Amsterdam UMC
University Medical Centers

Lowe syndrome

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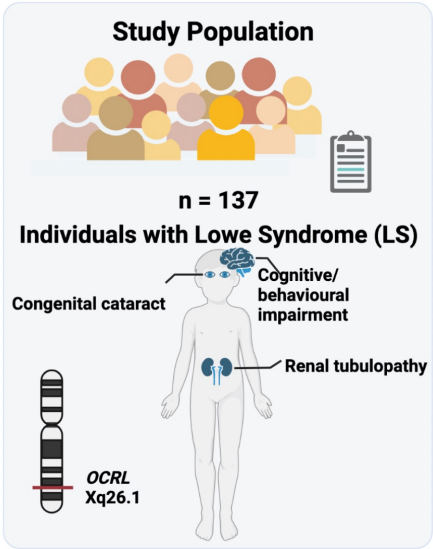
Disclosures

- No relevant disclosures

Oculo-cerebro-renal syndrome of Lowe

- First described by Lowe in 1952
- OMIM # *309000*
- X-linked recessive inheritance
- Mutation in *OCRL-1* gene
- 30% *de novo* mutations, 3% mosaicism. In 10% no mutation found
- Prevalence ca. 1 in 500,000 (Italy), 1 in 2 million (Poland)
- Defective *Phosphatidyl-inositol(4,5)P_2 5-phosphatase*



Sena et al, J. Med. Genet 2022

Key manifestations

Eyes

- Congenital cataract, glaucoma

CNS

- Congenital hypotonia, absence of tendon reflexes
- Severe intellectual disability, IQ 40-50 (25% >70)
- Seizures in 50%
- Behavioral abnormalities

Kidney

- Generalized proximal tubular dysfunction (incomplete Fanconi syndrome)
- Progressive kidney failure

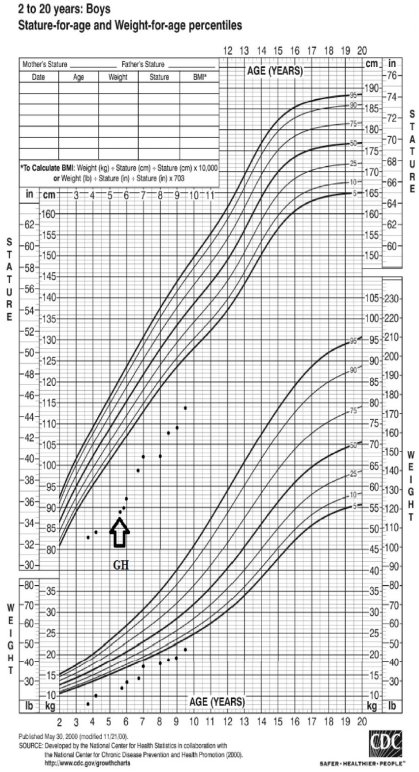
Other manifestations

Short stature
- Starting in infancy, unrelated to kidney (dys)function

Musculoskeletal
- Scoliosis
- Osteopenia / rickets
- Debilitating deforming arthopathy

Bleeding disorder
- Impaired primary hemostasis, coagulation tests normal
- Responds to tranexamic acid

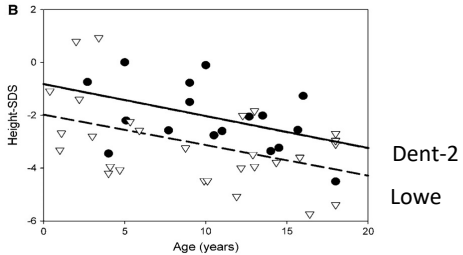
Increased CK / LDH



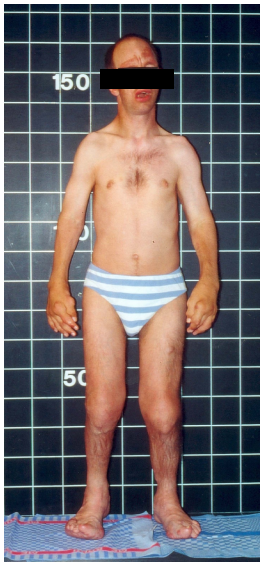
Iotova et al, Children 2023

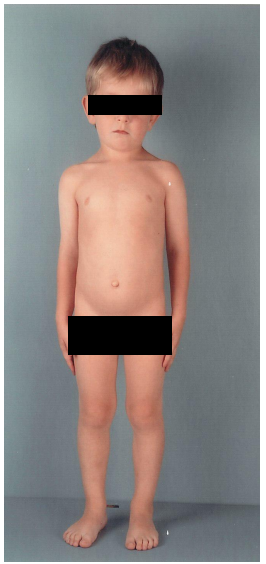
Dent-2

- Some 15% of patients with phenotype of Dent disease habour an *OCRL-1* mutation
- Milder phenotype mostly restricted to the kidneys – LMW proteinuria obligate finding
- “Lowe light”



On close examination
39 % ocular symptoms
46 % CNS symptoms
64 % CK/LDH ↑





Gianesello et al, Genes 2021 - Bökenkamp et al, J. Pediatr 2009

Time pattern of disease manifestations

Cataract
Muscle hypotonia
Tendon reflexes -
CK / LDH ↑
LMW-PU

Glaucoma
Growth retardation
Developmental
delay

Scoliosis

Tantrums etc
Corneal scarring
Interstitial fibrosis,
glomerulosclerosis

Cataract
AFP ↑

renal
Fanconi Sy

Arthropathy
ESKD

Prenatal | Neonate | 1-3 months | Infancy | Childhood | Adolescence | Adulthood

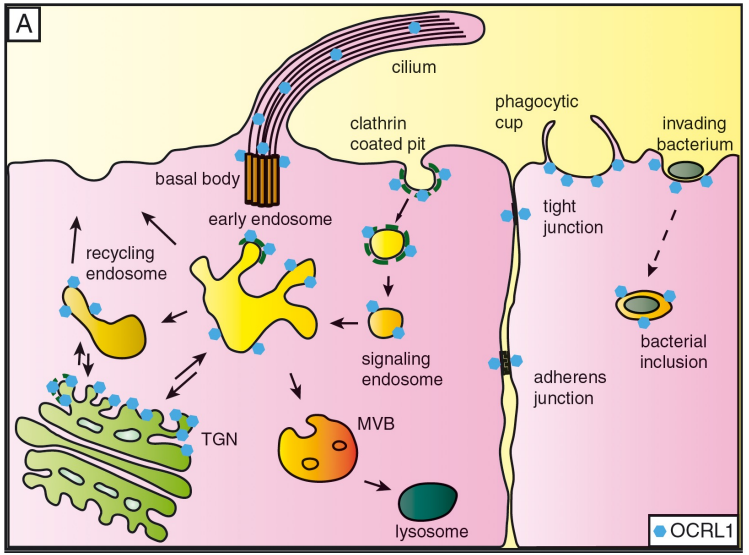
Any age: *Seizures, platelet dysfunction*

Bökenkamp et al, Pediatr. Nephrol 2016

OCRL-1 defect causes multisystem disease

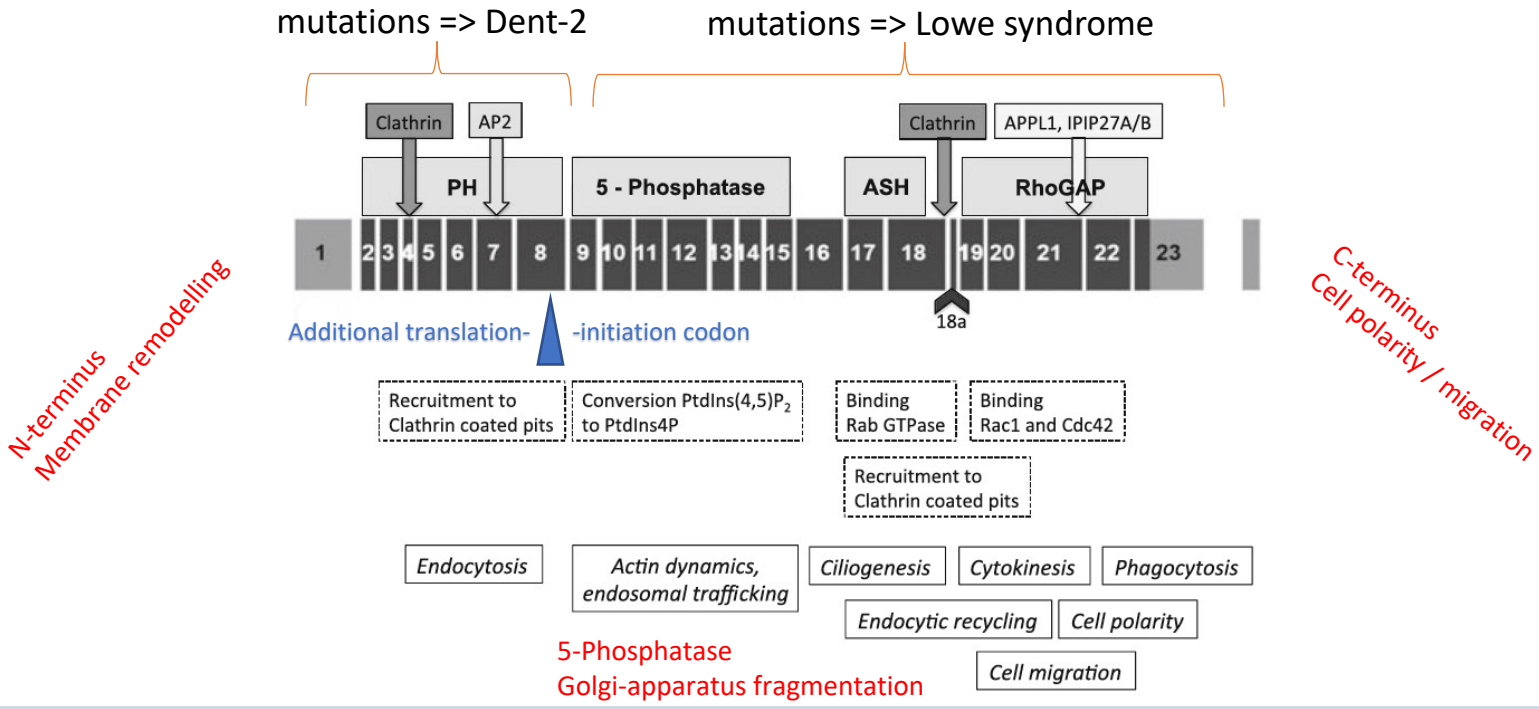
- Seven different phosphoinositides
- Phosphorylation of inositol ring determines **compartment identity**

- OCRL-1 involved in
  - Cell polarity / cilia formation
  - Cell migration
  - Cell adhesion
  - Cell signaling
  - Phagocytosis
  - Actin cytoskeleton remodeling
  - Membrane and endosomal trafficking



Mehta et al, Traffic 2014

OCRL-1 gene domains involved in different processes



Ramadesikan et al, Hum Mol Genet 2021. Sakakibara et al, NDT 2022. Bökenkamp et al, Pediatr. Nephrol 2016

No strict genotype-phenotype correlation

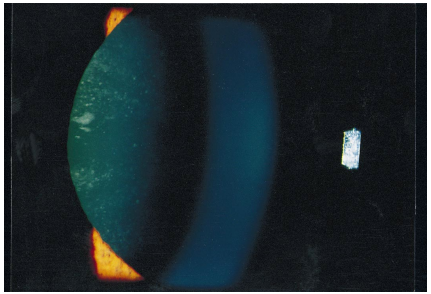
- At least five mutations reported manifesting with very different disease severity (Dent-2 vs. Lowe syndrome)
- Also differences in disease severity within a single family (ocular manifestations)
- Activity of PtdIns(4,5)P_2 5-phosphatase comparable in fibroblasts from Lowe and Dent-2 patients
- Modifying genes? *INPP5B* compensating for *OCRL*-defect?
- Environmental factors?

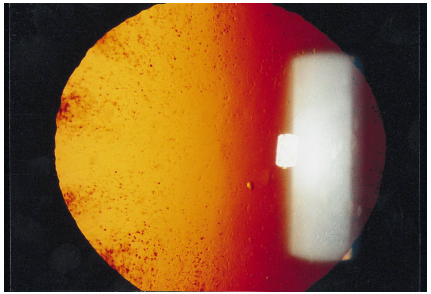
Hichri et al, Hum Mutat 2010

Female carriers

- In 60% Lowe syndrome transmitted by female carriers
- Asymptomatic clinically (only 10 cases of more severe manifestations reported)

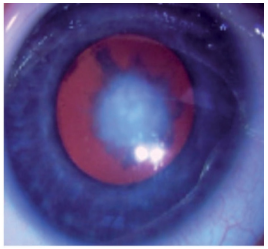
- Obligate finding in post-pubertal females: asymptomatic punctate lens opacities

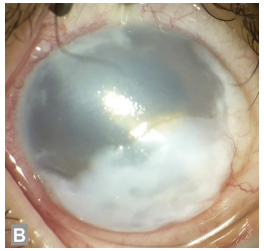




Lin T. et al, Ophthalmology 1999

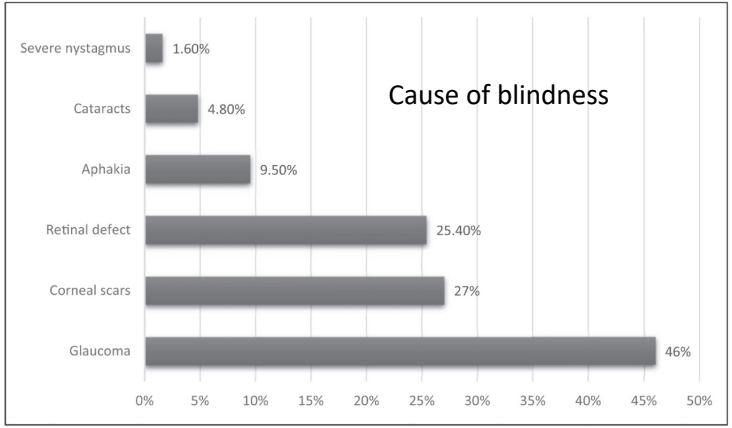
Eyes





- Congenital cataract requiring lens extraction in the first months
- Glaucoma manifesting around the age of 4 months, often requiring surgery
- Corneal keloid developing around the age of 7 years
- Avoid contact lenses

More than 50% legally blind (visual acuity ≤ 20/200)



Ma et al, Eur J Ophthalmol 2020 - Martin et al, Ophthalmology 2022

Nervous system

- Most debilitating clinical feature
- Muscle hypotonia of central origin. Absence of tendon reflexes.
- Elevated muscle enzymes CK / LDH
- Motor milestones delayed (independent ambulation achieved at 6 to 13 years)
- Seizures in 50%
- Behavioral abnormalities
  - Temper tantrums in response to frustration
  - Stubbornness, irritability
  - Repetitive purposeless movements (e.g. hand flapping)
  - Aggression, auto-mutilation
- Distinct from individuals with comparable intellectual and visual impairment

Risperidone?
Paroxetine?
Clomipramine?

Renal Fanconi syndrome

Number of manifestions may increase with time

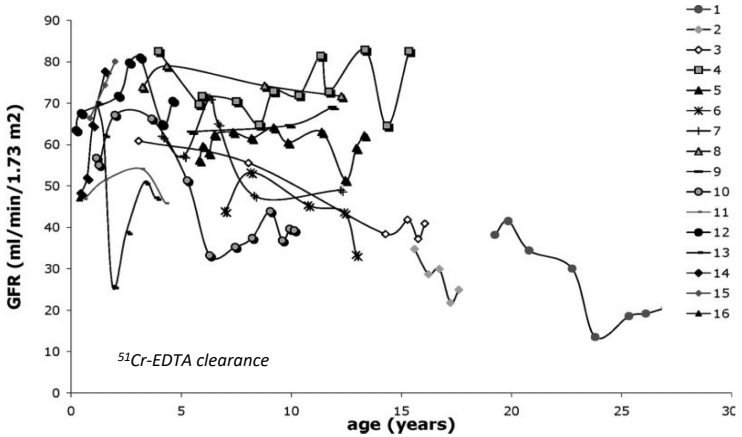
	Recker et al (N = 28)	Bökenkamp et al (N = 36)	Böckenhauer et al (N = 16)	
LMW proteinuria	100%	100%	100%	First abnormality, detectable at birth
Hypercalciuria	68%	83%	94%	
Nephrocalcinosis/-lithiasis	43%	44%	53%	Less than in Dent 1 despite comparable hypercalciuria
Aminoaciduria	72%	82%	88%	More than in Dent- 1 and in Dent-2
RTA	79%	33%	44%	Osteopenia / rickets
Phosphate wasting	58%	43%	20%	
Potassium wasting	44%	21%	NA	
Glycosuria	4%	7%	0%	Less than in other forms of Fanconi sy

Treatment symptomatic as in other forms of renal Fanconi syndrome

Recker et al. Pediatr Nephrol 2015 - Bökenkamp et al, J. Pediatr 2009 - Böckenhauer et al, cJASN 2009

Kidney function

- Calculation of eGFR using kreatinine problematic (low muscle mass)
- Use cystatin C (or a k-value of 26 in the Schwartz equation with creatinine in µmol/l)
- Progressive decline of GFR, unrelated to presence of nephrocalcinosis
- ESKD mostly in adulthood
- Incidental reports of dialysis and transplantation

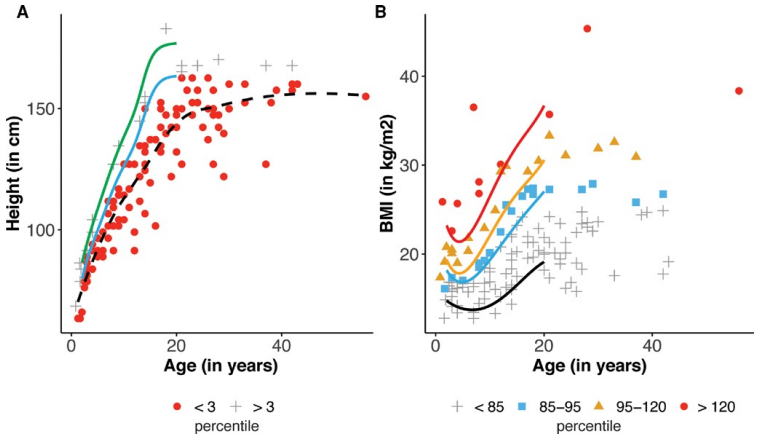


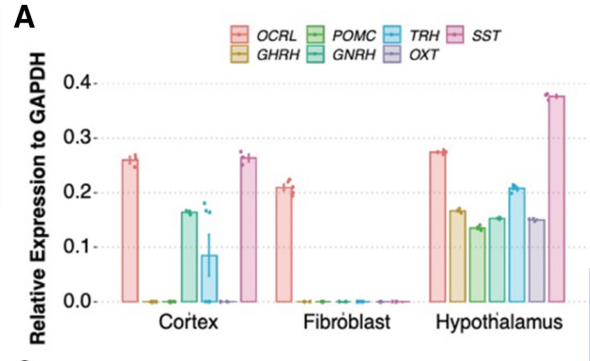
Böckenhauer et al, cJASN 2009

Endocrine function

- Postnatal growth failure (80% < 3rd centile)
- Unrelated to kidney function, resistant to correction of renal tubular dysfunction
- Undescended testis about 50%
- Delayed puberty (median age 15 years)

- OCRL highly expressed in hypothalamus

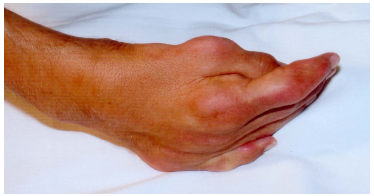




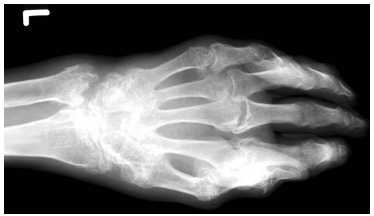
Sena et al, J. Med. Genet 2022

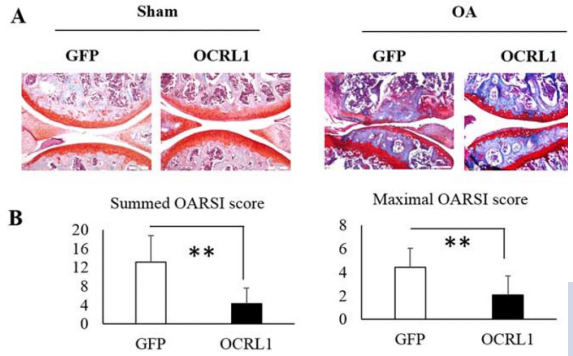
Osteoarthritis

- Debilitating deforming arthropathy
- No specific treatment



- OCRL expressed in human cartilage
- Upregulation of OCRL effective against osteoarthritis in animal model
- Related to presence of the RhoGAP domain





Zhu et al, Arthritis Rheumat 2015 - Bökenkamp et al, Pediatr. Nephrol 2016

Cause of death

- Many reviews state that death typically occurs in the 3rd or 4th decade
- Zaniew: literature search for case reports and contact with treating physicians:
  - 15 cases
  - Death at 4 days to 44 years, median 7 years
  - (Presumed) causes:
    - Pneumonia / respiratory failure in 4
    - Sepsis in 1
    - Seizures in 1
    - Sudden death in sleep in 2
    - Ewing sarkoma in 1
    - Severe acidosis in 1
    - Cardiac failure 2 years after kidney transplantation
    - unknown in 4

Nota bene – only 2 patients died with /of ESKD (at age of 18 and 44 years)

Zaniew et al, Poster IPNA 2019

Take home

- Lowe syndrome is a severe multisystem disease
- Extra-renal manifestations determine burden of the disease
- Mortality is unrelated to renal failure in most patients
- Incomplete renal Fanconi syndrome
- Slowly progressive loss of kidney function
- Creatinine less suitable for monitoring, use cystatin C

- Nephrologists are not involved in the care of many Lowe patients
- Importance of patient organizations (e.g. Lowe Sy Association [US], Lowe Trust [GB])