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Phenotypic and Molecular Heterogeneity Linked to the Magnesium Transporter CNNM2

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Abstract : Metal cation transport mediator (CNNM) gene family comprises 4 isoforms that are expressed in various human tissues. Structurally, CNNMs are complex proteins that contain an extracellular N-terminal domain preceding a DUF21 transmembrane domain, a 'Bateman module' and a C-terminal cNMP-binding domain. Mutations in CNNM2 cause familial dominant hypomagnesaemia. Growing evidence highlights the role of CNNM2 in neurodevelopment. Mutations in CNNM2 have been implicated in epilepsy, intellectual disability, schizophrenia, and others. In the present study, we aim to elucidate the function of CNNM2 in the developing brain. Thus, we present the genetic origin of symptoms in two family cohorts. In the first family, three siblings of a consanguineous Palestinian family in which parents are first cousins, and consanguinity ran over several generations, presented a varying degree of intellectual disability, cone-rod dystrophy, and autism spectrum disorder. Exome sequencing and segregation analysis revealed the presence of homozygous pathogenic mutation in the CNNM2 gene, the parents were heterozygous for that gene mutation. Magnesium blood levels were normal in the three children and their parents in several measurements. They had no symptoms of hypomagnesemia. The CNNM2 mutation in this family was found to locate in the CBS1 domain of the CNNM2 protein. The crystal structure of the mutated CNNM2 protein was not significantly different from the wild-type protein, and the binding of AMP or MgATP was not dramatically affected. This suggests that the CBS1 domain could be involved in pure neurodevelopmental functions independent of its magnesium-handling role, and this mutation could have affected a protein partner binding or other functions in this protein. In the second family, another autosomal dominant CNNM2 mutation was found to run in a large family with multiple individuals over three generations. All affected family members had hypomagnesemia and hypermagnesuria. Oral supplementation of magnesium did not increase the levels of magnesium in serum significantly. Some affected members of this family have defects in fine motor skills such as dyslexia and dyslalia. The detected mutation is located in the N-terminal part, which contains a signal peptide thought to be involved in the sorting and routing of the protein. In this project, we describe heterogenous clinical phenotypes related to CNNM2 mutations and protein functions. In the first family, and up to the authors' knowledge, we report for the first time the involvement of CNNM2 in retinal photoreceptor development and function. In addition, we report the presence of a neurophenotype independent of magnesium status related to the CNNM2 protein mutation. Taking into account the different modes of inheritance and the different positions of the mutations within CNNM2 and its different structural and functional domains, it is likely that CNNM2 might be involved in a wide spectrum of neuropsychiatric comorbidities with considerable varying phenotypes.

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