CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Adrenoleukodystrophy

Ernst Krasemann¹, Stephan Kemp² and Andreas Gal^{*,3}

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Adrenoleukodystrophy (ALD), adrenomyeloneuropathy (AMN), Addison disease and cerebral sclerosis, melanodermic leukodystrophy.

1.2 OMIM# of the disease

300100 (ALD).

1.3 Name of the analysed genes or DNA/chromosome segments

ABCD1.

1.4 OMIM# of the gene(s)

300371 (ABCD1).

1.5 Mutational spectrum

Mainly (about 71%) point mutations, spread over all 10 exons. Approximately 26% smaller rearrangements (mainly insertions and deletions affecting <20 base pairs), 3% deletions of one exon or more exons. The majority of the families have a unique ('private') mutation, the rate of *de novo* mutations is about 5%.¹

1.6 Analytical methods

Bidirectional sequencing of genomic DNA is the routine analytical method both for males and females. If no disease-causing mutation has been found, in particular in a female, dosage testing should be performed by qPCR or MLPA.

1.7 Analytical validation

Bi-directional sequencing of genomic DNA. After the index case was tested, additional family members (and/or control samples) should be genotyped. The results obtained should be compared with database entries (www.x-ald.nl) and data in the literature. Verification of the sequence variants found by sequencing is done with an independent molecular genetic method (eg, restriction analysis, ASO-PCR, and so on). Quality control is important through sample exchange.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

Birth prevalence of hemizygotes is about 1:42 000 and that of hemizygotes plus heterozygotes is about 1:16 800.

1.9 If applicable, prevalence in the ethnic group of investigated person

ALD has been identified in all ethnic groups.

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

2. TEST CHARACTERISTICS

Genotype or disease		A: True positives	C: False negative
		B: False positives	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)

Nearly 100% in males and females if both sequencing and dosage testing are performed.

2.2 Analytical specificity

(proportion of negative tests if the genotype is not present)

Practically 100%.

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.

Practically 100% in males and females if both sequencing and dosage testing are performed.

¹MVZ Fenner & Krasemann, Hamburg, Germany; ²Amsterdam Center for Metabolism, Academic Medical Center, Amsterdam, The Netherlands; ³Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

*Correspondence: Professor A Gal, Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Tel: +49 40 7410 52120; Fax: +49 40 7410 55138; E-mail: gal@uke.de

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.

Practically 100%.

2.5 Positive clinical predictive value

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

About 95% for hemizygotes and about 70% for heterozygotes, whereas carriers develop milder symptoms (AMN) and at a later age than do male patients.

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:

Practically 100% in males and females if both sequencing and dosage testing are performed.

Index case in that family had not been tested:

Practically 100% in males and females if both sequencing and dosage testing are performed.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected (To be answered if in 1.10 '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

Depending on the methods used can be low (blood drawing) or considerable (MRI and electrophysiology).

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Good cost effectiveness for biochemical method (analysis of very long-chain fatty acids), small cost (~100 €); imaging (MRI) is very expensive.

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

No	☐	
Yes	☒	
	Therapy (please describe)	<i>In most cases, results of the biochemical analysis and of imaging are sufficient to make treatment decisions, for example, early bone marrow transplantation for male patients with childhood cerebral disease, and symptomatic therapy.²</i>

(Continued)

Prognosis (please describe)	<i>Bone marrow transplantation has been demonstrated to have a beneficial effect, is life saving and can stop or reverse the disease when performed at the earliest stage of cerebral disease.³</i>
Management (please describe)	<i>The use of Lorenzo's oil may reduce the risk for the childhood cerebral phenotype when administered to asymptomatic boys carrying a disease-causing mutation.</i>

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history (To be answered if in 1.10 '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):

Yes, adequate therapeutic options (see 3.1.4), informed family planning.

If the test result is negative (please describe):

'Relief' with regard to the familial risk, informed family planning.

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)?

See 3.2.1 for 'test result is positive'.

3.3 Genetic risk assessment in family members of a diseased person (To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes, X-linked inheritance.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

Yes, DNA diagnostic can be very helpful and straightforward for relatives of a clinically asymptomatic or oligosymptomatic index patient or in rare cases of somatic mosaicism. Finding a disease-causing mutation in a patient makes testing of obligate heterozygotes unnecessary.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnosis?

Yes.

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)

Results of molecular genetic diagnostics may influence family planning. Often it helps clarifying the situation and allows patients and relatives to choose the most appropriate options.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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