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Compound heterozygous mutations in the multiple PDZ domain protein (MPDZ) cause a case of mild non-progressive communicating hydrocephalus

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Congenital hydrocephalus (CH) results from the accumulation of excessive amounts of cerebrospinal fluid (CSF) in the brain often leading to severe neurological impairments. However, the adverse effects of CH can be reduced if the condition is detected and treated early. Earlier reports demonstrated that some CH cases are caused by mutations in *L1CAM* gene encoding the neural cell adhesion molecule L1. However, a recent study has shown that a homozygous truncating mutation in multiple PDZ domain protein, which is an important factor in the assembly and localization of integral membrane proteins encoded by *MPDZ* gene, is responsible for a severe form of CH that is inherited in an autosomal recessive pattern. In this study, an Emirati family with one child affected by CH was clinically evaluated followed by whole-exome sequencing and Sanger sequencing. In addition, *in silico*, cellular and molecular assays have been used to confirm pathogenicity of the identified variants and establish disease mechanism. Whole Exome Sequencing revealed two compound heterozygous novel mutations (c.394G>A and c.1744C>G) in the affected child in the *MPDZ* gene. Segregation analysis revealed that each of the parents is heterozygous for one of the two mutations and therefore passed that mutation to the affected child. *In silico* and bioinformatics analyses as well as experimental data revealed that the two mutations are most likely disease causing. The compound heterozygous mutations identified in this study are most likely the cause of CH in the affected child, further confirming *MPDZ* as a gene underlying some CH cases.

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