, denaturation-based screening techniques can be performed on equimolar mixtures of patient and control DNA.

1.7 Analytical validation

Mutations are responsible for a loss-of-function of the corresponding allele. Analytical validation should systematically integrate conservation analysis of the mutant nucleotide(s) and aminoacid(s), as well as the surrounding sequence(s). The variation(s) should systematically be searched in databases of polymorphisms and pathogenic variations.

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)

The incidence is extremely low although no accurate data exist. Estimates vary between 1/100 000 to 1/500 000 live births. The frequency does not seem to vary between different ethnical backgrounds, although in some populations a high level of consanguinity possibly favours the occurrence of new cases).[2]

1.9 Diagnostic setting

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

Comment:

A first comment must be made concerning differential diagnostics:

One main differential diagnosis has to be considered in the classical neonatal or infantile form of the disease. This syndromic condition, named Autosomal Recessive Cutis Laxa Type 1 (ARCL1b) is caused by mutations in *FBLN4* gene encoding fibuline 4. ARCL1b associates diffuse arterial tortuosity combining stenosis and aneurysms with severe to mild cutis laxa, inconstant diaphragmatic and inguinal hernias and facial dysmorphism.[3–5] Differential diagnosis between those two conditions can be considered on the basis of slight dysmorphic differences of the face, a tendency to more generalised and severe cutis laxa in ARCL1b patients.[4]

In cases when the ATS is revealed by late childhood or adulthood cardiovascular complications, the differential diagnosis includes

[1]AP-HP, Département de Génétique, Hôpital Européen Georges Pompidou, Paris, France; [2]Université Paris Descartes, PRES Sorbonne Paris Cité, Paris, France; [3]Centre de Référence des Maladies Vasculaires Rares, Paris, France; [4]Unité de Cardiologie, Hôpital Pasteur, CHU de Nice, Nice, France; [5]Unité de Cardiologie pédiatrique, Hôpitaux universitaires de Nice CHU-Lenval, Nice, France; [6]Service de Cytogénétique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [7]Centre Chirurgical Marie Lannelongue, Université Paris-Sud, Centre de Référence Malformation Cardiaques Congénitales Complexes M3C, Paris, France; [8]Pôle de Cardiologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

*Correspondence: Dr J Albuisson, AP-HP, Département de Génétique, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France. Tel: +33 156093881; Fax: +33 156093884; E-mail: juliette.albuisson@egp.aphp.fr

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connective tissue disorders affecting the arterial system as Loeys–Dietz syndromes (LDS),[6] and Ehlers–Danlos syndromes (EDS), particularly the vascular form. All differential diagnoses of ATS are available for diagnostic testing and should be explored in case of negativity of *SLC2A10* screening (see 2.3).

A second comment is necessary concerning prenatal diagnosis: ATS severity is variable and its outcome is currently unpredictable. As early severe morbidity and early demise have frequently been reported, prenatal diagnosis can be offered for this disease when the mutations have been identified.

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)

Almost 100%. When only one mutation has been identified by sequencing, the test should be completed by a semi-quantitative technique, allowing the detection of loss or gains of one or more exons of the gene. In these conditions the AS is close to 100%. When two heterozygous mutations are found, parental testing should always be performed to confirm compound heterozygosity.

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

100%. As this is a recessive disorder, two loss-of-function mutations are expected, and false-positive results with two unknown variants in a patient's *SLC2A10* genomic sequence are not to be expected.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)

The clinical sensibility 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.

When the clinical diagnosis has correctly been established, very few false negative patients are expected. The high level of global arterial tortuosity, associated with arterial stenosis (mostly of the pulmonary circulation) and specific dysmorphic features in infancy are generally sufficient to propose the diagnosis of ATS. However, as mentioned in 1.9, differential diagnoses can be proposed in infancy or in adulthood.[9]

Molecular screening of genomic sequences of *FBLN4* (for ARCL1b), *COL3A1, COL5A1* and *COL5A2* (for EDS) and *TGFB2, TGFBR1/2* and *SMAD3* (for LDS) can be performed depending on the clinical presentation of the patient, in case of negativity of *SLC2A10* screening.

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.

Same comment as for 2.3.

2.5 Positive clinical predictive value
(life time risk to develop the disease if the test is positive).

100% if a prenatal diagnosis is performed. Not applicable in adulthood as this condition is a recessive childhood disorder.

2.6 Negative clinical predictive value
(probability of developing 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:

100%.

Index case in that family had not been tested:

Assuming the clinical diagnosis is right, 100%. In case of erroneous diagnosis, it depends on the differential diagnosis, which can either correspond to recessive or dominant conditions. All differential diagnoses corresponding to adult-onset, dominant disorders should be cautiously kept in mind as penetrance is highly variable depending on families and age of the patients.

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)	The diagnosis can be strongly suggested by classical neonatal or infantile presentation. Though, all cases should be confirmed by a genetic test as explained above.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

In classical cases, clinical diagnosis can be strongly suggested by combining family history, physical examination, echocardiography and arterial imaging like angioMRI or CT.[1]

Patients are often born from consanguineous marriages. They generally present at birth with facial dysmorphism including beaked nose, blepharophimosis, hypertelorism, downslanting palpebral fissures and a small mouth with retrognathism. A hyperextensible skin or mild cutis laxa can exist. Fingers are long and thin. Inguinal hernias are frequent, but diaphragmatic hernias rarely occur.[1,6]

Infants with ATS may develop dyspnoea revealing pulmonary hypertension, due to stenoses of the pulmonary arteries or branches, which can be confirmed by cardiovascular imaging (ultrasound, catheterisation, angioCT or angioMRI) showing truncal or branch stenosis of the pulmonary arteries followed by a dilated segment.

Generalised severe arterial tortuosity is present, and can be associated with venous tortuosity.[7] The aortic arch often shows elongation and tortuosity, followed by a stenotic prediaphragmatic aortic segment.[7,8]

All medium-sized arteries are highly tortuous,[9] and may show localised aneurysms and stenoses. This high level of tortuosity may result in functional stenosis at multiple levels.

This typical presentation allows clinicians to make the diagnosis of ATS.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Clinical and imaging methods are actually used to get an accurate clinical evaluation of the patients, which is necessary for their long-term follow-up, particularly concerning interventional or surgical treatment.

When a genetic test is available, it should always be performed to propose familial screening and genetic counselling of carriers and prenatal diagnosis, if necessary.

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

No	☐
Yes	☒
Therapy (please describe)	Not applicable.
Prognosis (please describe)	Not applicable.
Management (please describe)	Not applicable.

Comment:

Catheter interventions (balloon dilatation ± stenting), cardiovascular surgery of aneurysms and stenoses, associated with medical treatment of general and/or pulmonary hypertension, are the therapeutic cornerstones of the disorder. There is no modification of the treatment to expect after genotyping.

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)
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 1.9 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?
Not applicable.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Not applicable.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Not applicable.

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

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?
Yes, prenatal diagnosis can be performed in foetuses of parents having an affected child. It might also be proposed in the offspring of an affected adult and a carrier partner.

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)

In populations where consanguineous marriages occur frequently, heterozygous carrier identification might be useful in a patient's relative, if prenatal diagnosis for the offspring is considered.[2]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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