CLINICAL UTILITY GENE CARD

Clinical utility gene card for: *ALG6* defective congenital disorder of glycosylation

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European Journal of Human Genetics (2015) 23, doi:10.1038/ejhg.2014.146; published online 23 July 2014

1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Deficiency of Dol-P-Glc: Man₉GlcNAc₂-PP-Dol α -1,3-glucosyltransferase, glucosyltransferase 1 deficiency, ALG6-CDG, CDG-Ic.

1.2 OMIM# of the disease

603147.

1.3 Name of the analysed genes or DNA/chromosome segments

ALG6.

1.4 OMIM# of the gene

604566.

1.5 Mutational spectrum

Twenty-three variants have been reported, including 11 missense variants, 1 nonsense variant, 5 deletion variants, 4 splicing variants, and 1 duplication variant. In one patient, a portion of chromosome 1 including *ALG6* was deleted as a *de novo* event¹⁻⁴ (www.lovd.nl/*ALG6*). The standard reference sequence indicating reported variants (ENSG00000088035) and a reference for exon numbering (ENST00000371108) can be found at <http://www.ensembl.org>.

1.6 Analytical methods

Sanger sequencing of the 14 coding exons and flanking intronic sequences of the *ALG6* gene (NCBI reference sequence: NM_013339.3).

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):

Fifty-four patients have been reported.²⁻¹⁷ 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: ALG6-CDG is an autosomal recessive disorder. Its phenotype is mostly characterized by a mild to moderately severe neurological disorder (psychomotor disability, epilepsy, hypotonia, optic dysfunction/hypotrophy, and, on brain imaging, a thin corpus callosum and cerebral/cerebellar hypotrophy) and feeding problems. A minority of patients show a severe, early-onset neuro-gastrointestinal presentation.^{3,10,12,14} Other reported manifestations are facial dysmorphism, skeletal abnormalities such as brachytelephalangy, bleeding/clotting problems, hepatomegaly, cardiomyopathy, and recurrent infections. Striking biochemical abnormalities are unusually low levels of serum cholesterol, blood coagulation factor XI, and anticoagulation factors antithrombin, protein C, and protein S, as well as variable hypoalbuminemia, increased serum transaminases, low serum LDL-cholesterol, and endocrinological abnormalities. Serum transferrin isoelectrofocusing shows a type 1 pattern, and fibroblast dolichol-linked oligosaccharide (DLO) analysis an increase of Man₉GlcNAc₂. The diagnosis has to be confirmed by mutation analysis of *ALG6*. Since the DLO analysis is cumbersome, produces sometimes equivocal results, and is only available in very few centers, an upcoming strategy 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	C: False negative
		B: False positives	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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Received 12 April 2014; revised 18 June 2014; accepted 25 June 2014

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.^{18–20}

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**(lifetime risk to develop the disease if the test is positive)**

100%, based on positive serum transferrin isoelectrofocusing screening and ALG6 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 ALG6-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)	ALG6-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; fetal transferrin isoelectrofocusing leads to false results.²¹

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.

ACKNOWLEDGEMENTS

This work was supported by EuroGentest2 (Unit 2: 'Genetic testing as part of health care'), a Coordination Action under FP7 (Grant Agreement Number 261469) and the European Society of Human Genetics.

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