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CLINICAL UTILITY GENE CARD

# Clinical utility gene card for: *ALG1* defective congenital disorder of glycosylation

Jaak Jaeken*[,1], Dirk Lefeber[2] and Gert Matthijs[3]

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## 1. DISEASE CHARACTERISTICS

### 1.1 Name of the disease (synonyms)

Deficiency of GDP-Man:$GlcNAc_2$-PP-Dol mannosyltransferase, mannosyltransferase 1 deficiency, ALG1-CDG, CDG-Ik.

### 1.2 OMIM# of the disease

608540

### 1.3 Name of the analysed genes or DNA/chromosome segments:

*ALG1*.

### 1.4 OMIM# of the gene

605907.

### 1.5 Mutational spectrum

Thirteen variants have been reported: ten missense variants, two splicing variants and one deletion variant. The most frequent variant is c.773C>T (p.Ser258Leu)[1–6] (www.lovd.nl/ALG1). The standard reference sequence indicating reported variants (ENSG00000033011) and a reference for exon numbering (ENST00000262474) can be found at http://www.ensembl.org.

### 1.6 Analytical methods

Sanger sequencing of the thirteen coding exons and flanking intronic sequences of the *ALG1* gene using primers designed to discriminate between this gene and its documented pseudogenes (NCBI reference sequence: NM_019109.4).

### 1.7 Analytical validation

Sanger sequencing identifies the 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):

Nineteen patients (belonging to fourteen families) have been reported[1–10] and thirteen unpublished patients (from nine families) are known to the authors. 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:

ALG1-CDG belongs to the five most common *N*-glycosylation disorders together with PMM2-CDG, ALG6-CDG, MPI-CDG and SRD5A3-CDG. It is an autosomal recessive disease with a broad clinical spectrum, and with early death at the second day of life to survival beyond the age of 20 years.[1–10] Its phenotype is characterized by a predominant neurological involvement. Constant features are an intellectual developmental disorder (mostly severe) and hypotonia (sometimes only infantile). A majority of patients show dysmorphism (facial dysmorphism, inverted nipples, fat pads, contractures, arachnodactyly a.o.), microcephaly (mostly neonatal), intractable seizures (with neonatal or later onset), visual disturbances (strabismus, nystagmus, retinopathy and/or (in some patients) severe visual loss), tremor, ataxia, severe infections/episodes of unexplained fever and cerebral abnormalities (cerebral infarct, general atrophy and/or periventricular white matter abnormalities). Symptoms reported in only one or a few patients are feeding problems, gastrointestinal problems (diarrhoea and ascites), growth retardation, hearing loss, areflexia, spastic tetraparesis, stereotypic movements, peripheral neuropathy, repiratory problems (including pleural effusion), pericardial effusion, oedema, hepatomegaly, cholestatic jaundice, portal hypertension, Budd–Chiari syndrome, nephrotic syndrome, spontaneous haemorrhage and venous thrombosis. Biochemical abnormalities are decreased levels of serum LDL cholesterol, blood coagulation factor XI and anticoagulation factors antithrombin, protein C and protein S, as well as variable hypoalbuminemia, increased serum transaminases, decreased serum cholinesterase and immunoglobulins, and endocrinological abnormalities (such as decreased serum IGF1 and IGFBP3).

[1]Centre for Metabolic Disease, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium; [2]Department of Neurology, Laboratory of Genetic, Endocrine and Metabolic Diseases, Radboudumc, Nijmegen, The Netherlands; [3]Centre for Human Genetics, KU Leuven, Leuven, Belgium
*Correspondence: Professor J Jaeken, Centre for Metabolic Disease, University Hospital Gasthuisberg, Herestraat 49, BE 3000 Leuven, Belgium. Tel: +32 16 343827; Fax: +32 16 343842; E-mail: jaak.jaeken@med.kuleuven.be
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Serum transferrin isoelectrofocusing, capillary zone electrophoresis or HPLC show a type 1 pattern, and analysis of short dolichol-linked oligosaccharides (DLO) in fibroblasts shows an increase of $GlcNAc_2$-PP-dolichol. The diagnosis has to be confirmed by mutation analysis of *ALG1*. As the DLO analysis, especially of short DLO's, is cumbersome, produces sometimes equivocal results, and is only available in very few centres in a research setting, an upcoming strategy is to subject the DNA to Next-Generation Sequencing methods such as a CDG panel of genes known to be involved in CDG or whole-exome sequencing. The identification of the variant that affects function will permit heterozygote detection in the family and prenatal diagnosis.

Since the patients with ALG1-CDG may have dysmorphic features resembling those observed in PMM2-CDG (that is, inverted nipples, subcutaneous fat pads), ALG1-CDG should be considered when PMM2-CDG was searched and ruled out by PMM2 molecular 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)**

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.[11–13]

**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 *ALG1* 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 the family history for a nonaffected 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 ALG1-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) | ALG1-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; foetal transferrin isoelectrofocusing leads to false results.[14]

## 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. It will also help the parents in the process of accepting the disease although no curative treatment is yet available.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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