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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Cystinosis

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Cystinosis.

1.2 OMIM# of the disease
Nephropathic infantile form (MIM #219800), nephropathic juvenile form (MIM #219900) and non-nephropathic adult form (MIM #219750).

1.3 Name of the analysed genes or DNA/chromosome segments
CTNS, 17p13.2.

1.4 OMIM# of the gene(s)
606272.

1.5 Mutational spectrum
Multi-exon 57-kb deletion, small insertions, deletions, duplications, point mutations (missense, nonsense), splice-site mutations, promoter mutations, genomic rearrangements.[1–6]

The 57-kb deletion is detected in up to 76% of affected northern European alleles and is due to a founder effect arising around the middle of the first millennium AD.[1,2]

Currently, approximately 100 mutations in the *CTNS* are described by HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), however, novel mutations are still being reported, especially when genetically different populations are tested.[7,8]

The standard reference sequence indicating reported variants (ENSG00000040531) and a reference for exon numbering (ENST00000046640) can be found at www.ensembl.org.

1.6 Analytical methods
The 57-kb deletion: rapid PCR assay with the 57-kb deletion breakpoint primer sets, FISH analysis, and MLPA typing. Sanger sequencing of the total coding region, the exon-intron boundaries, and promoter region of the *CTNS* gene. Analysis of microsatellite markers for detection of uniparental heterodisomy of the chromosome 17.[6]

1.7 Analytical validation
The segregation of the mutations should be confirmed in the parents. Pathogenicity of novel missense variants has to be verified by testing a set of at least 100 control chromosomes of the same ethnic origin and by *in-silico* prediction methods (like SIFT, PolyPhen and/or Align). *CTNS* gene transcripts should be analysed in patients with exon-skipping or splice-site mutations.[9] Analysis of functional consequences of the *CTNS* mutation on protein level in cell models is available in a few laboratories in the world.

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)
Birth prevalence: 1:100 000 to 1:200 000. Increased incidence in some populations: for example Brittany, France: 1:26 000.

1.9 If applicable, prevalence in the ethnic group of the investigated person
Not applicable.

1.10 Diagnostic setting

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

Comment:

The common 57-kb deletion encompasses the first nine exons and a part of exon 10 of the *CTNS* gene and the upstream 5′ region that encodes for the *CARKL* gene and the first two non-coding alternative exons of the transient receptor potential vanilloid 1 receptor (*TRPV1*) gene.

So far, there is no evidence confirming pathological involvement of the *CARKL* and the *TRPV1* genes in the clinical phenotype of cystinosis patients.

The *CARKL* gene encodes for the enzyme sedoheptulose kinase responsible for the phosphorylation of sedoheptulose into sedoheptulose-7-phosphate within the pentose phosphate pathway. Patients carrying the common 57-kb deletion accumulate sedoheptulose. Increased concentration of sedoheptulose in blood or urine can be used for identifying patients with the homozygous 57-kb deletion.[10,11]

The *TRPV1* gene encodes for the TRPV1 expressed in the primary sensory neurons and activated by heat and various chemical compounds, including capsaicin.[12] Two first non-coding exons of the *TRPV1* are removed by the 57-kb deletion. Hypothetically, the reduced sweating and crafting for spicy food described in cystinosis patients might be attributed to a decreased function of the TRPPV1 receptor.

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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)

Close to 100%.

Not all found variants have been tested functionally,[13] and therefore a theoretical possibility exists that some of them might be rare polymorphisms. The pathogenicity of most mutants has been confirmed by *in-silico* prediction methods.

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

Close to 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.

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%.

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:

100%.

Index case in that family had not been tested:

Depending on the degree of relationship and consanguinity (25% risk for developing disease in siblings). Less than 1% chance to develop the disease in other relatives in populations with a low degree of consanguinity.

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)	Split-lamp cornea examination

*Although not widely available, *in vivo* confocal microscopy of the cornea or skin are valuable tools for diagnosing cystinosis.[14,15]

3.1.2 Describe the burden of alternative diagnostic methods to the patient

In the majority of cases, the diagnosis of cystinosis is based on the high degree of clinical suspicion (presence of renal Fanconi syndrome, corneal cystine accumulation) and on the biochemical detection of elevated cystine levels in white blood cells (WBC) or preferentially in polymorphonuclear cells having a higher degree of cystine accumulation.

Biochemical methods of cystine measurement (high-performance liquid chromatography or tandem mass spectrometry) are time consuming, require rapid blood processing for cell isolation and can only be performed in specialised laboratories experienced in this measurement.

Young children may have rather low cystine accumulation in WBC and low amount of corneal cystine crystals, complicating the diagnosis of cystinosis shortly after birth and during the first months of life.

Corneal crystals may be absent until 16 months of age.[16]

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

The cost effectiveness of clinical eye investigation and biochemical cystine measurements is very high.

The differences in price between tests depend on the laboratory and the country where testing is performed. Clinical eye examination is always cheaper compared with biochemical or genetic testing, but it is not contributive in patients below 1–2 years of age.[16]

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

No	☐	
Yes	☒	
	Therapy (please describe)	Early genetic diagnosis of cystinosis allows early initiation of treatment with cystine-lowering drug cysteamine (β-mercaptoethylamine).
	Prognosis (please describe)	Renal and extra-renal function survival in cystinosis is dependent on the age of onset of cysteamine therapy.[16–21]
	Management (please describe)	(1) Symptomatic treatment of cystinosis consists of free access to water and replacement therapy with potassium, bicarbonate, phosphate salts and vitamin D, and in older patients with thyroxin, insulin and sex hormones (if required). Young patients are frequently treated with indomethacin to reduce diuresis and urinary electrolyte losses. Growth hormone may be indicated in patients with stunted growth despite adequate nutrition and electrolyte balance.[20–22]

(2) Systemic cysteamine therapy (1.3-1.9 g/m^2/day) should be administered immediately after making the diagnosis and continued life-long (also after kidney transplantation) to reduce cystine WBC levels to <1 nmol cystine/mg protein.[20,22]
(3) Topical cysteamine eye drops (0.5%) should be administered at least 4 times daily to reduce corneal cystine crystals.[16]
(4) Renal transplantation

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):

In affected persons cysteamine therapy should be started immediately after the diagnosis. Early therapy postpones renal failure and the development of extra-renal manifestations of cystinosis.

If the test result is negative (please describe)

No further medical follow-up will be required in subjects from families with a known genetic defect. In case of an unknown mutation in the family, at-risk individuals should be followed medically.

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)?
No life-style adaptations or other type of prevention can be applied. No medical follow-up will be required in persons with a negative genetic test within a family with identified mutations.

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?
Yes.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?
Yes. If the index case has known mutations, siblings, parents and other family members can be screened for disease or carriership.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?
Yes. Genetic test results in the index case allow prenatal diagnosis in the next siblings. In populations with a high degree of consanguinity, carriership in partners can be tested as well.

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.

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)

Yes, for performing genetic counselling in a family.

In general, there is no consensus on genetic testing of partners of affected female patients planning pregnancies. Some genetic laboratories recommend to screen partners for the mutations common in their population (for example: for 57-kb deletion in the Northern European population). Male cystinosis patients are infertile.[23]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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