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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: *B4GALT7*-defective congenital disorder of glycosylation

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Deficiency of UDP-galactose:*O*-beta-D-xylosylprotein 4-D-galactosyltransferase, deficiency of xylosylprotein 4-beta-galactosyltransferase, polypeptide 7, deficiency of galactosyltransferase I, B4GALT7 deficiency, B4GALT7-CDG, progeroid form of Ehlers–Danlos syndrome, type 1, Ehlers–Danlos syndrome with short stature and limb anomalies, Larsen of Reunion Island syndrome.

1.2 OMIM# of the disease

130070.

1.3 Name of the analysed gene or DNA/chromosome segments

B4GALT7.

1.4 OMIM# of the gene(s)

604327.

1.5 Mutational spectrum

Seven variants have been reported: six missense variants and one variant with a loss of function frameshift duplication (www.lovd.nl/B4GALT7). The c.808C>T (p.(Arg270Cys)) variant is the most prevalent one. Six variants have occurred within the region that codes for the catalytic protein domain. The standard reference sequence indicating reported variants (ENSG00000027847) and a reference for exon numbering (ENST00000029410) can be found at http://www.ensembl.org.

1.6 Analytical methods

Sanger sequencing of the eight coding exons and flanking intronic sequences of the *B4GALT7* gene (NCBI reference sequence: NM_007255.2).

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 effect on function 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):

Twenty-eight genetically confirmed patients (from 25 families) have been reported.[1–5] 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: Deficiency of galactosyltransferase I is an autosomal recessive disorder of *O*-glycosylation, first reported in 1990.[1] It is a proteoglycan defect, more specifically in the glycosaminoglycan biosynthesis. Glycosaminoglycans are attached to the serine residue of a core protein via a tetrasaccharide linkage (consisting of one xylose, two galactoses and one glucuronic acid residue). Other disorders of this 'linkeropathy' group are: XYLT1-CDG, XYLT2-CDG, B3GALT6-CDG and B3GAT3-CDG. These diseases belong to the congenital disorders of glycosylation (CDG), a large group of genetic defects in protein and lipid glycosylation. Most CDG are multisystem disorders with prominent neurological involvement. Nearly 100 CDG have been described. Subtype identification is challenging owing to the large clinical and genetic heterogeneity. There are protein glycosylation defects in *N*- and *O*-glycosylation. Most *N*-glycosylation disorders are recognized by serum transferrin isoelectrofocusing, whereas mucin-type *O*-glycosylation defects are diagnosed by apo C-III isoelectrofocusing.

All or the majority of reported patients with B4GALT7-CDG showed facial dysmorphism (including triangular face, sparse scalp hair, low-set ears, widely spaced eyes, narrow mouth and abnormal dentition), mild to severe intellectual/developmental disability, short stature, hypermobility, hypotonia, hyperelastic skin, limb bowing, *pes planus*, advanced bone age, radio-ulnar synostosis, and radial head and phalangeal dislocation. Less frequent findings comprised delayed/abnormal wound healing, wide forehead, flat face, proptosis, blue

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sclerae, glaucoma, bifid uvula, cleft palate, long slender fingers and toes, syndactyly and osteopenia. The large majority of the reported patients (22) are living on Reunion Island (in the ethnic group called 'white creoles'). These Reunion Island patients lack osteopenia and recurrent fractures. They all carry the same homozygous c.808C>T (p.(Arg270Cys)) variant (founder effect). Current screening tests for defects in *O*-glycosylation (mainly apo C-III isoelectrofocusing) show normal results. The diagnosis of B4GALT7-CDG is based on the clinical acumen of the physician and confirmed by mutation analysis of *B4GALT7*. 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				
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)
Not applicable as there is no test available.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
See 2.1.

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.
See 2.1.

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.
See 2.1.

2.5 Positive clinical predictive value
(life-time risk of developing the disease if the test is positive)
See 2.1.

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:
See 2.1.
Index case in that family had not been tested:
See 2.1.

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
Not applicable.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Not applicable.

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

No	☐	
Yes	☒	
	Therapy (please describe)	Treatment of B4GALT7-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)	B4GALT7-CDG is a multisystem disease, mainly involving skeleton, joints, skin and eyes. 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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