A novel OCRL1 gene mutation in a Turkish child with Lowe syndrome

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Oculocerebrorenal syndrome, also known as Lowe syndrome (OMIM 309000), is an X-linked recessive disorder that was first reported by Lowe et al. in 19521. The diagnostic triad of LS includes bilateral congenital cataract, mental retardation and renal tubular dysfunction of Fanconi type. In addition to mental retardation, various neurological signs may be present, such as developmental delay, seizures, hypotonia, areflexia, and/or behavioral abnormalities2.

Lowe syndrome (LS) is a rare disorder, the incidence of which is only a few cases per 100,000-500,000 births3. Most of the patients are asymptomatic at birth. The severity of the renal disease can vary between patients and determines the prognosis4. The responsible gene, located at Xq26.1, is OCRL1, and it encodes a phosphatidylinositol-4, 5-biphosphate-5 phosphatase that is found in the Golgi complex3. A mutation in the OCRL1 gene locus, which contains 24 exons, causes this syndrome by a reduction in the contents of OCRL1 protein. Here, we report a novel frameshift mutation in a patient with LS who was first diagnosed at the age of 11.

Case Report
An 11-year-old boy was admitted to our hospital with failure to thrive and difficulty in walking. He was a term baby, delivered by spontaneous vaginal route with a birth weight of 4000 g, and the perinatal history was unremarkable. He had bilateral cataract surgery on postnatal day 4 and at the age of three months. His parents were non-consanguineous and he had two healthy brothers.

The physical examination revealed a height of 107 cm (-5.46 SDS) and a weight of 22 kg (-1.52 SDS) in addition to frontal bossing, normally placed large ears, deep-set eyes, strabismus, hypermetropia, deformation of teeth, and enamel hypoplasia (Fig. 1). Bilateral X-bain deformity in lower extremities was present (Figs. 2, 3). Stereotypic hand movements were detected in the neurological examination.

Laboratory findings were as follows: urine pH 7.5, specific gravity 1015, protein (+2), glucose (-), few leukocytes in microscopic examination, blood pH 7.35, HCO3 23 mmol/L, base excess: -2, urea 49 mg/dl, serum creatinine 0.7 mg/dl, sodium 142 mmol/L, potassium 4.3 mmol/L, uric acid 3 mg/dl (normal 2-5.5), calcium 10.9 mg/dl (normal 8.8-10.8), phosphorus 4.4 mg/dl (normal 4-7), alkaline phosphatase 220 U/L (normal 42-362), free thyroxine 1.38 ng/dl (normal 0.89-1.76), thyroid stimulating hormone 2.06 (0.4-4.0), parathyroid hormone...
16.2 pg/ml (normal 15-65), and 25 (OH) vitamin D 30.4 ng/ml (normal 20-32). Calciuria was 1.16 mg/kg/d (normal <4) and proteinuria was 117 mg/m²/h (normal <4). Fractional sodium excretion was 1.02% (normal 0.3-1.6%), fractional potassium excretion was 33.9% (normal <10-15%), fractional uric acid excretion was 18% (normal 11-17%), and ratio of phosphorus tubular maximum to glomerular filtration (TmP/GFR) was 3.52 (normal 2.8-4.4). β2 microglobulin level was 117 mg/L (normal 0.02-0.25). The GFR calculated according to Schwartz formula was 84 ml/min/1.73 m², and creatinine clearance calculated upon 24-hour collected urine was 130 ml/min/1.73 m². On radiography, the epiphyses of the radius and ulna appeared normal. There were no findings of rickets, but severe osteoporosis was detected. Dual energy X-ray absorptiometry (DEXA) revealed a Z-score of 4.9. Renal ultrasonography was normal. The cranial magnetic resonance imaging (MRI) showed multiple gliotic lesions, which were hypointense on T1-weighted and hyperintense on T2-weighted images, and lacunar lesions in the bilateral periventricular white matter consistent with periventricular leukomalacia (Fig. 4). Intelligence quotient level was below 70.

We considered a diagnosis of LS on the basis of clinical and laboratory findings and sent the blood samples of the patient and his mother for genetic analysis with informed consent. The analysis of the patient’s samples revealed a hemizygous two nucleotide deletion in exon 22, which resulted in a p.Val787GlyfsX788 amino acid substitution, a frameshift mutation and a premature termination codon at position 788. His mother was not a carrier for this mutation. Thus, it was thought to be a de novo mutation. He was treated with angiotensin converting enzyme inhibitor for proteinuria and with calcitriol and calcium for osteoporosis.

Discussion
Diagnosis of oculocerebrorenal syndrome, namely LS, is based on specific ophthalmologic, neurologic and renal abnormalities. Cataract is an important finding among all clinical features. It develops in utero and is caused by altered migration of the crystalline embryonic epithelium. A history of cataract surgery in the neonatal and early infantile period provided an important clue for the diagnosis of LS in
Neurological features of LS are developmental delay, hypotonia, seizures, areflexia, cognitive impairment, behavioral disturbances, and abnormal findings in brain imaging studies, such as brain atrophy, delayed myelination, pachygyrias, and hydrocephalus. Our patient had motor and mental retardation, and an IQ of 70, but had no history of hypotonia or seizures. He also had stereotypic hand movements, which have been previously reported in patients with LS. In addition, there were gliotic lesions suggestive of periventricular leukomalacia in his MRI sections. Similar gliotic findings were found in previous cases with LS.

The renal findings of LS include low molecular weight proteinuria, hypercalciuria, hematuria, hyperuricosuria, glycosuria, metabolic acidosis due to proximal tubular bicarbonate wasting, and hypophosphatemia due to renal phosphate wasting. These findings may be associated with renal rickets, osteomalacia and pathological fractures. It is known that the severity of renal disease in LS changes from asymptomatic to renal Fanconi syndrome and even chronic renal failure. Not all the features of renal Fanconi syndrome, but rather selective tubular dysfunction findings, are expected in LS. In a series of patients with genetically proven LS, low molecular weight proteinuria and albuminuria were the prominent findings, although none had glycosuria and only some had generalized aminoaciduria, tubular phosphate loss and rickets, hypercalciuria, or nephrocalcinosis. In our case, tubular proteinuria was the prominent renal finding. Slightly increased fractional potassium and uric acid excretion were present; however, other tubular functions were in normal range and there was no metabolic acidosis. He had X-bain deformity, dental findings and...
severe osteoporosis suggestive of rickets, but interestingly, his laboratory findings were not compatible with hypophosphatemic rickets, although he had no history of treatment for rickets. As a result, we may consider that our patient had a mild form of renal tubular defect. Clinical findings are adequate for the diagnosis of LS; however, genetic analysis is necessary for genetic counseling. The responsible gene is located on the long (q) arm of the X chromosome at position 26.1. The OCRL1 gene provides instructions for making an enzyme that is present in cells throughout the body. More than 120 mutations in the OCRL1 gene have been identified in individuals with LS. A review of the reported mutations in the OCRL1 gene in subjects with LS suggests that they are not uniformly distributed throughout the gene. The mutations described in the literature are concentrated in half of the 24 exons, exons 10–19 and 21–23. This cluster is recognized as a ‘hot spot’ for mutations in the OCRL1 gene, and is therefore a prime target for screening. Satre et al. and Lin et al. found 52% and 76% mutations of the OCRL1 gene, respectively, in this cluster. In our case, there was a p.Val787GlyfsX788 amino acid substitution in exon 22, which caused a frameshift and a premature termination codon at position 788. This mutation has not yet been determined in another patient with LS.

In conclusion, congenital cataract, neurological findings and proximal tubular dysfunction revealed the diagnosis of LS in our patient. Genetic analysis confirmed the diagnosis, and a new mutation was identified in our patient, but not in his mother. We postulated that this novel de novo mutation may be associated with absence of severe tubular defects and rachitic findings.

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