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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Lowe syndrome

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DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)
Lowe syndrome.
Oculocerebrorenal syndrome.
Oculo-cerebro-renal syndrome.
OCR syndrome.

1.2 OMIM# of the disease
Lowe syndrome (MIM #309000).

1.3 Name of the analyzed genes or DNA/chromosome segments
OCRL, Xq25–q26.1.

1.4 OMIM# of the gene(s)
OCRL, 300535.

1.5. Mutational spectrum
The *OCRL* gene was identified by positional cloning[1] and its genomic structure, comprising 24 exons occupying 52 kb, has been elucidated.[2] Since then, more than 200 Lowe syndrome patients with *OCRL* defects have been identified, which were extensively reviewed by Hichri *et al.*[3] Disease-causing variants are scattered throughout the gene and the majority of patients (63%) display frameshift, nonsense or splice defects[3] leading to mRNA decay or premature termination of the resultant OCRL-1 protein. Missense variants and gross deletions account for 33 and 4% of the cases, respectively.[3] No variant affecting the alternative exon 19 has been reported so far.

Human wild-type *OCRL* gene and OCRL-1 protein with their corresponding exon and amino acid numbering are deposited in GenBank, acc. nos. NM_000276.3 and AAB03839. *OCRL* variants are included in the Human Gene Mutation Database (http://www.hgmd.org/) or can be obtained via the Leiden Open Variation Database (http://www.ncbi.nlm.nih.gov/lovd/home.php?select_db=OCRL).

1.6 Analytical methods
Bi-directional Sanger sequencing of PCR-amplified products comprising the total coding region and the exon–intron boundaries of the *OCRL* gene. For detection of genomic *OCRL* rearrangements and/or precise gene quantification, the multiplex ligation-dependent probe amplification might be used.[4]

1.7 Analytical validation
Confirmation of the detected variant at least from a second amplicon, preferentially from an independent biological sample of the index case. Pathogenicity of novel missense variants has to be verified by (i) testing a set of at least 100 chromosomes from normal ethnically matched controls, (ii) considering its deposition in SNP databases and (iii) using *in-silico* prediction methods. Gene transcripts should be analyzed in case of splice variants. The gold standard is analysis of functional consequences of the respective *OCRL* variant in cell models, performed in a few laboratories in the world.[3,5–7] In case of suspected splice site variants, *OCRL* mRNA should be analyzed.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)
1:500 000.[8]

If known to be variable between ethnic groups, please report
Not applicable.

1.9 Diagnostic setting

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

Comment: In affected boys, bilateral cataracts, one of the cardinal symptoms of Lowe syndrome, develop *in utero* and are almost invariably present at birth.[3,8,9] Other ocular findings include microphthalmia, enophtalmos and glaucoma, the latter developing in the first three decades in 50–60% of the patients. About 25% of Lowe syndrome patients have corneal scarring and keloids.

CNS pathology manifests as neonatal and infantile hypotonia with areflexia and delay in motor development.[8] Seizures are observed in about half of the patients. Typically, patients have mildly elevated creatine kinase and/or lactate dehydrogenase levels.[10] Intellectual disability is a cardinal finding with only 10% of patients having normal intelligence. Behavioral abnormalities (stereotypic behavior, self-injury, tantrums, aggression/irritability, repetitive non-purposeful movements) are common, too.

The renal phenotype is characterized by proximal tubular dysfunction. Impaired reabsorption of low-molecular-weight proteins is

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present in all patients, while disturbances in other tubular functions are variable:[10,11] Generalized aminoaciduria in 80%, phosphate and potassium wasting (in 40 and 20%, respectively), proximal renal tubular acidosis in 35% and slowly progressive renal failure leading to end-stage renal failure in the second and third decade. Unlike other tubular functions, glucose reabsorption is less affected. Like patients with Dent disease (see below), the majority of patients have hypercalciuria (80%), while nephrocalcinosis is observed less often (40–50%). The pattern of tubular dysfunction in the two forms of Dent disease and Lowe syndrome was compared by Bokenkamp *et al.*[10]

Additional features of Lowe syndrome are postnatal growth retardation and a debilitating non-inflammatory teno-arthropathy present in 50% of adult patients.

In a subgroup of patients with *OCRL* variants, the clinical phenotype is dominated by the renal manifestations of the disease and the ocular and cerebral findings are very subtle. These patients are classified as having Dent-2 disease (MIM #300555).[10,12] Reported extra-renal abnormalities were mild growth retardation, clinically unapparent cataract in 2/28, subtle mental retardation in 9/23 and elevated creatine kinase or lactate dehydrogenase in all.[10] In selected cases the classification as Lowe syndrome or Dent-2 disease can be somewhat arbitrary. The characteristics of the two forms of Dent disease and Lowe syndrome are summarized in Table 1.

2. TEST CHARACTERISTICS

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)

Close to 100%. The sensitivity of sequence analysis of PCR-amplified products approaches 100%. Many variants have been tested functionally, and the pathogenicity of most variants has been predicted by publically available algorithms. Nonetheless, errors may occur due to allele dropout and variants outside the coding region in the promoter, polyA site, enhancers or intronic variants may be missed.

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

Nearly 100%. In rare cases, variants may erroneously be interpreted as pathogenic.

Table 1 Clinical and laboratory characteristics of Lowe syndrome compared with Dent-1 (*CLCN5* mutation) and Dent-2 (*ORCL* mutation) disease[8–10]

	Dent-1 (CLCN5+)	*Dent-2 (OCRL+)*	*Lowe (OCRL+)*
Cataract	No	10% (asymptomatic)	Almost 100%
Intellectual impairment	No	30% (mild)	90%
Growth retardation	No	Postnatal, mild (−1 to −2 SD)	Postnatal, severe (−2 to −6 SD)
Elevated LDH or CK	36%	100%	100%
LMW-PU	100%	100%	100%
Hypercalciuria	90%	86%	83%
Nephrocalcinosis	75%	39%	44%
Aminoaciduria	41%	52%	82%
RTA	3%	4%	33%
Phosphate wasting	22%	24%	43%
Potassium wasting	15%	6%	21%
Glycosuria	17%	11%	7%
Renal failure	30%	32%	74%

Abbreviations: CK, creatine kinase; LDH, lactate dehydrogenase; LMW-PU, low-molecular-weight proteinuria; RTA, renal tubular acidosis; SD, standard deviation.

2.3. Clinical sensitivity
(Proportion of positive tests if the disease is present)

Variants in *OCRL* account for 80–90% of cases with a phenotype of Lowe syndrome.[3]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)

100%.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if test is positive)

Almost 100%. Still, a small number of patients with *OCRL* variants have a predominantly renal phenotype and are classified as having Dent-2 disease on clinical grounds. In a large series, 6 out of 136 families with an *OCRL* variant were classified as Dent-2.[3] There have been incidental reports of Lowe syndrome and Dent-2 in patients harboring the same variant, even within one family.[3]

2.6 Negative clinical predictive value
(Probability of not developing the disease if the test is negative)

Almost 100%, still in some patients with clinical features of Lowe syndrome no *OCRL* variants were detected.[3]

3. CLINICAL UTILITY

3.1 (Differential) diagnostics: the person is clinically affected
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):	Ophthalmological examination

Comment: The combination of clinical findings, biochemical demonstration of renal tubular dysfunction and slit-lamp examination is diagnostic.

Slit-lamp examination can be used for identification of female carriers.[8]

3.1.2. Describe the burden of alternative diagnostic methods to the patient

The alternative methods to diagnose Lowe syndrome are generally non-invasive. The diagnosis of Lowe syndrome is suggested by congenital cataract, which is almost uniformly present. Recognition of the cerebral manifestations is based on a thorough neurological examination. The biochemical diagnosis of Lowe syndrome is not invasive (spot urine for low-molecular-weight proteinuria, hypercalciuria and variable presence of other proximal tubular dysfunctions).

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

The cost effectiveness of the physical examination in combination with an ophthalmological examination and simple biochemical tests is high.

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

Not for Lowe syndrome. In patients with the mild Dent-2 phenotype, who might be missed clinically, nephrological follow-up is warranted.[12]

3.2 Predictive setting: the tested person is clinically unaffected but carries an increased risk based on family history

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

Not for Lowe syndrome. In case of the milder Dent-2 phenotype, nephrological follow-up should be initiated.[12]

3.2.2 Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been done?

Urine could be tested for the presence of low-molecular-weight proteinuria, which is an obligate finding in Dent-2 disease. In case of Dent-2 disease, nephrological follow-up should be initiated.[12]

3.3 Genetic risk assessment in family members of a diseased person

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 by ophthalmological examination and urine analysis for low-molecular-weight proteinuria.

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

Yes. Still, variable clinical expression has to be considered (cf. 2.5).

3.4 Prenatal diagnosis

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

Yes. Still, variable clinical expression has to be considered (cf. 2.5).

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 a patient or his/her relatives?

Establishing an unequivocal molecular diagnosis may be helpful for the family.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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