RESEARCH ARTICLE

Human Mutation

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From Lowe Syndrome to Dent Disease: Correlations between Mutations of the *OCRL1* Gene and Clinical and Biochemical Phenotypes

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ABSTRACT: Mutations of *OCRL1* are associated with both the Lowe oculocerebrorenal syndrome, a multisystemic and Dent-2 disease, a renal tubulopathy. We have identified a mutation in 130 Lowe syndrome families and 6 affected by Dent-2 disease with 51 of these mutations being novel. No founding effect was evidenced for recurrent mutations. Two mutations initially reported as causing Dent-2 disease were identified in patients, including two brothers, presenting with Lowe syndrome thus extending the clinical variability of *OCRL1* mutations. mRNA levels, protein content, and PiP_2-ase activities were analyzed in patient's fibroblasts. Although mRNA levels were normal in cells harboring a missense mutation, the OCRL1 content was markedly lowered, suggesting that enzymatic deficiency resulted mainly from protein degradation rather than from a catalytic inactivation. Analysis of a splicing mutation that led to the elimination of the initiation codon evidenced the presence of shortened forms of OCRL1 that might result from the use of alternative initiation codons. The specific mapping of the frameshift and nonsense mutations, exclusively identified in exons 1–7 and exons 8–23, respectively, for Dent disease and Lowe syndrome together with the possible use of alternative initiation codons might be related to their clinical expression, that is, Lowe syndrome or Dent-2 disease.
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KEY WORDS: OCRL1; Lowe syndrome; Dent 2 disease; phosphatidylinositol 4, 5 biphosphate homeostasis

Introduction

Lowe Syndrome

The oculocerebrorenal syndrome of Lowe (OCRL; MIM♯ 309000) is a rare X-linked multisystem disorder presenting with major abnormalities in the eyes, the kidneys, and the central nervous system [Loi, 2006; Lowe et al., 1952]. OCRL is a rare disease with a prevalence estimated between 1 and 2 boys per million people. Ocular abnormalities include a constant prenatal development of cataracts and frequent associated signs such as glaucoma, microphthalmos, decreased visual acuity, and corneal keloid formation. Neonatal hypotonia, intellectual impairment, and areflexia are also cardinal features. The majority of patients have a cognitive delay and behavioral troubles including temper tantrums and aggressiveness are frequently noted. Brain magnetic resonance imaging (MRI) may show periventricular cystic lesions [Loi, 2006; Schneider et al., 2001]. Fanconi syndrome, a generalized impairment of the proximal tubular cells functions, is a major feature.

Onset of the tubular dysfunction can vary between patients, and the severity tends to worsen with age. Low molecular weight proteinuria (LWMP) is invariably present and aminoaciduria, hypercalciuria, and bicarbonaturia are frequently included. Progressive glomerular dysfunction leads usually to renal failure. Skeletal muscle abnormalities may develop as secondary consequences of hypotonia or renal dysfunction. Nontender joint swelling and subcutaneous nodules are also frequently described in affected patients and may reflect a primary abnormality of connective tissue growth. Lowe syndrome results from mutations of the *OCRL1* gene (MIM♯ 300535) that encodes a phosphatidyl inositol 4,5 biphosphate ($PI(4,5)P_2$) phosphatase.

Dent Disease

Dent disease (Dent-1; MIM♯ 300009), is a X-linked proximal renal tubulopathy, characterized by LWMP, hypercalciuria, and

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