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CLINICAL UTILITY GENE CARD UPDATE

Clinical utility gene card for: Fabry disease – update 2016

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Fabry disease, Anderson-Fabry disease.

1.2 OMIM# of the disease
301500.

1.3 Name of the analysed gene(s) or DNA/chromosome segment(s)
Alpha-galactosidase A, *GLA*.

1.4 OMIM# of the gene(s)
300644.

1.5 Mutational spectrum
Disease-causing variants are mostly point mutations (~70%) spread over the 7 exons, in addition to small (<60 nucleotides) and large (≥60 nucleotides) rearrangements accounting for about 28% and 2%, respectively.[1] Public lists of locus-specific DNA sequence variants are available (http://fabry-database.org; www.GalafoldAmenability Table.com)

1.6 Analytical methods
Bidirectional sequencing (Sanger) of the seven coding exons and the exon-intron boundaries. In case of females, MLPA or qPCR should be performed if no disease-causing variant has been found by Sanger sequencing. Occasionally, *GLA* is included in a NGS (next-generation sequencing) panel aimed to detect disease-causing variants of genes frequently implicated in various clinical conditions suggestive of Fabry disease, such as hypertrophic cardiomyopathy or terminal kidney insufficiency.

1.7 Analytical validation
Bidirectional sequencing; control of results by parallel use of alternative molecular genetic methods (eg restriction analysis, ASO-PCR etc); analysis of samples of family members (as positive and negative controls); comparison with the database entries and data in the literature; quality control through sharing samples. In the case of variants of unknown clinical significance discovered in the frame of screenings of newborns or high-risk patient cohorts, careful evaluation of pathogenic nature is mandatory.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
One per 30 000–80 000 births for the classic phenotype.

1.9 If applicable, prevalence in the ethnic group of investigated person
High prevalence of the c.936+919G>A variant (traditional designation: IVS4+919G>A) both in adult patients with 'idiopathic' hypertrophic cardiomyopathy and newborns in the Taiwan Chinese population (Reference sequences used for variant description are HGNC: 4296, NG_007119.1, NM_000169.2, and NP_000160.1).[2]

1.10 Diagnostic setting

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

Comment: In contrast to the majority of X-linked metabolic diseases, large proportion of female carriers do manifest disease-specific clinical features (figures vary considerably from author to author and could be up to 80%, according to the unpublished data of the authors). Compared to male patients, disease phenotypes in females appear usually at a later age and are less severe.[3] Echevarria and colleagues suggested that in carriers with skewed X-inactivation (allele ratios >75:25), there is a positive correlation between overall severity of clinical phenotype, allele selection and degree of X-chromosome inactivation.[4] Nevertheless, for females, a reliable diagnosis of Fabry disease can only be made by gene analysis.

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)
In case of bidirectional sequencing of all coding exons and short adjacent intronic sequences, ca. 0.98 in males and 0.96 in females (unpublished data of the authors).

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
1.00

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

In case of bidirectional sequencing of all coding exons and short adjacent intronic sequences, ca. 0.98 in males and 0.96 in females (unpublished data of the authors).

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 quantification can only be made case by case.

Practically 100%

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
In case of proven disease-causing mutations, almost 100% of males and up to 80% of females develop signs and/or symptoms of the disease (unpublished data of the authors), whereas expressivity is very variable both within the same family and among different families carrying the same disease-causing variant.

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 shown to carry a proven disease-causing variant:

Practically 100%

Index case in that family had not been tested:

Depending on age and degree of relationship, ca. 98% in males and ca. 96% in females, if bidirectional sequencing of all coding exons and short adjacent intronic sequences was performed (unpublished data of the authors).

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: 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	☐

Male patients with the classic form of the disease have very low alpha-galactosidase A activity and can be diagnosed by an enzyme assay in blood leukocytes or using dried blood spots. Some male patients with attenuated forms of the disease have considerable residual alpha-galactosidase A activity (5–30%), although still far below the reference range.

Diagnosis must be confirmed in all male cases by enzyme assay in blood leukocytes and DNA sequence analysis. The activity of alpha-galactosidase A may be normal in female carriers. Therefore, a diagnosis of Fabry disease in females can only be made by molecular genetic tests. Before enzyme replacement therapy is initiated, the diagnosis should be verified by detection of the disease-causing variant.

The c.937G>T/p.(Asp313Tyr) change results in a serum pseudo-deficiency of alpha-galactosidase A activity and is not disease-causing. Similarly, a number of *GLA* variants previously thought to be disease-causing have been shown recently to be neutral or of unknown significance (see ref. 5 and references therein).

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Small (blood sample drawing)

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Results of the enzyme assay are usually available within 3–7 days. Measuring enzyme activity for diagnosis (in males) costs presently significantly less than molecular genetic analysis.

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

No	☐	
Yes	☒	
	Therapy (please describe)	Depending on the disease-causing variant found and the clinical phenotype, enzyme replacement and/or chaperon therapy may be indicated. Adjunctive symptomatic therapeutic measures are also often necessary.
	Prognosis (please describe)	Classic form of Fabry disease is a relentless progressive storage disorder. Without specific therapy, male patients as well as a subset of female patients are at risk of developing life-threatening complications.
	Management (please describe)	In case of enzyme replacement therapy, lifelong intravenous infusions of recombinant alpha-galactosidase A.

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):	Therapeutic options, see 3.1.4; informed family planning if a carrier status has been diagnosed.
If the test result is negative (please describe):	In case of potential heterozygotes, the knowledge of not having an elevated carrier risk results in 'relief' with regard to the familial risk, and allows an informed decision on family planning and prenatal diagnosis.

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)?
Enzyme replacement or chaperon therapy can only be initiated if a proven disease-causing *GLA* variant has been detected or the mutation is 'amenable'. Since life expectancy of patients without targeted therapy is significantly reduced both in males and females, regular monitoring and timely diagnosis of disease-specific signs and symptoms are essential. The major causes of morbidity and mortality of Fabry disease are terminal kidney insufficiency, cardiovascular disease and stroke. Therefore, management of patients with Fabry disease requires a multidisciplinary team of medical sub-specialists.[6]

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, X-linked inheritance.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes. Knowing the disease-causing mutation allows targeted DNA sequence analysis in relatives whose health problems could not be assigned yet to a medical entity.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes.

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).

Gene analysis allows diagnosis of carrier state in female relatives of probands.

CONFLICT OF INTEREST

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