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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: *DPAGT1* defective congenital disorder of glycosylation

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Deficiency of UDP-GlcNAc:Dol-P-GlcNAc-P transferase 1, deficiency of Dol-P:GlcNAc-P transferase 1, deficiency of GlcNAc-1-P transferase 1, congenital myasthenic syndrome with tubular aggregates 2, CMSTA2, DPAGT1-CDG, CDG-Ij.

1.2 OMIM# of the disease

608093.
614750.

1.3 Name of the analysed genes or DNA/chromosome segments

DPAGT1

1.4 OMIM# of the gene(s)

191350.

1.5 Mutational spectrum

Twenty-five variants have been reported: twenty-one missense variants, three splicing variants and one duplication vari ant[1–11] (www.lovd.nl/DPAGT1). The standard reference sequence indicating reported variants (ENSG00000172269) and a reference for exon numbering (ENST00000354202) can be found at http://www.ensembl.org.

1.6 Analytical methods

Sanger sequencing of the nine coding exons and flanking intronic sequences of the *DPAGT1* gene (NCBI reference sequence: NM_000011.10).

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:

Forty-one patients (from seventeen families) have been reported.[1–15] 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: DPAGT1-CDG is an autosomal recessive disease that presents as one of the two different phenotypes: an encephalopathy in the context of a multisystem disorder[1,2,4–7,9,13] and, on the other hand, a congenital myasthenic syndrome.[3,8,10–12,14,15] The multisystem presentation (28 patients) is, as a rule, a severe disease. Twenty-three patients died between 6 weeks and 5 years. Two siblings had a milder presentation, and were 34 and 32 years old when reported. All patients showed moderate to severe psychomotor disability, and most patients had microcephaly, hypotonia, and epilepsy. Less frequent symptoms were feeding difficulties, apnoea, respiratory insufficiency, chronic anaemia, cataracts, hypotrophy, hypertrichosis, frequent episodes of aspiration, hypertonia of the extremities, hypo- and hyperreflexia, joint contractures, and abnormal brain magnetic resonance imaging (MRI). Features reported only once included a foetal hypokinesia syndrome, tremor, night blindness, inverted nipples, fat pads, skin dimples on thighs, bilateral papillar atrophy, bilateral cochlear impairment, fiber type disproportion on muscle biopsy, and abnormal brain PET scan. Biochemical abnormalities included increased serum transaminases (4 patients) and creatine kinase (1 patient), hypoproteinemia (1 patient), decreased antithrombin (1 patient), and a type 1 pattern on serum transferrin isoelectrofocusing in all patients. The congenital myasthenic syndrome presentation has been reported in 13 patients. The first symptoms were noted between birth and 17 years. Ages at report ranged from 6 to 58 years. One patient died at 26 years from a respiratory crisis. Clinical features included a predominantly proximal muscle weakness with absent or minimal craniobulbar symptoms. The syndrome was mostly slowly progressive but some patients showed mild improvement in childhood or adolescence. All

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patients responded favourably to acetylcholinesterase inhibitors such as pyridostigmine. Muscle cramps, difficulty in swallowing and chewing, and scoliosis have been reported in a few patients, as well as delayed motor development and intellectual disability. Serum creatine kinase levels were normal. Hypoglycosylation of serum transferrin was present in only 4/8 patients. Electromyography showed myopathic features but not always of the facial muscles. A frequent sign was a decremental response on 3-Hertz repetitive nerve stimulation. Tubular aggregates in muscle biopsy were noted in 4/7 patients (not in early biopsies). Analyses of motor end plates demonstrated a reduction of end plate acetylcholine receptors. Brain MRI, performed in a few patients, was normal. It has to be noted that three other congenital disorders of glycosylation can cause a congenital myasthenic syndrome: GFPT1-CDG (16), ALG2-CDG (17), and ALG14-CDG (17).

The diagnosis has to be confirmed by mutation analysis of *DPAGT1*. An upcoming strategy is to analyse a panel of genes known to be involved in CDG and, when this is 'negative', to perform whole-exome sequencing. The identification of the variant(s) that affect(s) function will permit heterozygote detection in the family as well as prenatal diagnosis.

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% for the multisystem presentation when using the serum transferrin isoelectrofocusing test. In the congenital myasthenic syndrome presentation, this test was positive in only about half of the reported patients.

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.[16–18]

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% for the multisystem presentation but only around 50% for the congenital myasthenic syndrome presentation.

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 a positive serum transferrin isoelectrofocusing screening and *DPAGT1* mutation analysis.

2.6 Negative clinical predictive value
(probability of not developing 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% for the multisystem presentation, and around 50% for the congenital myasthenic syndrome presentation.

Index case in that family had not been tested:

100% for the multisystem presentation, and around 50% for the congenital myasthenic syndrome presentation.

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)	The congenital myasthenic syndrome presentation responds to anticholinergic inhibitors. Treatment of the multisystem presentation 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)	The encephalopathic form is a multisystem disease. Follow-up by a multidisciplinary team is thus important. Also the myasthenic syndrome presentation needs regular follow-up to adapt medication.

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.[19]

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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