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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Alström syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Alström syndrome, ALMS.

1.2 OMIM# of the disease
203800.

1.3 Name of the analysed genes or DNA/chromosome segments
ALMS1.

1.4 OMIM# of the gene(s)
606844.

1.5 Mutational spectrum
There have been 98 different disease-causing mutations described thus far including nonsense (49%), indels (43%), and rare compound frameshift, and splice site (3%).[1] Two missense alterations of uncertain pathogenicity were reported by Joy *et al*.[2] The majority of those are clustered in exon 16 (41%), exon 10 (27%), and exon 8 (25%) of *ALMS1*. Compound heterozygosity is common. Chromosomal translocations and large deletions are rare but have been reported.[3,4]

1.6 Analytical methods
Bi-directional sequencing of coding regions of genomic DNA with flanking intronic sequences.[5]

1.7 Analytical validation
Both strands are sequenced. When a mutation is identified, validation of the results using a second primer set or using a second technique (PCR with restriction enzyme digestion) is recommended and external validation for DNA sequencing through international quality assurance schemes, when possible. Interpretation of the molecular genetic results can be ambiguous, as synonymous substitutions, SNPs and mutations can be non-disease causing (neutral).

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
Less than 1:100 000 in European populations. The frequency is higher in isolated populations with a high incidence of consanguinity.[6]

1.9 If applicable, prevalence in the ethnic group of investigated person
There is a higher frequency of some particular *ALMS1* mutations in certain ethnic populations, for example 10535ins(n)19 in French Acadians and 10775delC in up to 20% of patients of English descent.[1,7] In common with many autosomal recessive diseases, the prevalence is higher in populations where consanguineous marriages are common.

1.10 Diagnostic setting

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

Comment:
Several other conditions have overlapping phenotypes, and should be evaluated in the differential diagnosis, particularly in the young child: Bardet–Biedl syndrome (BBS), Leber congenital amaurosis (LCA), and idiopathic cardiomyopathy in infants. BBS is predominately characterized by obesity, polydactyly, developmental delay and learning difficulties, and rod-cone dystrophy with a slower progression and no photodysphoria. Hearing loss is less common in BBS. A first diagnosis of LCA is often given in the young infant without dilated cardiomyopathy, but should be reconsidered if additional symptoms develop. In an infant with nystagmus, photodysphoria, and cardiomyopathy, Alström syndrome should be considered first. Conversely, idiopathic cardiomyopathy in infants who also have retinal degeneration is a strong indicator of Alström syndrome. Other disorders sometimes included in the differential diagnosis that could lead to mis-diagnosis are as follows: mitochondrial dysfunction, retinitis pigmentosa with hearing loss, Usher syndrome, and Wolfram syndrome.

Prenatal and predictive diagnosis can be undertaken if both mutated alleles are identified in the parents. Predictive diagnosis is only of limited relevance because the first symptoms of Alström syndrome appear in infancy.

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)
The proportion of both mutations found in this recessive disease is about 63%, in about 33%, only one of the two mutations will be

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found. In 4% neither of the mutations will be found with the method described (DNA-sequencing only). Therefore, only one mutation found in the context of appropriate clinical presentation, may confirm diagnosis of Alström syndrome.[8] A negative result using current methods does not exclude the diagnosis, if classic clinical features are present.

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

The phenotype is progressive and can be quite variable. Given the rarity of the syndrome and the progressive phenotype, depending on the age of the patient and the clinical symptoms, it can be concluded that a finding of only one mutation together with age appropriate symptoms may confirm the diagnosis of Alström syndrome; therefore the clinical sensitivity can be estimated being about 96%.[8]

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.

The proportion is practically 100. In very rare occasions one mutation may be detected in a healthy carrier.

2.5 Positive clinical predictive value
(life-time risk of developing the disease if the test is positive)
Alström syndrome develops in infancy. If *ALMS1* mutations are identified in the child, the risk to develop further symptoms of the disorder is 100%. There have been no reported cases of incomplete penetrance.

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:

When a pathogenic *ALMS1* mutation is identified in the index case, the negative predictive value is 100%.

Index case in that family had not been tested:

Further testing for family members may be appropriate in rare circumstances, but should only be proposed when the pathogenic mutation(s) has been identified in an index case.

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)	☐

Comment:
The clinical diagnosis of Alström syndrome in an infant or very young child requires the presence of a characteristic infancy onset retinal dystrophy with photodysphoria and either obesity or cardiomyopathy. In childhood, early adolescence, and adulthood, additional phenotypes evolve. Insulin resistant diabetes can occur from puberty and may be preceded by acanthosis nigricans. Triglycerides are often elevated. Many patients develop cardiomyopathy in infancy or adolescence. Recurrent lower respiratory tract infections are common in early childhood and non-alcoholic fatty liver disease develops during puberty. Chronic renal failure is seen in up to 25% of patients during the second decade. Multiple organ fibrosis is found at post mortem.

In Alström syndrome, the combination of the late onset of some features, such as cardiac, hepatic, and renal disease, and the existence of other genetic syndromes with similar cardinal manifestations, such as BBS, often leads to confusion among clinicians and possible misdiagnosis. Alström syndrome belongs to a growing class of human diseases, referred to as ciliopathies.

The diagnosis of Alström syndrome is often difficult in young children because many of the clinical features (hearing loss, insulin resistance, diabetes, and congestive heart failure) develop over time. Therefore, diagnostic requirements differ as the child grows, underscoring the challenge in such cases. To address phenotypic variability and the progressive nature of these clinical features, a three-tiered set of diagnostic criteria that takes into account the patient's age has been recommended for correct diagnosis of Alström syndrome.[8]

3.1.2 Describe the burden of alternative diagnostic methods to the patient
Diagnosis can be established on the basis of a constellation of appropriate clinical features (vision and hearing loss, cone-dystrophy by electroretinogram, echocardiography, presence of metabolic abnormalities), depending upon the age of the patient.[8]

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

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

No	☐	
Yes	☒	
	Therapy (please describe)	Treatment is based upon symptoms and indications for drug therapy (type 2 diabetes, hypertension, cardiac function, hormonal imbalances), and are not altered in patients with a molecular diagnosis as compared with those in whom an *ALMS1* mutation has not been identified. Appropriate treatment should be prescribed for all patients with a diagnosis of Alström syndrome based upon clinical features and investigations alone.
	Prognosis (please describe)	Despite optimal clinical care, the prognosis is poor in many patients. The identification of an *ALMS1* mutation will not lead to a different prognosis when compared with patients with Alström syndrome for whom a mutation has not been identified.
	Management (please describe)	Clinical management is complex. Regular assessments for vision and hearing loss, as well as echocardiography follow-up and monitoring of metabolic alterations should occur with or without identification of the *ALMS1* molecular defect. Blindness and

(Continued)

hearing loss should be anticipated, so special adaptations should be made available in the educational setting. All patients should be integrated in a multi-disciplinary clinic. One key function of these clinics is to anticipate and screen for treatable co-morbidities including hypertension, non-alcoholic fatty liver disease, glucose abnormalities, microalbuminuria and lipid abnormalities. The results of genetic testing will influence genetic counselling and diagnosis of younger affected children in the same family.
Patients without a molecular diagnosis might be more frequently subjected to diagnostic biopsy procedures in comparison with patients with known mutation.

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?
To our knowledge, predictive testing has not been carried out yet, but prenatal testing has. However, it might be useful to perform predictive testing in a yet unaffected neonate, sibling to a patient with Alström syndrome with two known mutations. First symptoms occur during the first months of life and the description of the consequences applies for healthy neonates with an increased risk based on family history.

If the test result is **positive** (please describe):

In early childhood there is a high risk to develop dilated acute cardiomyopathy, often misdiagnosed as idiopathic and sometimes with fatal outcome. Therefore monitoring of heart function should be mandatory as well as teaching the parents in early recognition of the symptoms of heart failure.

The widespread major organ fibrosis can be occult resulting in underestimation of risk of cardiorespiratory death in the context of pneumonia or anaesthesia. Early intensive care assessment is vital in these circumstances.

If the test result is **negative** (please describe):

In some affected patients, *ALMS1* mutations may not be identified. A negative genetic test in the context of the appropriate clinical phenotype does not exclude the diagnosis of Alström syndrome and the described precautions are recommended throughout life.

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)?
Regular clinical monitoring, particularly heart and renal function and if vision loss begins or if other symptoms develop.

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 – autosomal recessive inheritance.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes, family members who are possible carriers can be screened for the causative *ALMS1* mutations if both mutated alleles have been identified in the index case.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
First symptoms occur early in childhood. However, it may be possible to test a younger sibling of an index patient before the development of the first symptoms.

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, prenatal diagnosis can be undertaken if both mutated alleles are identified in the parents.

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).

The diagnosis has huge consequences for patients and relatives. Apart from medical consequences, educational and social intervention for a child is essential. Therefore, an unambiguous diagnosis is of great value. Additionally, providing 'an answer' for patients and parents allows them to seek contact with other persons with Alström syndrome or with patient organizations, which can be of great benefit in coping with the condition.

There is little benefit to clarify the carrier status in a relative of a patient with Alström syndrome, as long as his/her spouse is not also a relative of an Alström patient. In case the patient wishes to know his carrier status he should receive qualified genetic counselling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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