Case Report
A Novel OCRL Gene Mutation in a Child with Lowe Syndrome

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Abstract

Oculocerebrorenal (OCRL) syndrome, also called Lowe syndrome, is a rare genetic disease caused by mutations in the *OCRL* gene, which is located at Xq25-26 and encodes inositol polyphosphatidylinositol-4,5-biphosphate (PIP$_2$) 5-phosphatase in the Golgi apparatus. The syndrome mostly affects Caucasian or Asian males, and is characterised by bilateral congenital cataracts, renal Fanconi syndrome with proteinuria, albuminuria, aminoaciduria, and phosphaturia, as well as neurologic features such as growth and mental retardation, seizures, and behavioral stereotypes. Here, we describe a 4-year-old boy diagnosed with Lowe syndrome on the basis of congenital cataracts, language delay, and renal tubular dysfunction. On genetic analysis, the patient was found to carry a novel mutation that causes an amino acid substitution in exon 11 of the *OCRL* gene.

Introduction

Lowe syndrome is an X-linked recessive disorder that affects multiple organs, especially the eyes, central nervous system, and kidney. The estimated prevalence is 1-2 in 1,000,000 patients.[1] The disorder is also called Oculocerebrorenal (OCRL) syndrome, and is characterised by bilateral congenital cataracts, glaucoma, hypotonia, seizures, cognitive impairment, and selective proximal tubulopathy. It is caused by mutations in the *OCRL* gene on

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chromosome Xq25-q26.[2] At least 200 *OCRL* gene mutations have been reported so far, of which 90% are located in two hot spots in exons 10-18 and 19-23.[3] The gene has important roles in several subcellular compartments, and affects various processes, including phagocytosis, cytokinesis, cell adhesion and migration, cell polarisation, and ciliogenesis.[4] OCRL is localised to the trans-Golgi network and regulates membrane traffic. OCRL regulates endosome sorting, signaling, and recycling by binding to clathrin on clathrin-coated vesicles. It is recruited to phagosomes at a late stage in their formation. OCRL is also present within the basal body of the cilium, playing an important role in ciliogenesis by facilitating the trafficking of ciliary components into the cilium. OCRL is localised to adherens junctions, tight junctions, and lamellipodia and modulates the migration and adhesion of fibroblasts. Furthermore, this molecule helps to maintain cell polarity and is localised to the midbody, where cytokinesis occurs.[4]

Mutations in OCRL have been identified in Dent patients as well as in Lowe syndrome patients. Dent disease is characterised by selective proximal renal tubulopathy caused by mutations in the voltage-gated chloride channel and chloride/proton antiporter. OCRL mutations have been observed in 15% of Dent disease patients.[5]

Some reports have demonstrated a correlation among genotype, phenotype, and prognosis. Thus, it is important to identify the causative mutation to facilitate genetic counseling and early detection. Here, we report a novel nonsynonymous mutation in a patient with mild Lowe syndrome.

Case Report

A 4-year-old boy was admitted to our hospital with proteinuria. He was born at 41 weeks by vaginal delivery, with birth weight 3,220 g and unremarkable perinatal history. He was diagnosed with thick cortical deposits in both eyes one day after birth, and underwent bilateral cataract surgery at two months. However, visual acuity remains poor. The patient has no history of seizure, hypotonia, and edema. The family is otherwise healthy and nonconsanguineous, and the patient has one healthy younger sister. On physical examination, height was measured at 100.5 cm (3rd-5th percentile), weight at 15.3 kg (below 3rd percentile), and head circumference at 52 cm (75th-90th percentile). The patient had low-set ears, deep-set eyes, frontal bossing, and micrognathia with a low nasal bridge and tooth malformation.

Urine had a pH of 6.0 and specific gravity of 1.024 and was protein 3+ and glucose-negative. A few leukocytes were observed by microscopy. Blood chemistry results were within normal values. The blood gas analysis revealed a pH of 7.394, which was normal. HCO_3 was decreased to 17.2 mM. Free thyroxine, thyroid stimulating, parathyroid hormone, and 25 (OH) vitamin D levels were within the normal ranges.

The calcium to creatinine ratio in random urine samples was within the normal range. The protein to creatinine ratio was increased to 463.8 mg/mmol (normal <20 mg/mmol). Fractional sodium excretion, fractional potassium excretion, and fractional uric acid excretion were normal. The β2 microglobulin levels exceeded 50.00 mg/L (normal 0.02-0.25 mg/L). The glomerular filtration rate calculated according to the Schwartz formula was normal, and creatinine clearance calculated from urine collected over 24 h was within the normal ranges. The total protein in urine collected over 24 h was 1.73 g.

On radiography, the epiphyses of the radius and ulna were found to have no abnormalities. There was no evidence of rickets. Renal ultrasonography indicated possible left congenital megaureter, but renal scan was normal.

Neurological examination did not indicate retardation of motor function, but intelligence quotient was 79. Receptive and expressive language were delayed by 14 and 19 months, respectively. He was diagnosed with Attention Deficit Hyperactivity Disorder, although brain magnetic resonance imaging was normal.

As described above, he presented congenital cataract, proteinuria and developmental delay with mild intelligence impairment. These clinical and laboratory findings were suggestive of Lowe syndrome. Polymerase chain reaction sequencing of the patient's deoxyribonucleic acid (DNA) isolated from blood samples revealed a hemizygous single-nucleotide substitution (c.953G>T) in exon 11 on chromosome Xq26.1, resulting in a p.Arg318Leu amino acid substitution in OCRL. The mutation is novel and has not been previously reported. Because the patient's mother was normal, the mutation is *de novo*.

The patient was treated for proteinuria with angiotensin converting enzyme inhibitor.

Discussion

Lowe syndrome is a rare multisystem disorder affecting the eyes, brain, and kidney, and is characterised by congenital bilateral cataracts, mental retardation, hypotonia, and renal Fanconi syndrome. Of these, congenital cataract is a defining feature, and the patient underwent bilateral cataract surgery as a neonate. Nevertheless, even though neonatal cataracts are present in many patients, the final diagnosis is typically reserved until about two or three years later in most patients,[6] as congenital cataracts, hypotonia, failure to thrive and developmental delay, facial dysmorphism, and proteinuria are also associated with chromosomal anomalies and infectious disease. In any case, Kim et al[6] concluded that it is important to consider Lowe syndrome in the differential diagnosis of a male infant with congenital cataract and hypotonia. In particular, useful markers for suspecting Lowe syndrome include tubular proteinuria, and elevated aspartate transaminase, lactate dehydrogenase, and creatine kinase.

Fanconi syndrome is the most common renal symptom associated with Lowe syndrome, and is characterised by renal tubular acidosis, bicarbonaturia, aminoaciduria, phosphaturia, proteinuria, and impaired urine concentrating ability. Severity may differ among patients, tends to worsen with age, and is correlated with prognosis.[2]

Many affected children are asymptomatic at birth, but present clear symptoms after a few months, and some patients progress to chronic kidney disease between the second and fourth decades of life.[6]

Many causative mutations are amino acid substitutions in the 5-phosphatase domain of OCRL, suggesting that impaired catalytic activity contributes to pathogenesis. In particular, these mutations impact actin polymerisation,[7] a key process in the formation, maintenance, and proper function of tight and adherens junctions, which are essential for the function of renal proximal tubules and for the differentiation of lens fiber cells.

There are no clear genotype–phenotype correlations for Dent disease and Lowe syndrome.[8] The same mutations in OCRL have been reported in both diseases.[1] The two disease phenotypes show continuity from severe Lowe syndrome with ocular, neurological, and renal impairment to mild Dent disease, which shows only renal impairment. However, atypical Lowe syndrome patients only show incomplete ocular symptoms or moderate neurological symptoms.[1]

Our patient presented congenital cataracts, proteinuria, and mild mental retardation, which are consistent with a diagnosis of Lowe syndrome. Notably, the patient carried a p.Arg318Leu amino acid substitution in exon 11 of the *OCRL* gene (Figure 1), a variant that has never been reported in other cases of Lowe syndrome or Dent disease. Previous reports have reported mutations at the same site, i.e., p.Arg318Cys mutations in Dent disease and Lowe syndrome and p.Arg318His in Dent disease.[1,9]

According to the criteria for classifying pathogenic variants established in the American College of Medical Genetics and Genomics Standard and Guidelines, a novel missense amino acid substitution at the same site as another pathogenic missense mutation is classified as PM5 (Pathogenic moderate5, Different amino acid change of a known pathogenic change) category.[10] Because p.Arg318Cys and p.Arg318His are already known pathogenic, our novel mutation (p.Arg318Leu) is appropriate to the PM5. The clinical findings and identification of the OCRL mutation may help genetic counselling, and improve patient management.
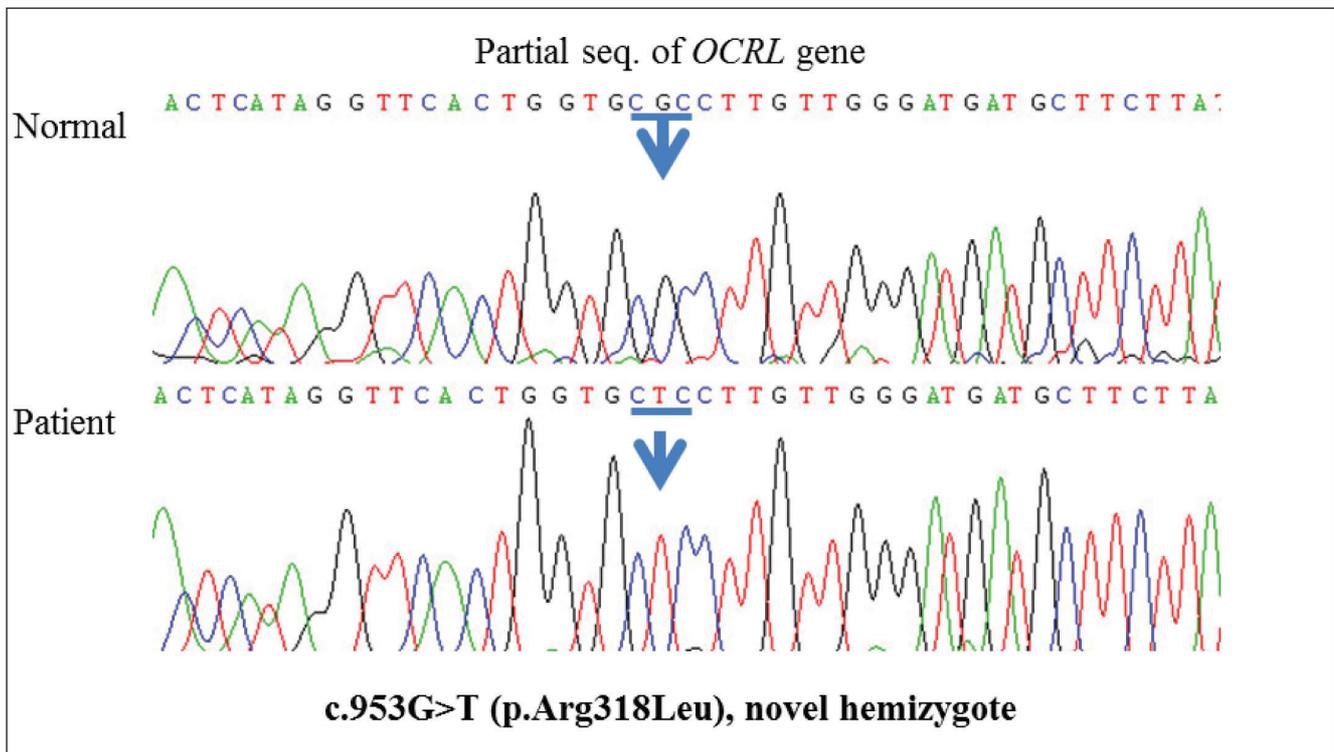

Figure 1   DNA sequencing electropherograms showing a hemizygous c.953G>T mutation in OCRL.

Acknowledgement

Conflict of Interest

Authors declare no conflict of interest.

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