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CLINICAL UTILITY GENE CARD

SRD5A3 defective congenital disorder of glycosylation: clinical utility gene card

Jaak Jaeken[1] · Dirk J. Lefeber[2] · Gert Matthijs[3]

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

CDG-Iq; ocular coloboma with ichthyosis, brain malformations, and endocrine abnormalities; Kahrizi syndrome; mental retardation, cataract, coloboma, and kyphosis, autosomal recessive; polyprenol reductase deficiency; SRD5A3-CDG; SRD5A3 deficiency; SRD5A2L1 deficiency; steroid 5α-reductase 3 deficiency; steroid 5-α-reductase 2-like deficiency.

1.2 OMIM# of the disease

612379/612713.

1.3 Name of the analysed gene or DNA/chromosome segments

SRD5A3.

1.4 OMIM# of the gene

611715.

1.5 Mutational spectrum

At least 15 variants have been reported: 11 nonsense variants, 3 missense variants, and a large deletion (www.lovd.nl/SRD5A3). The standard reference sequence indicating reported variants (ENSG00000128039) and a reference for exon numbering (ENST00000264228.9) can be found at http://www.ensembl.org.

1.6 Analytical methods

Sanger sequencing of the five coding exons and flanking intronic sequences of the SRD5A3 gene (NCBI reference sequence: NM_024592.4).

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.

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 38 genetically confirmed patients (from 26 families) have been reported [1–19]. The frequency and the prevalence of the disease are not known.

1.9 Diagnostic setting

	Yes.	No.
A. (Differential) diagnosis	☒	
B. Predictive Testing	☒	
C. Risk assessment in Relatives	☒	☐
D. Prenatal	☒	☐

Comment:

The clinical presentation of steroid 5α-reductase 3 (SRD5A3) deficiency has first been reported in 2001 [1]

✉ Jaak Jaeken
jaak.jaeken@kuleuven.be

[1] Department of Development and Regeneration, Centre for Metabolic Diseases, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium

[2] Department of Neurology, Translational Metabolic Laboratory, Radboudumc, Nijmegen, The Netherlands

[3] Department of Human Genetics, KU Leuven, Leuven, Belgium

and the molecular defect in 2010 [6, 7]. SRD5A3 is located in the endoplasmic reticulum (ER) membrane and catalyzes the conversion of polyprenol to dolichol. Dolichol-specific kinase transfers a phosphate from cytidine triphosphate to dolichol, and synthesis of dolicholphosphate is the step just before the start of N-glycosylation and O-and C-mannosylation. SRD5A3-CDG is one of the some 130 known congenital disorders of glycosylation (CDG), genetic defects in protein and lipid glycosylation. Most CDG are multisystem disorders with predominant neurological involvement.

All SRD5A3-CDG patients showed psychomotor disability, and in the majority there were various combinations of other neurological abnormalities (hypotonia, ataxia, midline brain malformation, global/cerebellar vermis hypoplasia), as well as facial dysmorphism, ophthalmological abnormalities (nystagmus, visual loss, coloboma, optic disk/nerve hypoplasia) and cutaneous symptoms (hyperpigmentation, dry skin, hypertrichosis, ichthyosis, loose skin, palmoplantar keratoderma). Symptoms reported in a minority of patients were a.o. feeding problems, cardiac malformations/hypertrophy, joint hypermobility, and hepatosplenomegaly. Symptoms that may develop over time are kyphosis, cataracts and retinitis pigmentosa. Biochemical abnormalities include increased serum transaminases, hypothyroidism, and decreased blood clotting factors antithrombin and protein C. Most patients have been reported from Afghanistan, the Czech Republic, Iran, Pakistan, Poland, Puerto Rico and Turkey. Screening for the disease is performed by serum transferrin isoelectrofocusing, showing a type 1 pattern. The diagnosis is confirmed by mutation analysis of the gene. Identification of the pathogenic variant(s) will permit heterozygote detection in the family, and prenatal diagnosis.

2. TEST CHARACTERISTICS

	Genotype or disease		A: True positives	C: False negative
	Present	Absent	B: False positives	D: True negative
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 e.g. due to chronic alcoholism or bacterial sialidase.

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

(life time risk to develop the disease if the test is positive)

100%, based on positive serum transferrin isoelectrofocusing screening and *SRD5A3* 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*

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 SRD5A3-CDG is purely symptomatic.
	Prognosis (please describe)	The prognosis regarding quality of life is mainly determined by the nature and the degree of the brain and eye involvement.
	Management (please describe)	Since SRD5A3-CDG is a multi-system disease, follow-up by a multidisciplinary team is mandatory.

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. It will also help patients and parents of affected children in the process of accepting the disease although no curative treatment is yet 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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