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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: *MAN1B1* defective congenital disorder of glycosylation

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Deficiency of Golgi mannosyl-oligosaccharide α1,2-mannosidase, MAN1B1 deficiency, MAN1B1-CDG.

1.2 OMIM# of the Disease

614202.

1.3 Name of the Analysed Gene or DNA/Chromosome Segments

MAN1B1.

1.4 OMIM# of the Gene(s)

604346.

1.5 Mutational Spectrum

Nineteen variants have been reported, including 11 missense variants, 1 nonsense variant, 5 deletion variants, and 2 splicing variants, but the clinical significance is not fully clarified for most of these variants.[1–3] (www.lovd.nl/MAN1B1). The standard reference sequence indicating reported variants (ENSG00000177239) and a reference for exon numbering (ENST00000474902) can be found at http://www.ensembl.org.

1.6 Analytical Methods

Sanger sequencing of the 13 coding exons and flanking intronic sequences of the *MAN1B1* gene (NCBI reference sequence: NM_016219.4).

1.7 Analytical Validation

Sanger sequencing identifies variants in >99% of patients. Deep intronic variants, large deletions, and duplications would not be detected using this approach. Novel variants with uncertain pathogenic nature are of course possible.

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):

Thirty-one patients (from 20 families) have been reported.[1–3] The frequency and the prevalence of the disease are not known.

1.9 Diagnostic Setting

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

Comment: MAN1B1-CDG is an autosomal recessive disorder. All reported patients showed intellectual/developmental disability, ranging from mild to severe. Most patients also presented abnormal speech development and hypotonia.[1–3] In the majority of patients there was facial dysmorphism (mainly down-slanting palpebral fissures, prominent eyebrows with lateral thinning, prominent bulbous nose tip, tent-shaped mouth with thin upper lip, and large ears) and truncal obesity. Behavioural problems have been reported in about half of the patients, particularly verbal and physical aggression, inappropriate sexual behaviour and overeating. A subset of patients showed mild dolichocephaly, long and thin fingers, and increased skin laxity and joint hyperlaxity. No clear phenotype–genotype correlations could be found. Biochemical abnormalities such as increased serum transaminases and abnormal coagulation tests were present in only a few patients. Serum transferrin isoelectrofocusing shows a type 2 pattern. Mass spectrometry of transferrin shows a specific accumulation of hybrid type N-glycans. The diagnosis has to be confirmed by mutation analysis of *MAN1B1*. An upcoming strategy, after finding and confirming an abnormal serum transferrin isoelectrofocusing pattern, is to subject the DNA to a CDG panel of genes known to be involved in CDG. The identification of the pathogenic variant will permit heterozygote detection in the family, and prenatal diagnosis.

2. TEST CHARACTERISTICS

	Genotype or disease		A: true positives B: false positives	C: false negative D: true negative
	Present	Absent		
Test				
Pos.	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Neg.	C	D	Pos. predict. value:	A/(A+B)
			Neg. predict. value:	D/(C+D)

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2.1 Analytical Sensitivity
(proportion of positive tests if the genotype is present)

Close to 100% when using the serum transferrin isoelectrofocusing test.

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

Close to 100% when using the serum transferrin isoelectrofocusing test. This test can be positive in secondary glycosylation disturbances such as galactosemia and hereditary fructose intolerance, and due to bacterial sialidase.[4–6]

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.

Close to 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.

Close to 100%.

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

100%, based on positive serum transferrin isoelectrofocusing screening and *MAN1B1* mutation analysis.

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:
100%.

Index case in that family had not been tested:
100%.

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)	

3.1.2 Describe the burden of alternative diagnostic methods to the patient

The blood sampling for the serum transferrin isoelectrofocusing screening test and that for the mutation analysis is a minor burden to the patient.

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

It differs among countries. In Belgium and The Netherlands the cost of these tests is largely carried by the national assurance organism.

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

No	☐	
Yes.	☒	
	Therapy (please describe)	Treatment of MAN1B1-CDG is purely symptomatic.
	Prognosis (please describe)	Molecular testing is essential for confirmation of the diagnosis and the genetic counselling of the families concerned.
	Management (please describe)	MAN1B1-CDG is a multi-system disease with major neurological involvement. Follow-up by a multidisciplinary team is important.

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?

Usually yes, by testing the potential heterozygous persons (carriers) in the family.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

No.

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 should be performed by molecular analysis.

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)

Knowledge of the diagnosis will stop unnecessary further investigations, and will help the parents in the process of accepting the disease although no curative treatment is available.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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