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Case Report

A novel *OCRL1* mutation in a Chinese child with Lowe syndrome

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Abstract: Lowe syndrome, also known as oculocerebrorenal syndrome of Lowe (OCRL), is a rare X-linked recessive genetic disease characterized by multisystem involvement including congenital cataracts, infantile hypotonia, mental retardation and renal tubular dysfunction. Lowe syndrome is caused by mutation of *OCRL1* gene localized at Xq25-26.1, which encodes a phosphatidyl inositol 4,5 biphosphate phosphatase. We report a 4-month-old boy with congenital cataracts, hypotonia, delayed motor developmental milestone, tendon hyporeflexia, proteinuria and aminoaciduria. *OCRL1* gene mutation analysis showed a novel frame shift mutation, c.2441-2442delCT, p. (Ser814fs), in exon 21. This pathogenic mutation was predicted to cause the presence of premature termination codons and produce truncated OCRL1 protein. The mother of this patient was a heterozygous carrier.

Keywords: Lowe syndrome, *OCRL1*, cataract, mutations, low molecular weight proteinuria

Introduction

Lowe syndrome, also known as oculocerebrorenal syndrome of Lowe (OCRL, OMIM309000), is an X-linked multisystem disorder affecting the eyes, the nervous system and the kidneys [1]. It is a rare disease. It is estimated that the prevalence of the general population is about 1/200000-1/500000 [2]. Cataract is the most common ocular abnormalities. It develops in the fetal period. Ocular abnormalities also include microphthalmos, glaucoma and decreased vision. Proximal tubulopathy and psychomotor retardation are common.

OCRL1 gene mutations lead to the occurrence of Lowe syndrome. *OCRL1* gene is located on chromosome Xq25-26.1. OCRL1 protein is a type II inositol polyphosphate 5-phosphatase involved in the PI (4, 5) P2 homeostasis [3-5]. We report a novel OCRL1 gene mutation in a Chinese boy with Lowe syndrome.

Case report

The patient was a boy of four months old. He was a healthy Chinese couple's first child. The boy was born at 38-weeks' gestation via vaginal delivery. His mother had no pregnancy complications. His birth weight was 3680 g and birth length was 51 cm. No neonatal asphyxia and pathologic jaundice were recorded. His mother and grandmother were suffered from bilateral cataracts. He was admitted for an examination because of white pupil and proteinuria.

Physical examination revealed body weight of the patient was 7200g (-1SD), length was 64 cm (-1SD) and head circumference was 43.5 cm (+1SD). He had frontal bossing, bilateral congenital cataracts, hypermobility of the joint and decreased muscle tone. He couldn't raise his head and couldn't roll over till admission. His knee tendon reflex couldn't be drawn out.

The patient had proteinuria, aminoaciduria and lactaciduria. Urine routine examination were as follows: specific gravity 1.010, urine pH 6.0, protein (2+)~(3+), glucose (-). Urinary total protein was 1731.3 mg/L, urinary protein/urinary creatinine was 793.2 g/mmol (0~50 g/mmol). β_2-microglobulin was 23.6 mg/L(0~0.3 mg/L), α_1-microglobulin was 44.1 mg/L (0~0.8 mg/L), retinol binding protein was 4.6 mg/L (0~0.7

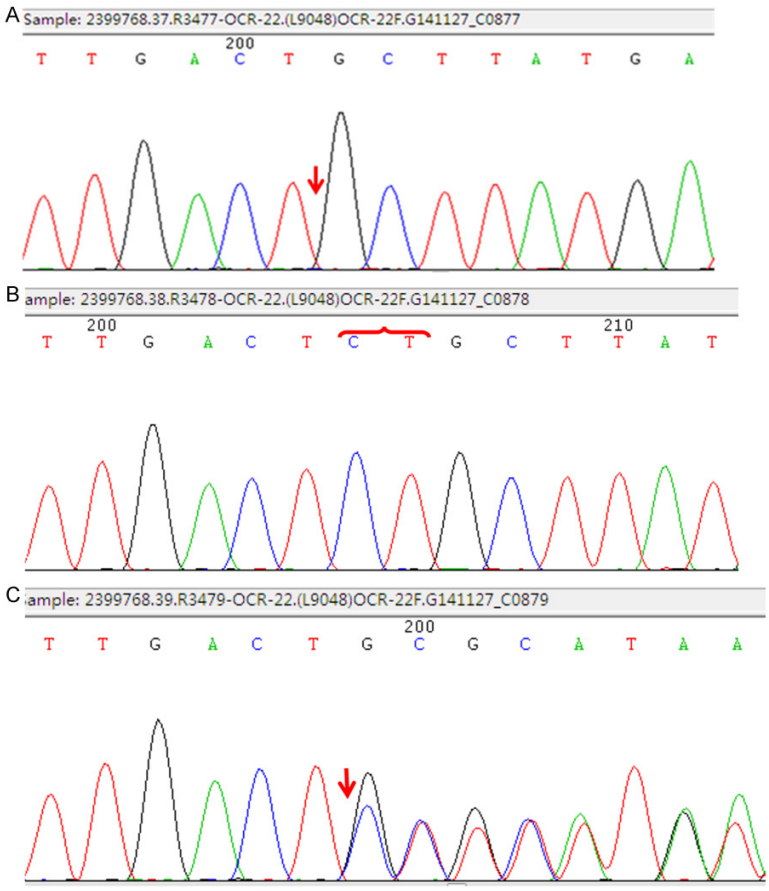

Figure 1. Genetic analysis of *OCRL1* in the patient and his parents. A: Patient, a novel frameshift mutation in exon 21 (c.2441-2442delCT). B: The father of the patient, exon 21 was normal. C: The mother of the patient, a heterozygous mutation in exon 21. Down arrow indicates the site of mutation.

mg/L) and albumin 360.7 mg/L (0~30 mg/L). Creatinine clearance was normal according to his age (70.5 ml/min/1.73 m^2). Moderately elevated Gly, Ser, Thr and lactate in the urine were detected by gas chromatography mass spectrometry (GC-MS). Renal ultrasound showed no abnormalities. Aspartate aminotransferase and alkaline phosphatase activities were mildly elevated (69 U/L and 328 U/L respectively). Electrolytes, serum creatinine and blood urea nitrogen were within their normal ranges. IgM antibodies of epstein-barr virus and TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) in sera were all negative. Metabolic acidosis was not detected. The cranial magnetic resonance imaging (MRI) was normal.

According to the clinical manifestations of congenital cataracts, hypotonia, tendon hyporeflexia, delayed motor developmental milestone, proteinuria and aminoaciduria, the patient was clinical diagnosed as having Lowe syndrome.

To confirm this clinical diagnosis, the blood samples of the boy and his parents were sent to genetic testing after informed consent. No gene copy number variations with clinical significance were detected by chromosomal microarray analysis (CMA). *OCRL1* mutation analysis showed a frameshift mutation, c.2441-2442delCT, p. (Ser814fs), in exon 21 in this boy. This pathogenic mutation was predicted to cause a premature stop codon in *OCRL1* and result in the OCRL1 protein truncation. The mother of this patient was a heterozygous carrier. His father was normal. This is a novel frameshift mutation in the *OCRL1* gene. Genetic analysis is summarized in **Figure 1**.

Discussion

Lowe syndrome or OCRL was first reported by Lowe et al. in 1952 [1]. The typical clinical manifestations of this disease were congenital cataracts, proximal tubulopathy, mental retardation, and progressive growth failure. Cataract develops in utero. Almost all of the affected boys present bilateral dense congenital cataract. It is due to the change of crystalline embryonic epithelium migration [6]. Glaucoma presents in 50% of patients. It can be detected within one year of age or even later [2]. Neurologic abnormalities include serious hypotonia, psychomotor retardation, absence of the deep tendon reflex, seizures and stereotypic behavioral abnormalities, etc [1, 2]. The dysfunction of proximal renal tubule cells (Fanconi syndrome) is a major feature. Renal tubulopathy includes low molecular weight proteinuria (LMWP), hypercalciuria, aminoaciduria, bicarbonaturia and hyperphosphaturia [2, 7]. As the age increases, the severity tends to be worse. Low molecular proteinuria

may be the first to occur when the renal tubular function is impaired [8]. Many children are asymptomatic in renal involvement at birth. In this case, white pupil was the earliest discovered symptom. The parents took the child to see an ophthalmologist. Before cataract surgery, medical examination found proteinuria and then transferred to pediatrics to continue treatment.

Because Lowe syndrome is an X-linked recessive genetic disease, probands are males and they have typical manifestations of this disease. In this study, the patient presented with congenital cataracts, hypotonia, motor retardation, tendon hyporeflexia and renal tubular dysfunction. The patient with the novel mutant gene did not present special clinical characteristics. The diagnosis age of this patient was 4 months old, so there was no obvious mental retardation and vitamin- D resistant rickets.

Females with Lowe syndrome are rare. If this happened, they were usually sporadic cases, but they all manifested full phenotype. The genetic basis will be discussed in later section.

Female carriers may have no clinical manifestation except of cataracts. About 95% of female carriers with cataracts after puberty can be found by slit lamp examination [9, 10]. In this study, the eyes of the patient's mother and grandmother were checked by slit lamp and they were both suffer from mild cataracts. The early detection of the female carrier state is very important, for which can contribute to prenatal genetic counseling. Ophthalmological evaluation (slit lamp examination) is considered to be a reliable principal method to identify the female carriers of Lowe syndrome, particularly in women of reproductive age. But because there are age-related opacities in the general population, it is difficult to separate heterozygous carriers from this group clearly, which is the major limitation in using ophthalmological evaluation to detect the carriers [9].

According to the clinical manifestation and laboratory examination, we can make the correct clinical diagnosis. Then we can use genetic analysis of *OCRL1* and enzyme examination to confirm the diagnosis [11, 12]. Measurement of the activity of the enzyme PIP2P 5-phosphatase in cultured skin fibroblasts can confirm the diagnosis. The effected males may have less than 10% of normal activity of the enzyme [2]. At present, enzymology diagnosis is difficult in most hospitals, but genetic diagnosis is feasible because commercial genetic testing is available. In this case, we diagnosed the disease by typical clinical manifestations and genetic analysis.

Clinicians may not think of this disease first because of the low incidence of it. There are a number of diseases that associated with congenital cataract, developmental delays, hypotonia and proximal renal dysfunction in one or several symptoms. Lowe syndrome needs to be differentiated from these disorders, including Dent disease, congenital infections (such as TORCH infections), peroxisomal disorders, cystinosis, galactosemia, hereditary fructose intolerance and congenital myopathies. The IgM antibodies of TORCH in our patient were all negative, so we can exclude the TORCH infections. The appearance of renal involvement can exclude peroxisomal disorders and congenital myopathies diagnosis within the first months of life. The blood and urine metabolites screening by GC-MS or genetic testing can rule out the genetic metabolic disease.

Dent disease needs to be identified specifically. Dent disease is a rare X-linked recessive inherited disease, mainly involving the proximal renal tubules [13]. Dent disease has two genetic backgrounds. According to the different genetic background, the diseases were classified as Dent-1 disease and Dent-2 disease. Dent-1 disease is caused by mutations in the voltage-gated chloride channel and chloride/proton antiporter 5 gene (CLCN5) [14] and Dent-2 disease is caused by mutation in the *OCRL1* gene [15]. Dent disease is characterized by LMWP, hypercalciuria and nephrolithiasis. However, the patients with Dent disease don't suffer from congenital cataract which is a typical feature of Lowe syndrome.

Lowe syndrome is caused by *OCRL1* gene mutations. *OCRL1* gene contains 24 exons with exon 1 being a non-coding exon and exon 18a as an alternatively spliced exon. The coding region includes exons 2-23 [11]. The *OCRL1* gene encodes a 105-kD phosphatidylinositol 4, 5-bisphosphate-5-phosphatase. It was reported that OCRL1 protein can be expressed in different tissues or cells including fibroblasts except lymphocytes [3, 4]. The protein localized

primarily in the lysosomes, the trans-Golgi network and the endosomes [5]. Phosphoinositides are phosphorylated metabolites of phosphatidylinositol and play an important role in cell physiology, including signaling, cytoskeletal regulation, and membrane trafficking [16]. It is supposed that this enzyme deficiency makes for transport dysregulation of Golgi vesicular, causing ocular, neurological and renal dysfunction [17]. Up to now about 200 *OCRL1* mutations have been identified. Most mutations are deletions, frameshifts and translation terminators. Splice-site mutations and missense mutations are less frequent.

The genetic basis of females with Lowe syndrome was lyonization in the heterozygous females or de novo translocation that disrupted the *OCRL1* locus. In addition, there are somatic mosaicism and germline mosaicism in 4-5% of the women [18, 19].

In this study, we identified a novel mutation in the *OCRL1* gene (c.2441-2442delCT) p.(Ser814fs) in exon 21, which has not been previously reported. This mutation was a frameshift mutation which could cause the presence of premature termination codons and predicted to produce truncated OCRL1 protein. This frameshift mutation was identified in the C-terminal RhoGAP-like domain spanning exon 20-23 [20-24] and involved amino acids located in well-conserved domains. The Rho-GAP domain lacks the catalytic arginine and is catalytically inactive. This mutation does not affect the inherent enzyme activity, but it may change the intracellular localization and stability of OCRL1 protein, contributing to the disease manifestations [25].

Dent-2 disease and Lowe syndrome are both harboring *OCRL1* gene mutation, but they present different clinical phenotypes. There are some studies to explore this phenomenon. Bökenkamp A et al. considered Dent-2 disease was a mild variant of Lowe syndrome. They charted review of data from 93 patients with identified *CLCN5* gene and Lowe syndrome of *OCRL1* gene mutations. They concluded that there was a phenotypic continuum within patients with Dent-2 disease and Lowe syndrome, which suggested that there were individual differences in the ability to compensate for loss of Lowe syndrome of Lowe gene function [26]. Hichri H et al. reported two patients harbored a same *OCRL1* gene mutation, but clinical phenotypes were different. One displayed severe Lowe syndrome phenotype and the other displayed Dent-2 phenotype comprising atypical forms of Lowe syndrome. They thought that a possible explanation of this clinical variability might be the presence of modifying factors (compensatory phosphatases, interacting proteins, etc.) whose expression would depend on the genetic background of the different patients [7].

Because there is still no effective treatment for Lowe syndrome, genetic counseling, including female carrier detection and prenatal diagnosis, is advisable to avoid reoccurrence. Genetic mutations in proband should be detected first and be documented. The *OCRL1* gene analysis is a specific method for the diagnosis of female carriers if the mutation is known in the proband. If the mother is a carrier, her male offspring has a 50% chance of being normal, a 50% chance of being affected; her female offspring has a 50% chance of being normal, a 50% chance of being a carrier [2]. If the defined *OCRL1* gene mutations cannot be detected in either parent of a proband, it is possible that there is a germline mosaicism in a parent or a de novo mutation in the proband. It is reported that germline mosaicism is in 4.5% of males affected with Lowe syndrome and *De novo* mutation is in 32% of males affected with Lowe syndrome [2, 7, 12]. It is necessary to take everything into account for genetic counseling.

In conclusion, Lowe syndrome can be diagnosed by clinical manifestations and genetic analysis. Genetic counseling can contribute to avoid reoccurrence within the same family.

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Disclosure of conflict of interest

None.

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References

[1] Lowe CU, Terrey M and Mac LE. Organic-aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation; a clinical entity. AMA Am J Dis Child 1952; 83: 164-184.

[2] Loi M. Lowe syndrome. Orphanet J Rare Dis 2006; 1: 16.

[3] Attree O, Olivos IM, Okabe I, Bailey LC, Nelson DL, Lewis RA, McInnes RR and Nussbaum RL. The Lowe's oculocerebrorenal syndrome gene encodes a protein highly homologous to inositol polyphosphate-5-phosphatase. Nature 1992; 358: 239-242.

[4] Olivos-Glander IM, Janne PA and Nussbaum RL. The oculocerebrorenal syndrome gene product is a 105-kD protein localized to the Golgi complex. Am J Hum Genet 1995; 57: 817-823.

[5] Lowe M. Structure and function of the Lowe syndrome protein OCRL1. Traffic 2005; 6: 711-719.

[6] Tripathi RC, Cibis GW and Tripathi BJ. Pathogenesis of cataracts in patients with Lowe's syndrome. Ophthalmology 1986; 93: 1046-1051.

[7] Hichri H, Rendu J, Monnier N, Coutton C, Dorseuil O, Poussou RV, Baujat G, Blanchard A, Nobili F, Ranchin B, Remesy M, Salomon R, Satre V and Lunardi J. From Lowe syndrome to Dent disease: correlations between mutations of the OCRL1 gene and clinical and biochemical phenotypes. Hum Mutat 2011; 32: 379-388.

[8] Bockenhauer D, Bokenkamp A, van't Hoff W, Levtchenko E, Kist-van Holthe JE, Tasic V and Ludwig M. Renal phenotype in Lowe Syndrome: a selective proximal tubular dysfunction. Clin J Am Soc Nephrol 2008; 3: 1430-1436.

[9] Roschinger W, Muntau AC, Rudolph G, Roscher AA and Kammerer S. Carrier assessment in families with lowe oculocerebrorenal syndrome: novel mutations in the OCRL1 gene and correlation of direct DNA diagnosis with ocular examination. Mol Genet Metab 2000; 69: 213-222.

[10] Lin T, Lewis RA and Nussbaum RL. Molecular confirmation of carriers for Lowe syndrome. Ophthalmology 1999; 106: 119-122.

[11] Nussbaum RL, Orrison BM, Janne PA, Charnas L and Chinault AC. Physical mapping and genomic structure of the Lowe syndrome gene OCRL1. Hum Genet 1997; 99: 145-150.

[12] Monnier N, Satre V, Lerouge E, Berthoin F and Lunardi J. OCRL1 mutation analysis in French Lowe syndrome patients: implications for molecular diagnosis strategy and genetic counseling. Hum Mutat 2000; 16: 157-165.

[13] Dent CE and Friedman M. Hypercalcuric rickets associated with renal tubular damage. Arch Dis Child 1964; 39: 240-249.

[14] Fisher SE, van Bakel I, Lloyd SE, Pearce SH, Thakker RV and Craig IW. Cloning and characterization of CLCN5, the human kidney chloride channel gene implicated in Dent disease (an X-linked hereditary nephrolithiasis). Genomics 1995; 29: 598-606.

[15] Hoopes RR Jr, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus J, Simckes A, Tasic V, Toenshoff B, Suchy SF, Nussbaum RL and Scheinman SJ. Dent Disease with mutations in OCRL1. Am J Hum Genet 2005; 76: 260-267.

[16] Di Paolo G and De Camilli P. Phosphoinositides in cell regulation and membrane dynamics. Nature 2006; 443: 651-657.

[17] Suchy SF, Olivos-Glander IM and Nussabaum RL. Lowe syndrome, a deficiency of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in the Golgi apparatus. Hum Mol Genet 1995; 4: 2245-2250.

[18] Coutton C, Monnier N, Rendu J and Lunardi J. Development of a multiplex ligation-dependent probe amplification (MLPA) assay for quantification of the OCRL1 gene. Clin Biochem 2010; 43: 609-614.

[19] Peces R, Peces C, de Sousa E, Vega C, Selgas R and Nevado J. A novel and de novo deletion in the OCRL1 gene associated with a severe form of Lowe syndrome. Int Urol Nephrol 2013; 45: 1767-1771.

[20] Erdmann KS, Mao Y, McCrea HJ, Zoncu R, Lee S, Paradise S, Modregger J, Biemesderfer D, Toomre D and De Camilli P. A role of the Lowe syndrome protein OCRL in early steps of the endocytic pathway. Dev Cell 2007; 13: 377-390.

[21] Faucherre A, Desbois P, Satre V, Lunardi J, Dorseuil O and Gacon G. Lowe syndrome protein OCRL1 interacts with Rac GTPase in the trans-Golgi network. Hum Mol Genet 2003; 12: 2449-2456.

[22] Hyvola N, Diao A, McKenzie E, Skippen A, Cockcroft S and Lowe M. Membrane targeting and activation of the Lowe syndrome protein OCRL1 by rab GTPases. EMBO J 2006; 25: 3750-3761.

[23] Peck J, Douglas Gt, Wu CH and Burbelo PD. Human RhoGAP domain-containing proteins: structure, function and evolutionary relationships. FEBS Lett 2002; 528: 27-34.

[24] Choudhury R, Diao A, Zhang F, Eisenberg E, Saint-Pol A, Williams C, Konstantakopoulos A, Lucocq J, Johannes L, Rabouille C, Greene LE and Lowe M. Lowe syndrome protein OCRL1 interacts with clathrin and regulates protein

trafficking between endosomes and the trans-Golgi network. Mol Biol Cell 2005; 16: 3467-3479.

[25] Pirruccello M and De Camilli P. Inositol 5-phosphatases: insights from the Lowe syndrome protein OCRL. Trends Biochem Sci 2012; 37: 134-143.

[26] Bokenkamp A, Bockenhauer D, Cheong HI, Hoppe B, Tasic V, Unwin R and Ludwig M. Dent-2 disease: a mild variant of Lowe syndrome. J Pediatr 2009; 155: 94-99.