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GENETIC DISEASES AND MOLECULAR GENETICS

SP019 RECURRENT FXYD2 P.GLY41ARG MUTATION IN PATIENTS WITH ISOLATED DOMINANT HYPOMAGNESEMIA

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Introduction and Aims: Magnesium (Mg2+) is an essential mineral for cell growth, neuroplasticity and muscle contraction. Blood Mg2+ levels below 0.7 mmol/L may cause a heterogeneous clinical phenotype, including muscle cramps, epilepsy and disturbances in K+ and Ca2+ homeostasis. Over the last decade, the genetic origin of several familial forms of hypomagnesemia has been delineated. In 2000, mutations in FXYD2, encoding the γ-subunit of the Na+-K+-ATPase, were identified to cause isolated dominant hypomagnesemia (IDH) in a large Dutch family suffering from hypomagnesemia, hypocalciuria and chondrocalcinosis. However, additional patients were never identified.
Methods: Here, two families with hypomagnesemia and hypocalciuria were screened for mutations in the FXYD2 gene. Moreover, the patients were clinically and genetically characterized.
Results: We report a p.Gly41Arg FXYD2 mutation in two families with hypomagnesemia and hypocalciuria. The patients suffered from muscle cramps, chondrocalcinosis and epilepsy. The p.Gly41Arg substitution introduces a charged amino acid residue in the predicted transmembrane region of the γ-subunit of the Na+-K+-ATPase. As a consequence, the γ-subunit lacks post-translational modifications and is not routed to the plasma membrane. Interestingly, this is exactly the same mutation as was described in the original study. Haplotype analysis revealed an overlapping haplotype in all families, suggesting a founder effect. However, extensive genealogical analysis did not reveal a common ancestor in 9-12 generations.
Conclusions: The recurrent p.Gly41Arg FXYD2 mutation in two new families with isolated dominant hypomagnesemia confirms that the FXYD2 mutation causes hypomagnesemia. Until now, no other FXYD2 mutations have been reported which could indicate that other FXYD2 mutations will not cause hypomagnesemia or are embryonically lethal.