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Lowe Syndrome

Synonyms: Oculocerebrorenal Syndrome, Oculocerebrorenal Syndrome of Lowe

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Summary

Clinical characteristics

Lowe syndrome (oculocerebrorenal syndrome) is characterized by involvement of the eyes, central nervous system, and kidneys. Dense congenital cataracts are found in all affected boys and infantile glaucoma in approximately 50%. All boys have impaired vision; corrected acuity is rarely better than 20/100. Generalized hypotonia is noted at birth and is of central (brain) origin. Deep tendon reflexes are usually absent. Hypotonia may slowly improve with age, but normal motor tone and strength are never achieved. Motor milestones are delayed. Almost all affected males have some degree of intellectual disability; 10%-25% function in the low-normal or borderline range, approximately 25% in the mild-to-moderate range, and 50%-65% in the severe-to-profound range of intellectual disability. Affected males have varying degrees of proximal renal tubular dysfunction of the Fanconi type, including low molecular-weight (LMW) proteinuria, aminoaciduria, bicarbonate wasting and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, hypercalciuria, sodium and potassium wasting, and polyuria. The features of symptomatic Fanconi syndrome do not usually become manifest until after the first few months of life, except for LMW proteinuria. Glomerulosclerosis associated with chronic tubular injury usually results in slowly progressive chronic renal failure and end-stage renal disease between the second and fourth decades of life.

Diagnosis/testing

The diagnosis of Lowe syndrome is established in a male proband with typical clinical and laboratory findings and a hemizygous pathogenic variant in *OCRL* identified by molecular genetic testing. The diagnosis of Lowe syndrome is rare in females but can be established in a female proband who demonstrates the same clinical and laboratory findings as a male proband and who is found to have a heterozygous pathogenic variant in *OCRL* by molecular genetic testing.

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Management

Treatment of manifestations:

- Early removal of cataracts with postoperative glasses; management of glaucoma; early infant therapy, preschool intervention program and individualized education program throughout schooling; behavior modification plan; anticonvulsant therapy if seizures are present.
- Treatment of renal tubular dysfunction includes oral supplements of sodium and potassium bicarbonate or citrate to correct acidosis and hypokalemia, and oral phosphate and oral calcitriol (1,25-dihydroxyvitamin D_3) to correct hypophosphatemia and renal rickets; treatment of ESRD with chronic dialysis and renal transplant in selected individuals.
- Consider human growth hormone therapy to improve growth velocity; tube feedings may be needed to treat infant feeding problems associated with hypotonia; standard treatment for gastroesophageal reflux if present. Bracing or surgery for severe or progressive scoliosis or joint hypermobility; resection of fibromas and cutaneous cysts if painful or impairing function.

Surveillance: Intraocular pressure monitoring every six months for life, other eye evaluations at intervals determined by specialist; at least annual assessment of kidney function, growth, developmental progress; annual evaluation for scoliosis and joint problems; semiannual dental examinations.

Circumstances to avoid: Corneal contact lenses because of associated risk of corneal keloid formation and complexities of contact lens care; artificial lens implants because of probable increased risk of glaucoma.

Genetic counseling

Lowe syndrome is inherited in an X-linked manner. *De novo* pathogenic variants have been reported in 32% of males affected with Lowe syndrome. A high risk of germline mosaicism (4.5%) has been identified. When a mother is a heterozygous, each pregnancy has a 25% chance of an affected son, a 25% chance of a heterozygous daughter, a 25% chance of an unaffected son, and a 25% chance of a daughter who is not heterozygous. No affected male is known to have reproduced. Approximately 95% of heterozygous females older than age 15 years have characteristic findings in the lens of the eye on slit lamp examination by an experienced ophthalmologist using both direct and retroillumination. Once the *OCRL* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Lowe syndrome **should be suspected** in a proband with a combination of the following features:

- Bilateral dense congenital cataracts
- Infantile congenital hypotonia
- Delayed development
- Proximal renal tubular transport dysfunction of the Fanconi type characterized by low molecular-weight (LMW) proteinuria (including retinol binding protein, N-acetyl glucosaminidase, and albumin), aminoaciduria and varying degrees of bicarbonaturia and acidosis, phosphaturia and hypophosphatemia, and hypercalciuria.

Note: LMW proteinuria, characterized by the excretion of proteins such as retinal binding protein and N-acetyl glucosaminidase, is seen in Lowe syndrome, the allelic disorder Dent disease (see Genetically Related Disorders), and many other diseases associated with the Fanconi syndrome. In Lowe syndrome, LMW proteinuria can be seen early in life even in the absence of clinically significant aminoaciduria or other renal tubular abnormalities

[Laube et al 2004]. Thus, LMW may be the most sensitive early marker of the renal dysfunction occurring in this disorder.

Establishing the Diagnosis

Male proband. The diagnosis of Lowe syndrome **is established** in a male proband with typical clinical and laboratory findings and a hemizygous pathogenic variant in *OCRL* identified by molecular genetic testing (see Table 1).

Note: If a variant of unknown significance or no pathogenic variant is identified in a male with a clinical diagnosis consistent with Lowe syndrome, testing of inositol polyphosphate 5-phosphatase OCRL-1 activity in cultured skin fibroblasts is a possible option. Affected males have less than 10% normal activity of the enzyme. Such testing is abnormal in more than 99% of affected males and was shown to have high negative predictive value for Lowe syndrome in individuals referred with only partial overlap with Lowe syndrome phenotype who had no pathogenic variant found in *OCRL* [Hichri et al 2011].

Female proband. The diagnosis of Lowe syndrome in females is rare but **can be established** in a female proband with the same clinical and laboratory findings as a male proband and a heterozygous pathogenic variant in *OCRL* identified by molecular genetic testing. If a diagnosis of Lowe syndrome is established in a female, it is recommended that the clinician search for two pathogenic variants (one on each X chromosome) or an X-autosome translocation or other biologic cause for highly skewed inactivation of the X chromosome carrying the normal allele in a female heterozygote [Mueller et al 1991, Cau et al 2006].

Molecular Genetic Testing

Approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Lowe syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with atypical features or in whom the diagnosis of Lowe syndrome has not been considered are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1. When the phenotypic and laboratory findings suggest the diagnosis of Lowe syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *OCRL* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *OCRL* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2. When the diagnosis of Lowe syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Lowe Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
OCRL	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [4]
	Karyotype	Rare [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Monnier et al [2000], Hichri et al [2011], Recker et al [2015]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Translocations between an autosome and an X chromosome with a breakpoint through *OCRL* (Xq26.1) have been observed in females with Lowe syndrome [Hodgson et al 1986, Reilly et al 1988, Mueller et al 1991]; therefore, in an individual with Lowe syndrome in whom a pathogenic variant has not been detected by other methods, karyotype may be considered.

Clinical Characteristics

Clinical Description

Usually only males have the disorder. A few affected females with the clinical manifestations of Lowe syndrome have been reported [Cau et al 2006].

The major clinical manifestations found in males with Lowe syndrome involve the eyes, central nervous system, and kidneys. Nearly all post-pubertal heterozygous females have lens opacities; a few will have additional findings. With the wide availability of molecular genetic testing, phenotypic heterogeneity appears to be substantially greater than previously suspected, such that individuals who lack certain features of Lowe syndrome can still have pathogenic variants in *OCRL*.

Males

Eyes. Dense congenital cataracts, formed as a result of abnormal metabolism or migration of the embryonic lens epithelium, are found in all affected boys. Although present at birth, the cataracts may not be detected until a

few weeks of life. Rarely, the lens opacities are so mild that they do not affect visual development, even into the teen years.

- Microphthalmos and enophthalmos, related to the lens abnormality, are noted occasionally.
- Infantile glaucoma, present in approximately 50% of affected males, is difficult to control and often results in buphthalmos (enlarged eyes) and progressive visual loss [McSpadden 2000, Nussbaum & Suchy 2001]. Often the glaucoma is not detected until after the lenses have been removed. The glaucoma is severe and requires surgical, rather than medical, management.
- Strabismus, retinal dystrophy, secondary corneal scarring, and calcific band keratopathy with keloid formation [Cibis et al 1982] may cause additional visual impairment [McSpadden 2000, Nussbaum & Suchy 2001].

All boys have impaired vision; corrected acuity is rarely better than 20/100 [McSpadden 2000, Nussbaum & Suchy 2001]. With decreased visual acuity, nystagmus develops early in life, even with early and uncomplicated surgery. Self-stimulatory activity also increases, i.e., rhythmic flapping of the hands, eye rubbing, and repetitive rocking movements. Despite aggressive intervention, visual disability may progress to blindness.

Central nervous system. Generalized infantile hypotonia is noted soon after birth and is of central origin. Deep tendon reflexes are usually absent. Hypotonia may slowly improve with age, but neither normal motor tone nor strength is ever achieved.

- Feeding difficulties in infancy associated with poor head control, sucking, or swallowing may be a consequence of the hypotonia.
- Decreased motor tone also results in delayed motor milestones. Independent ambulation occurs in approximately 25% of boys between age three and six years and in 75% by age six to 13 years. Some never walk, requiring the use of a wheelchair for mobility [McSpadden 2000].

Approximately 50% of affected boys have seizure disorders, most often of the generalized type and usually starting before age six years [McSpadden 2000].

Behavior problems (i.e., self-stimulation or stereotypic and obsessive-compulsive behaviors) are frequent and include many problems common to visually and intellectually handicapped individuals. Occasionally, violent tantrums or aggressive and self-abusive behaviors occur [Charnas & Gahl 1991, Kenworthy et al 1993].

Almost all affected males have some degree of intellectual impairment. Between 10% and 25% of affected males function in the low-normal or borderline range, approximately 25% function in the mild-to-moderate range, and 50%-65% function in the severe-to-profound range of intellectual disability [Kenworthy et al 1993]. Delayed language development is evident in early childhood. Most individuals learn to communicate verbally to some extent by age seven years; some eventually become quite verbal [McSpadden 2000]. Love of music and rhythm are notable.

As adults, most affected men reside with their families. A few are functional enough to live in a group home or even independently with appropriate assistance and guidance.

Kidneys. Affected boys have varying degrees of proximal renal tubular dysfunction of the renal Fanconi type. The features of symptomatic Fanconi syndrome do not usually become manifest until after the first few months of life, except for low molecular-weight (LMW) proteinuria.

- LMW proteins are normally filtered by the glomerulus, then reabsorbed in the proximal tubule through endocytosis and metabolized in lysosomes in proximal tubular cells.
- When reabsorption and/or metabolism are dysfunctional, LMW proteins, including retinol-binding protein, beta-2-microglobulin, and the lysosmal enzyme N-acetyl glucosaminidase, are lost in the urine.

LMW proteinuria has been identified as early as just after birth [Laube et al 2004] and may be the most sensitive early marker for renal involvement of Lowe syndrome.

The molecular size of albumin is at the upper end of the size range for LMW proteins, so the small percentage of albumin that is normally filtered by the glomerulus is also reabsorbed and metabolized by the proximal tubule via the LMW protein transport process.

In Lowe syndrome, proximal renal tubular dysfunction often leads to clinically apparent albuminuria (urine dipstick albumin 1-4+; nephrotic range proteinuria >1 g/m^2/day in more than half), while serum albumin remains normal [Bökenkamp & Ludwig 2016]. Albuminuria is better known as a marker of glomerular injury in other diseases such as diabetes mellitus; in Lowe syndrome it likely reflects proximal tubular dysfunction, especially early in life before chronic renal failure occurs.

All boys have LMW proteinuria and albuminuria, likely due to downstream disordered endocytosis and postendocytic membrane trafficking in the proximal tubular cell [Cui et al 2010, De Matteis et al 2017]. Most boys have aminoaciduria [Bökenkamp & Ludwig 2016]. Some boys develop full-blown renal Fanconi syndrome with bicarbonaturia and renal tubular acidosis, phosphaturia with hypophosphatemia and renal rickets, sodium and potassium wasting, and polyuria with an apparent urine-concentrating defect from the massive solute loss in the urine. Few of these boys have renal glucose wasting, which is frequently observed in other diseases with full-spectrum renal Fanconi syndrome [Bockenhauer et al 2008, Bökenkamp & Ludwig 2016, Zaniew et al 2018]. Other boys have little or no bicarbonaturia and phosphaturia, but LMW proteinuria and hypercalciuria with nephrocalcinosis and nephrolithiasis (calcium oxalate and calcium phosphate stones) similar to Dent disease [Bockenhauer et al 2008, Bökenkamp & Ludwig 2016].

Progressive glomerulosclerosis likely results from progressive renal tubular injury, which eventually may lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) between the second and fourth decades of life [McSpadden 2000, Nussbaum & Suchy 2001, Zaniew et al 2018].

Life span. Most males do not live past age 40 years. In older individuals, death has been related to progressive renal failure or scoliosis. Death from dehydration, pneumonia, and infections occurs at all ages [McSpadden 2000].

Short stature. Although birth length is usually normal, linear growth velocity is below normal and short stature becomes evident by age one year. The average adult height is approximately 155 cm [McSpadden 2000]. CKD and acidosis along with renal rickets or other bone disease may contribute to the short stature. Some boys have been treated with growth hormone, resulting in an increase in height but persistence of short stature for age [Zaniew et al 2018].

Feeding and gastrointestinal concerns

- Slow weight gain may occur because of insufficient caloric intake.
- Gastroesophageal reflux, most common in infancy, may be seen at any age.
- Aspiration of food along with a decreased ability to cough effectively to clear lung fields may lead to atelectasis, pneumonia, or chronic lung disease.
- Poor abdominal muscle tone increases the risk for chronic constipation and the development of (predominantly inguinal) hernias.

Bone disease in affected boys may be related to Fanconi syndrome with phosphaturia, inadequate renal production of 1,25-dihydroxyvitamin D, and chronic acidosis as well as CKD. The bone disease may appear as classic changes of rickets on bone radiographs.

However, even in the presence of well-corrected Fanconi syndrome and no findings of rickets, some boys have repeat pathologic bone fractures with poor healing and bone demineralization on radiographs or bone densitometry [E Brewer, personal observation].

Whether some of the bone disease is related to inactivity resulting from muscle hypotonia and immobilization in severely affected boys or to a primary defect in bone mineralization/molecular transport requires further study.

Other musculoskeletal concerns

- Decreased truncal motor tone increases the risk of developing scoliosis, present in approximately 50% of affected boys [McSpadden 2000].
- Hypermobile joints may result in joint dislocation, especially of the hips and knees.
- In affected teenagers and adults, joint swelling, arthritis, tenosynovitis, and subcutaneous benign fibromas, often on the hands and feet and most especially in areas of repeated trauma, are noted frequently [Athreya et al 1983, Elliman & Woodley 1983].
- Elevated serum creatine kinase (CK), AST, and LDH are typical in Lowe syndrome and likely due to abnormal muscle metabolism [Charnas et al 1991, Bökenkamp & Ludwig 2016]. Decreased plasma carnitine concentration has been reported in approximately one third of individuals with Lowe syndrome [Charnas et al 1991], but the need for or efficacy of carnitine supplementation has never been studied, and therapy continues to be individualized.

Genitourinary issues

- Undescended testes (cryptorchidism) are noted in approximately one third of affected boys [McSpadden 2000, Recker et al 2015]. Isolated LH elevation at baseline and on GnRH stimulation testing was observed in an infant with undescended testes [Warner et al 2017].
- Puberty may be delayed in onset; otherwise, male secondary sexual development is normal.

Teeth and skin findings. Dental malformations and generalized mobility of primary teeth with decreased or dysplastic dentin formation may also be related to a primary dental abnormality in Lowe syndrome [Harrison et al 1999].

Superficial cysts may occur in the mouth and on the skin, especially the scalp, lower back and buttocks.The skin cysts may become painful and occasionally infected. Histologic examination revealed epidermal cysts in which the dermis was lined by several layers of stratified squamous epithelium with a granular layer and filled with keratin flakes [Ikehara & Utani 2017]. Cysts have also been found in imaging studies of the kidneys and brain. These findings suggest that an abnormality in connective tissue may also be involved in the pathogenesis of the disorder [McSpadden 2000, Kim et al 2014, Murakami et al 2018].

Coagulation disorder. The OCRL-1 protein is found in human platelets. Prolonged or delayed bleeding following surgery, such as cataract extraction has been reported. An intrinsic platelet defect in these individuals that can be detected using a platelet function analyzer (PFA-100) was identified; other coagulation profile related tests, including platelet counts, gave normal results [Lasne et al 2010]. In another study, thrombocytopenia/low normal platelets were found in about 20% [Recker et al 2015].

Females

Approximately 95% of postpubertal heterozygous females have characteristic findings in the lens of each eye on slit lamp examination through a dilated pupil by an experienced ophthalmologist. The lens findings have correlated with the results of molecular genetic studies in predicting heterozygosity for the pathogenic variant in *OCRL* in postpubertal females [Lin et al 1999, McSpadden 2000, Röschinger et al 2000, Nussbaum & Suchy 2001]. While the lens findings may appear in prepubertal females as well (especially the less common axial posterior central opacity), their absence does not exclude the possibility of heterozygosity.

Most heterozygous females show numerous irregular, punctate, smooth, off-white (white to gray) opacities, present in the lens cortex, more in the anterior cortex than the posterior cortex, and distributed in radial bands that wrap around the lens equator. Classically, the nucleus is spared. On retroillumination, the opacities are distributed in a radial, spoke-like pattern and can be relatively dense in a wedge shape comparable to an hour or two on the face of a clock, alternating with a similar-sized wedge with few to no opacities.

A few heterozygous females (~10%) have a dense central precapsular dead-white cataract at the posterior pole of the lens that may be visually significant if it is large. Similarly, the cataracts in some heterozygous females may become visually significant by the fourth decade and require surgery without the diagnostic importance being recognized.

The manifestations of Lowe syndrome besides those seen in the lens are not observed in heterozygous females unless there is either rare X;autosome translocation with the X chromosome breakpoint at *OCRL* or extremely skewed X inactivation. In an example of the latter, a female with two structurally normal X chromosomes showed classic, severe Lowe syndrome as a result of a familial defect in X inactivation inherited from her father. The paternally derived X chromosome containing a normal *OCRL* gene remained inactive in 100% of cells, while the maternally derived X chromosome carrying a pathogenic variant of *ORCL* was active in 100% of cells tested [Cau et al 2006].

Genotype-Phenotype Correlations

To date, correlation of genotype with phenotype has not been established. Differing clinical courses have been noted in unrelated individuals with the same *OCRL* pathogenic variant [Leahey et al 1993]. It is also now apparent that pathogenic variants in *OCRL* that result in total loss of *OCRL* expression occur both in individuals with Lowe syndrome and in individuals with the allelic disorder, Dent disease, but there have not been families in which one affected male has Lowe syndrome and a male relative with the same pathogenic variant has Dent disease.

Penetrance

Penetrance is complete, with variability in severity of phenotype in affected males within any given family.

Nomenclature

Oculocerebrorenal syndrome, the formal term for this disorder, is synonymous with Lowe syndrome, and may be preferred to avoid eponymous syndrome nomenclature.

Prevalence

Lowe syndrome is an uncommon, pan ethnic disorder with an estimated prevalence of 1:500,000 in the general population, based on observations of the American Lowe Syndrome Association and the Italian Association of Lowe syndrome [Bökenkamp & Ludwig 2016].

The disorder has been seen in America, Europe, Australia, Japan, and India and is believed to occur worldwide.

Genetically Related (Allelic) Disorders

Pathogenic variants in *OCRL* have been found in 15% of individuals with Dent disease. Pathogenic variants in *OCRL* can therefore occur within individuals with the isolated renal phenotype of Dent disease who lack the cataracts, renal tubular acidosis, and neurologic abnormalities that are characteristic of Lowe syndrome; these individuals are classified as having Dent disease 2 [Hoopes et al 2005, Bökenkamp et al 2009, De Matteis et al 2017].

Although the renal tubulopathy in Lowe syndrome (which is mainly characterized by altered low molecular-weight protein and albumin reabsorption) and Dent disease is similar, it is generally milder in Dent disease. Of note, this milder Dent disease phenotype could not be attributed to lesser protein expression or enzyme activity.

Frameshift and nonsense *OCRL* variants associated with Dent disease 2 have been mapped to exons different from those causing Lowe syndrome [Hichri et al 2011]; however, *OCRL* missense and splicing variants and in-frame deletions that cause these two disorders do not map exclusively to specific gene regions.

- Frameshift and nonsense variants associated with Dent disease 2 are in the first seven exons. Missense variants associated with Dent disease 2 are most often, but not exclusively, located in exons 9-15, which encode the catalytic phosphatase domain.
- Frameshift and nonsense variants associated with Lowe syndrome are located in the middle and later regions of the gene, exons 8-23, which encode the catalytic phosphatase and the Rho-GAP-like domains [Tosetto et al 2009, Hichri et al 2011].

Differential Diagnosis

Low molecular-weight (LMW) proteinuria is a feature of Fanconi syndrome and can also be seen in other conditions including cystinosis, nephrotoxic drug injury to the tubules (e.g., aminoglycosides), and acute tubulointerstitial renal transplant rejection with tubular injury. However, the LMW proteinuria appears to be a more prominent feature of renal tubular dysfunction in Lowe syndrome and Dent disease than in these other disorders.

Like Lowe syndrome, generalized congenital infections (e.g., rubella) are associated with a combination of congenital or neonatal-onset cataracts, hypotonia, proximal renal tubular dysfunction, and/or delayed development and should be considered in the differential diagnosis of Lowe syndrome. Genetic disorders that may be associated with these features are summarized in Table 2.

Table 2. Disorders to Consider in the Differential Diagnosis of Lowe Syndrome

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Lowe syndrome	Distinguishing from Lowe syndrome
Zellweger spectrum disorder	*PEX1* *PEX6* *PEX12* *PEX26* *PEX10* *PEX2* *PEX5* *PEX13* *PEX16* *PEX3* *PEX19* *PEX14* *PEX11β*	AR	• Hypotonia • May have congenital cataracts • Retinal dystrophy • Renal cysts • DD • Poor feeding • Neonatal seizures common	• Distinctive craniofacial features (e.g., flat face, broad nasal bridge, large anterior fontanelle, widely split sutures) • SNHL • Liver dysfunction • Bony stippling (chondrodysplasia punctata) of patella(e) & other long bones may occur.
Nance-Horan syndrome (OMIM 302350)	*NHS*	XL	• Congenital cataracts • Hypotonia • ID • Dental anomalies (e.g., cone-shaped incisors & supernumerary teeth) • Heterozygous females have Y-shaped sutural cataracts & may have dental anomalies.	• Microcornea • No renal abnormalities • Facial dysmorphisms (e.g., anteverted pinnae) • Absence of characteristic facial appearance seen in Lowe syndrome (i.e., sunken orbits & bitemporal hollowing)

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Lowe syndrome	Distinguishing from Lowe syndrome
Smith-Lemli-Opitz syndrome	*DHCR7*	AR	• Congenital cataracts • Hypotonia • Renal anomalies (most commonly renal hypoplasia or agenesis, renal cortical cysts, hydronephrosis, & structural anomalies of collecting system) • Moderate-to-severe ID • Prenatal & postnatal growth restriction	Multiple major & minor malformations incl: • Microcephaly • Distinctive facial features • Cleft palate • Cardiac defects • Underdeveloped external genitalia in males • Postaxial polydactyly • 2-3 toe syndactyly
Congenital myotonic dystrophy type 1	*DMPK*	AD	• Cataracts • ID • Infantile hypotonia; severe generalized weakness at birth	• Respiratory insufficiency at birth • No significant renal disease
Disorders of mitochondrial oxidative phosphorylation [3]	See footnote 1.		• Seizures • Hypotonia at birth or developing in early infancy • Renal findings incl Fanconi syndrome, RTA, & renal failure are frequent (esp in Kearns-Sayre syndrome, mt encephalomyopathy & mt depletion syndrome) [3]	• Common features of mt disease incl: ptosis, external ophthalmoplegia, proximal myopathy, exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, diabetes mellitus • CNS findings (often fluctuating): encephalopathy, dementia, migraine, stroke-like episodes, ataxia • Note: Congenital cataract is seen in *GFER*-related mt myopathy (OMIM 613076) but is NOT typical for mt disorders
Cystinosis	*CTNS*	AR	• Renal Fanconi syndrome [2]; CKD • Poor growth; in untreated persons, failure to grow is generally noticed at age 6-9 mos. • Retinal disease	• Typical cystine crystals on slit lamp exam of cornea • No cataracts • Intellectual abilities low-normal • No hypotonia
Donnai-Barrow syndrome	*LRP2*	AR	• LMW proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, CKD [4] • Cataract may be seen in juveniles w/Donnai-Barrow syndrome.	• High myopia • No congenital cataracts • SNHL • Hypertelorism • Large anterior fontanelles • Hypotonia not typical; motor milestones only slightly delayed

AD = autosomal dominant; AR = autosomal recessive; CKD = chronic kidney disease; CNS = central nervous system; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; LMW = low molecular-weight; MOI = mode of inheritance; mt = mitochondrial; RTA = renal tubular acidosis; SNHL = sensorineural hearing loss; XL = X-linked

1. Mitochondrial disorders may be caused by defects of nuclear DNA or mtDNA: nuclear gene defects may be inherited in an autosomal recessive, autosomal dominant, or X-linked manner, mitochondrial DNA defects are transmitted by maternal inheritance.

2. Cystine-depleting therapy begun just after birth can attenuate the Fanconi syndrome.

3. Finsterer & Scorza [2017]

4. Anglani et al [2018]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Lowe syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Lowe Syndrome

System/ Concern	Evaluation	Comment
Eyes	Ophthalmologic exam to assess for cataract & glaucoma	Behavior problems may necessitate use of anesthesia for exam.
CNS	• Developmental & behavior assessments • EEG if seizures present to optimize therapy	
Kidneys	Assess renal tubular function.	Tests should incl: • Serum electrolytes, glucose, calcium, phosphorus, creatinine • Simultaneous urinalysis, urine pH, sodium, potassium, chloride, calcium, phosphorus, creatinine, amino acids, protein & retinol-binding protein, &/or N-acetyl glucosaminidase (if available) [1]
	If hematuria or hypercalciuria is present, renal ultrasound to look for nephrolithiasis or nephrocalcinosis.	
	If aciduria or phosphaturia present, test serum 1,25-dihydroxy vitamin D & parathyroid hormone plus bone radiographs to evaluate for renal rickets.	
Growth/ Feeding	• Growth parameters • Infants assessed for feeding problems & gastroesophageal reflux, incl a pH probe study	
Skeletal	Radiographs for bone pain or point tenderness to evaluate for fractures	
Dental	Thorough clinical exam after tooth eruption	Generalized mobility of all primary teeth as well as subrachitic changes due to renal rickets
Hematologic	Alert providers performing any surgical interventions of risk for delayed bleeding after apparent hemostasis in immediate post-op period.	
Other	Consultation w/clinical geneticist &/or genetic counselor	

1. Interpretation of these results allows diagnosis of type 2 renal tubular acidosis, hypokalemia, phosphate wasting with decreased tubular reabsorption of phosphate (TRP), hypercalciuria (urine calcium/creatinine ratio >0.02), amino aciduria, albuminuria (urine dipstick-positive albumin and urine protein/creatinine ratio >0.2), LMW proteinuria, and CKD (serum creatinine).

Treatment of Manifestations

Management of the varying clinical problems usually requires more than one medical specialist; experts in pediatric ophthalmology, nephrology, clinical biochemical genetics, metabolism, nutrition, endocrinology, neurology, child development, behavior, rehabilitation, general surgery, orthopedics, or dentistry may be involved.

Table 4. Treatment of Manifestations in Individuals with Lowe Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Cataract	• Early removal to promote proper visual stimulation & development • Postoperative glasses to improve vision & replace the crystalline lens power	NOT recommended: • Surgical implantation of artificial lenses (due to high prevalence of infantile glaucoma) • Contact lenses (due to risk for corneal keloids)
Glaucoma	Manage w/standard medical & surgical measures.	Often difficult to control medically & almost invariably requires surgery
Developmental delays	Early infant therapy, preschool intervention program & IEP throughout schooling	
Behavior problems	Behavior modification program	Medication may also be needed for behavior control.
Seizures	Anticonvulsant medication	
Renal tubular dysfunction	Oral supplements of sodium & potassium bicarbonate or citrate to correct acidosis & hypokalemia	Doses need to be titrated to individual needs based on "trough" blood concentrations of serum electrolytes (sodium, potassium, chloride, & total carbon dioxide).
	Treatment w/oral phosphate, along w/oral calcitriol (1,25-dihydroxyvitamin D_3) to correct hypophosphatemia & renal rickets from renal tubular dysfunction	Doses should also be titrated to individual needs based on trough blood concentration for phosphorus & serum concentrations of 1,25-dihydroxyvitamin D, calcium, & intact parathyroid hormone.
	IV replacement of fluids, bicarbonate, & electrolytes at times of illness assoc w/vomiting & diarrhea or when fasting (e.g., w/surgical procedures)	
ESRD	Chronic dialysis & renal transplant may be successful in some persons.	Progressive renal tubular injury → progressive glomerulosclerosis & CKD → ESRD (over yrs, usually by 2nd-4th decade)
Growth/ Feeding	Growth hormone therapy → improved growth velocity in some boys.	Potential benefits of such therapy must be weighed against its costs/limitations.
	• NG tube feedings or feeding gastrostomy w/or w/o fundoplication may be necessary to treat infant feeding & nutrition problems related to hypotonia. • Standard treatment for gastroesophageal reflux, if present	
Scoliosis & joint hypermobility	Bracing or surgery may be performed to arrest or correct severe or progressive scoliosis & joint hypermobility.	
Fibromas & cutaneous cysts	Resection may be needed if painful, recurrently infected, or limiting function.	

CKD = chronic kidney disease; ESRD = end-stage renal disease; IEP = individualized education program; NG = nasogastric

Surveillance

Table 5. Recommended Surveillance for Individuals with Lowe Syndrome

System/ Concern	Evaluation	Frequency
Eyes	Intraocular pressure monitoring	Every 6 mos life long
	Other ophthalmic eval	• As determined by specialist based on type & severity of eye abnormality • Promptly w/any signs of ↑ intraocular pressure (e.g., excessive tearing, eye rubbing, change in clarity/ transparency of cornea)
CNS	Developmental progress assessed & educational plan updated	2x/yr for 1st 3 yrs, then annually
	Brain imaging for any regression in abilities	
Kidneys	Kidney function assessment [1]	At least annually
	• If on supplemental bicarbonate or citrate, phosphorus or calcitriol or other vitamin D analog, need kidney function assessment [1] w/blood & urine tests • May need serum vitamin D-25 hydroxy to assess for parent vitamin D deficiency	Every 3-6 mos; more often after dose changes
	Radiographs of long bones & growth plates if renal bone disease is present	Regular intervals as needed, but no more than every 6 mos
Growth	Height/length & weight	• Every 1-2 mos in infants • Every 3-6 mos in older children & adolescents • Every 3 mos if on growth hormone
Skeletal	Monitor scoliosis & joint hypermobility	Annually
Dental	Exams by pediatric dentist	2x/yr

1. Testing includes measurement of (a) serum concentrations of electrolyte, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, albumin, intact parathyroid hormone, and 1,25-dihydroxyvitamin D and (b) urinalysis and random urine protein, calcium, and creatinine.

Agents/Circumstances to Avoid

Corneal contact lenses. Because of the associated risks of corneal keloid formation and the inherent difficulties that the person with Lowe syndrome has in managing personal contact lens care, conventional eye glasses seem safer than corneal contact lenses.

Artificial lens implants. Although some infants have had primary intraocular lens implantation at the time of cataract surgery, the associated risk of glaucoma appears higher in those infants with artificial lens implants. Therefore, artificial lens implants should be used with extreme caution, with intraocular pressure carefully monitored (under anesthesia if required) on a continual basis.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Lowe syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *ORCL* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote.

  Note: If a woman has more than one affected child and no other affected relatives and if the *OCRL* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. In one study group, two (4.5%) of 44 women were found to have germline mosaicism [Satre et al 1999, Monnier et al 2000].
- If a male is the only affected family member, the mother may be a heterozygote or have germline mosaicism, or the affected male may have a *de novo OCRL* pathogenic variant, in which case the mother is not a heterozygote. *De novo* pathogenic variants have been reported in approximately 32% of males with Lowe syndrome [Satre et al 1999, Monnier et al 2000].
- The mother of a child with Lowe syndrome who represents a simplex case (i.e., a single occurrence in a family) should be thoroughly evaluated by an experienced ophthalmologist for the characteristic punctate anterior radial lens opacities seen in female heterozygotes.

Sibs of a male proband. The risk to sibs of a proband depends on the genetic status of the mother:

- If the mother of the proband is heterozygous for an *OCRL* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be heterozygotes and will usually develop characteristic findings in the lens of each eye (see Clinical Description, Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *OCRL* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is still increased due to the possibility of maternal germline mosaicism which has been reported in five families with Lowe syndrome [Bökenkamp & Ludwig 2016].

Offspring of a male proband. Affected males are not known to reproduce.

Other family members. The proband's maternal aunts may be at risk of being heterozygous and the aunt's offspring, depending on their sex, may be at risk of being heterozygous or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *OCRL* pathogenic variant has been identified in the proband.

Slit lamp examination. Approximately 95% of heterozygous females older than age 15 years are observed to have characteristic findings in the lens of the eye on slit lamp examination by an experienced ophthalmologist using both direct and retroillumination; thus, ophthalmologic exam may be used as a method of heterozygote detection.

Biochemical enzymatic assays for inositol polyphosphate 5-phosphatase OCRL-1 activity are **not** accurate for heterozygote detection because of lyonization (random X-chromosome inactivation) in females [Lin et al 1999].

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of heterozygote status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adult females who are heterozygotes, or are at risk of being heterozygotes.

Prenatal Testing and Preimplantation Genetic Testing

Once the *OCRL* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Because of the relatively high rate (4.5%) of germline mosaicism, **every** mother of a male with Lowe syndrome, even with a negative family history, should be offered prenatal DNA testing if the pathogenic variant in her son is known, even if the results of dilated slit lamp examination or DNA testing suggest that she is not a heterozygote [McSpadden 2000].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Lowe Syndrome Association**
  PO Box 864346
  Plano TX 75086-4346
  Phone: 972-733-1338
  Email: info@lowesyndrome.org
  www.lowesyndrome.org

- **Lowe Syndrome Trust**
  77 West Heath Road
  London NW3 7TH
  United Kingdom
  Phone: +44 0 20 7794 8858; +44 0 20 8458 6791
  Email: lst@lowetrust.com
  www.lowetrust.com

- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision

- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Lowe Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
OCRL	Xq26.1	Inositol polyphosphate 5-phosphatase OCRL	OCRL @ LOVD at NCBI	OCRL	OCRL

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Lowe Syndrome (View All in OMIM)

300535	OCRL INOSITOL POLYPHOSPHATE-5-PHOSPHATASE; OCRL
309000	LOWE OCULOCEREBRORENAL SYNDROME; OCRL

Molecular Pathogenesis

Lowe syndrome results from loss of inositol polyphosphate 5-phosphatase OCRL-1 (phosphatidylinositol polyphosphate 5-phosphatase OCRL-1) activity. Although the exact mechanisms are unclear, the absence of the protein and elevated PtdIns (4,5) P_2 levels may affect these processes, which may influence all – or a combination of some – of the following:

- Cell membrane composition
- Actin cytoskeletal organization
- Endocytosis
- Lysosomal-autophagic pathway
- Primary ciliary synthesis and function

Loss of OCRL-1 ultimately leads to abnormal differentiation, cell migration, and function in certain cell types (i.e., renal tubule or lens epithelium). Such changes could result in the birth defects and other clinical

manifestations of Lowe syndrome [Zhang et al 1995, Suchy & Nussbaum 2002, Ungewickell et al 2004, De Matteis et al 2017].

The enzyme is present in the trans-Golgi network and the endosomal and lysosomal compartment of a variety of cell types, including brain, skeletal muscle, heart, kidney (cultured proximal renal tubular cells), lung, ovary, testis, cultured fibroblasts, placenta, chorionic villi samples, and cultured amniocytes.

Mechanism of disease causation. Lowe syndrome occurs through a loss-of-function mechanism. Reduced activity or absence of inositol polyphosphate 5-phosphatase OCRL-1 leads to elevated intracellular levels of its substrate, phosphatidylinositol (4,5) bisphosphate [PtdIns (4,5) P_2] [Zhang et al 1998], resulting in highly pleiotropic effects on a number of cellular processes. These processes include a defect in intracellular protein trafficking [Vicinanza et al 2011], impaired endocytic tubular transport [Festa et al 2019] and primary ciliary function [Luo et al 2013]. Impaired endocytosis is most closely implicated in the low molecular-weight proteinuria and other tubular defects, while ciliary function abnormalities are more closely implicated in the ophthalmologic complications.

Of the identified pathogenic variants, 93% have been located in exons 10-18 and exons 19-23 of *OCRL*, particularly in exon 15 [Satre et al 1999, Monnier et al 2000, Nussbaum 2001, Nussbaum & Suchy 2001]. Recent data suggest an association between pathogenic variants in the first eight exons of *OCRL* and Dent disease [Shrimpton et al 2009, Hichri et al 2011]; however, the correlation is not perfect [Tosetto et al 2009].

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