Digenic Mutations of Human OCRL Paralogs in Dent's Disease Type 2 Associated with Chiari I Malformation

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Introduction

OCRL1 and its paralog *INPP5B* encode phosphatidylinositol 5-phosphatases that localize to the primary cilium and have roles in ciliogenesis (1,2). Mutations in *OCRL1* cause the X-linked Dent disease type 2 (DD2; OMIM# 300555) (3), characterized by low-molecular weight proteinuria, hypercalciuria, and the variable presence of cataracts, glaucoma and intellectual disability without structural brain anomalies (4). Pathogenic mutations in *INPP5B* have not been described in humans. Here, we report the case of an 11-year-old boy with short stature and an above-average IQ; severe proteinuria, hypercalciuria and osteopenia resulting in a vertebral compression fracture; and Chiari I malformation (**figure 1**) with cervico-thoracic syringohydromyelia requiring suboccipital decompression, and his associated genetic findings.

Methods

DNA samples were isolated from the patient and both biological parents. Targeted exome capture followed by 74 base paired-end sequencing on the Illumina HiSeq 2000 platform. Bioinformatic analysis called de novo and transmitted single nucleotide variants and insertions/deletions. Mutations were confirmed by Sanger sequencing. PCR-based screens of known Dent-causing genes (*CLCN5*, *OCRL1*) were performed.

Results

Sequencing revealed a novel, de novo DD2-causing 462 bp deletion disrupting exon 3 of *OCRL1* (**figure 2**) and a maternally inherited, extremely rare (ExAC allele frequency 8.4×10-6) damaging missense mutation in *INPP5B* (p.A51V) which substitutes a conserved amino acid in the protein's critical PH domain (**figure 3**). In silico analyses of mutation impact predicted by SIFT, PolyPhen2, MetaSVM and CADD algorithms were all deleterious. No mutations were detected on the coding regions of CLCN5.

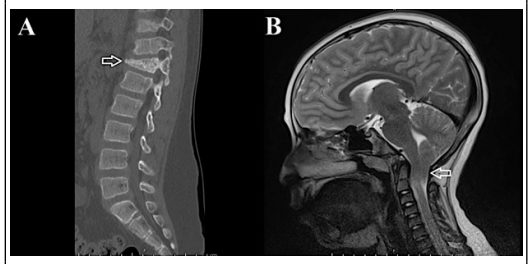
Conclusions

Our findings report a novel association of DD2 with Chiari I malformation and syringohydromyelia, and document the effects of digenic mutation of human OCRL paralogs. These lend genetic support to the hypothesis that impaired ciliogenesis may contribute to the development of Chiari I malformation, and implicates OCRL-dependent PIP3 metabolism in this mechanism.

Learning Objectives

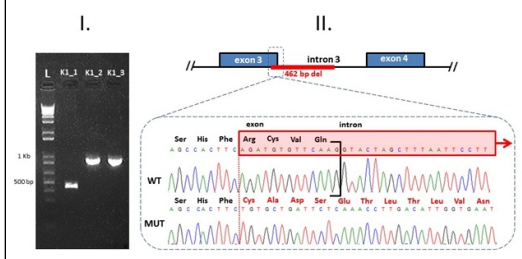
1. The role of PIP3 metabolism in neurosurgically-relevant brain structural malformations.
2. The use of whole-exome sequencing as a means of identifying variants in rare cases that present with neurosurgical diseases.

FIGURE 1.



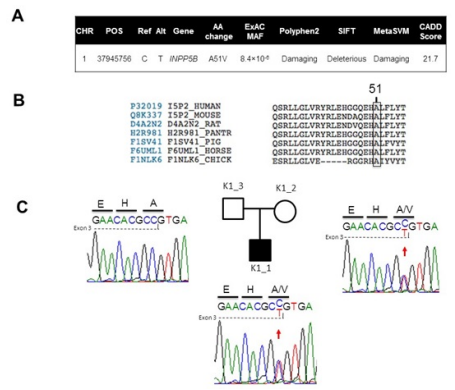
A. Sagittal spine CT demonstrating T12 a compression fracture (arrow) that occurred after a low-impact trauma in the setting of severe osteopenia. B. Sagittal T2-weighted MRI demonstrating Chiari I malformation.

FIGURE 2.



(I) Gel electrophoresis of PCR products amplified from the DNAs of affected child [K1_1], mother [K1_2] and father [K1_3] demonstrating a de-novo deletion in the proband. (II) Schematic depicting the mutant sequence, harboring a novel, de novo 462 bp deletion: c.187_199+449del (p.Arg63fsX) involving exon 3 of OCRL1.

FIGURE 3.



A. Analysis of INPP5B c.152C>T; p.A51V. B. Residue conservation analysis in orthologous proteins. C. Family structure and Sanger sequence chromatograms

References

1. Attree O, Olivos IM, Okabe I, Bailey LC, Nelson DL, Lewis RA et al. The Lowe's oculocerebrorenal syndrome gene encodes a protein highly homologous to inositol polyphosphate-5-phosphatase. Nature 1992; 358: 239–242.
2. Madhivanan K, Ramadesikan S, Aguilar RC. Role of Ocrl1 in primary cilia assembly. Int Rev Cell Mol Biol 2015; 317: 331–347.
3. Hoopes RR Jr, Shrimpton AE, Knohl SJ, Hueber P, Hoppe B, Matyus J et al. Dent Disease with mutations in OCRL1. Am J Hum Genet 2005; 76: 260–267. Epub 2004 Dec 30. Erratum in: Am J Hum Genet 2007; 81(3):634.
4. Bökenkamp A, Ludwig M. The oculocerebrorenal syndrome of Lowe: an update. Pediatr Nephrol 2016; 31: 2201–2212.

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