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CLINICAL UTILITY GENE CARD

Clinical Utility Gene Card For: *GALNT3* defective congenital disorder of glycosylation

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1. Disease characteristics

1.1 Name of the disease (synonyms)

Deficiency of UDP-*N*-acetyl-α-D-galactosamine:polypeptide *N*-acetylgalactosaminyltransferase 3, deficiency of GalNAc transferase 3, deficiency of GalNAcT3, GALNT3 deficiency, GALNT3-CDG, familial hyperphosphatemic tumoral calcinosis, HFTC, hyperostosis-hyperphosphatemia syndrome, lipocalcinogranulomatosis, familial Teutschlaender disease.

1.2 OMIM# of the disease

211900.

1.3 Name of the analysed gene or DNA/chromosome segments

GALNT3.

1.4 OMIM# of the gene

601756.

Review of the analytical and clinical validity, as well as of the clinical utility of DNA-based testing for mutations in *GALNT3* in diagnostic, predictive and prenatal settings, and for risk assessment in relatives.

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1.5 Mutational spectrum

At least thirty-five variants have been reported: eleven missense variants, twenty-two nonsense variants, and two splice variants (www.lovd.nl/GALNT3). There are no obvious hotspot variants. The standard reference sequence indicating reported variants (ENSG00000115339) and a reference for exon numbering (ENST00000392701) 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 *GALNT3* gene (NCBI reference sequence: NM_004482.3).

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 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:

At least sixty-six genetically confirmed patients (from 42 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	☒	

Table (continued)

B. Predictive testing	☒	
C. Risk assessment in relatives	☒	□
D. Prenatal	☒	□

Comment:

Deficiency of *N*-acetylgalactosaminyltransferase 3 is an autosomal recessive disorder of O-glycosylation, first reported in 2004 [4]. GalNAc transferase 3 belongs to a large family of at least 23 Golgi-associated enzymes and transfers GalNAc from the sugar donor UDP-GalNAc to serine and threonine residues thus initiating mucin-type O-glycosylation. GALNT3-CDG belongs 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. More than 100 CDG have been described. Subtype identification is challenging due to the large clinical and genetic heterogeneity. There are protein glycosylation defects in N-glycosylation and O-glycosylation.

GALNT3-CDG is the most prevalent genetic cause of familial tumoral calcinosis and is a hyperphosphatemic calcinosis. It is characterized by the presence of ectopic calcifications in soft tissues around major joints (shoulders, elbows, hips, knees etc.). In some patients, there are also vascular calcifications, angioid streaks of the retina, dental abnormalities, and/or testicular microlithiasis. This can lead to intolerable pain, skin ulcerations, and secondary skin and bone infections. Another presentation is the hyperostosis-hyperphosphatemia syndrome characterized by recurrent long bone lesions [5]. Both presentations represent a continuous spectrum of the same disease and can occur in the same patient. Clinical manifestations vary even within families, from asymptomatic to large, disabling calcifications. There is no phenotype-genotype correlation. The disease is predominantly present in black African and Middle-Eastern patients. A hallmark biochemical feature is persistent hyperphosphatemia with elevated or inappropriately normal 1,25 hydroxy-vitamin D. Serum calcium and parathyroid hormone levels are usually normal. Imaging tests of the calcifications can resemble those of several other disorders including primary hyperparathyroidism, vitamin D poisoning, dermatomyositis, and neoplastic conditions. The hyperphosphatemia is due to increased renal phosphate reabsorption secondary to decreased O-glycosylation of FGF23 by the deficient GALNT3 protein. By glycosylating FGF23, GALNT3 protects this phosphaturic protein from proteolytic processing. Intact serum FGF23 levels are thus decreased in GALNT3-CDG. Current screening tests for defects in O-glycosylation (mainly apo C-III isoelectrofocusing) show normal results The diagnosis of GALNT3-CDG is based on the clinical acumen of the physician and confirmed by mutation analysis of *GALNT3*. The identification of the pathogenic variant will permit heterozygote detection in the family, and prenatal diagnosis. Recent reviews provide more details [1, 6].

2. Test characteristics

	Genotype or disease		A: True positives	C: False negatives
	Present	Absent	B: False positives	D: True negatives
Test				
Postive	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 since 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 to develop the disease if the test is positive)
See 2.1.

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:
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 GALNT3-CDG is only symptomatic and has a pharmacological and a surgical component. Low phosphate diet, phosphate binders and phosphaturia-inducing therapies have been attempted with variable response. Since this is a rare disease, no randomized clinical trials have been performed. As to surgical treatment, some patients showed complete resolution of calcinosis lesions after removal while others required multiple repeated surgeries due to lesion recurrence [6]
Prognosis (please describe)	Molecular testing is essential for confirmation of the diagnosis and genetic counseling of the families concerned
Management (please describe)	GALNT3-CDG is a multi-system disease, mainly involving skin, bones, teeth and eyes. Follow-up by a multidisciplinary team is thus 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 patients and parents of affected children in the process of accepting the disease although no curative treatment is available.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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