CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Mucopolysaccharidosis type II

Michael Beck¹, Frits A Wijburg² and Andreas Gal^{*,3}

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (Synonyms)

Mucopolysaccharidosis type II (MPS type II, MPS2, Hunter disease).

1.2 OMIM# of the disease

309900.

1.3 Name of the analysed genes or DNA/chromosome segments

Iduronate 2-sulfatase (IDS).

1.4 OMIM# of the gene(s)

300823.

1.5 Mutational spectrum

Majority (~60%) point mutations, spread over the 9 exons, ca. 30% rearrangements affecting <20 nucleotides, ca. 10% rearrangements affecting >21 nucleotides, including a frequent and complex rearrangement due to homologous non-allelic recombination between the IDS gene and the neighbouring IDS pseudogene.¹

1.6 Analytical methods

Bidirectional sequencing.

1.7 Analytical validation

Bidirectional sequencing; control of results by another set of PCR oligonucleotide primers or an alternative molecular genetic methods (eg restriction analysis, ASO-PCR etc); simultaneous analysis of family members (as positive and negative controls); comparison with database entries and data in the literature; quality control through sharing samples.

1.8 Estimated frequency of the disease

(incidence at birth ('birth prevalence') or population prevalence)

It is estimated to be 1.3 per 100 000 male newborns.

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

1.10 Diagnostic setting

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

Comment: Female carriers cannot be identified clinically but only by genetic 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)

2.1 Analytical sensitivity

(proportion of positive tests if the genotype is present)

Almost 100%.

2.2 Analytical specificity

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

Not appropriate.

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.

Almost 100%.

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.

Practically 100%.

2.5 Positive clinical predictive value

(life-time risk to develop the disease if the test is positive)

Practically 100%.

¹Center for Child and Adolescent Medicine, University Medical Center Mainz, Mainz, Germany; ²Department of Pediatrics, Academic Medical Center, Amsterdam, The Netherlands; ³Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

*Correspondence: Professor A Gal, Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg D-20246, Germany. Tel: +49 40 7410 52120; Fax: +49 40 7410 55138; E-mail: gal@uke.de

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:

Almost 100%.

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) The activity of iduronate-2-sulfatase may be normal in female carriers, therefore genetic analysis is required to identify them. Before an enzyme-replacement therapy is initiated, the diagnosis should also be verified in all patients by detecting a disease-causing mutation. ²

3.1.2 Describe the burden of alternative diagnostic methods to the patient.

Small (blood drawing).

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Good cost effectiveness for biochemical analysis. MPS2 is diagnosed primarily by enzyme assay. In specialized centers, the results of an enzyme assay are usually available within 7 days. The biochemical diagnosis is significantly less expensive than a molecular genetic analysis.³

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

No	☒
Yes	☐
	Therapy (please describe)
	Prognosis (please describe)
	Management (please describe)

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):

Yes, definitely in female carriers. 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 a 'relief' with regard to the familial risk, and allows an informed decision on prenatal diagnosis.

3.2.2 Which options in view of lifestyle and prevention do a person at-risk have if no genetic test has been done (please describe)?

Calculation of the statistical risk for being a carrier, prenatal diagnosis by enzyme assay in case of a male fetus.

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?

No, except for obligate carriers.

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).

CONFLICT OF INTEREST

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