Hypomagnesemia with hypocalciuria

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Abstract
Magnesium wasting with hypocalciuria was first described by Geven et al. in 1987. In two presumably unrelated families, serum Mg\(^{2+}\) was found to be as low as 0.39 mmol/L without other plasma electrolyte abnormalities, including calcium (both serum and normal ionized), sodium, potassium, chloride and bicarbonate. Blood pH, renin activity and plasma aldosterone were in the normal range. The only abnormality found, in addition to hypomagnesemia, was lowered renal excretion of calcium. Family members of the probands had low serum Mg\(^{2+}\) also, but lacked clinical symptoms of Mg\(^{2+}\) depletion. Retention values of orally administered isotope 28 of Mg and the effects of Mg\(^{2+}\) infusion on renal reabsorption showed that the defect must be located in the kidney. In these two families the disorder was inherited as an autosomal dominant trait. The disease locus was designated HOMG2 (hypomagnesemia 2), it is located on chromosome 11q23. Within the linkage region, the FXYD2 gene, encoding the sodium-potassium-ATPase gamma-subunit was found. The Na\(^+,K^+\)-ATPase provides the driving force for active transport processes in the kidney, and is responsible for the maintenance of the transmembrane potential and the Na\(^+\)-gradient which drive passive reabsorption and facilitated Na\(^+\)-coupled transport. Mutation analysis of FXYD2 revealed a single heterozygous mutation in the patients of both families resulting in the substitution of a highly conserved hydrophobic Glycine residue within the putative transmembrane region with a hydrophilic Arginine residue. Transient expression studies have shown that this amino acid substitution results in bad processing and incorrect localization of the sodium-potassium-ATPase gamma-subunit.

Keywords
HOMG2, Magnesium wasting, low calcium renal excretion, autosomal dominant, 11q23 locus.
processes in the kidney, and is responsible for the maintenance of the transmembrane potential and the Na+-gradient which drive passive reabsorption and facilitated Na+-coupled transport, respectively. The gamma-subunit is assumed to modulate the function of the Na+,K+-ATPase by attenuating its affinity for Na+, K+ and ATP (Béguin et al., 1997; Arystarkhova et al., 1999; Therien et al., 1999). FXYD2 consists of 7 exons coding for two known splice-variants in human and rat (Kuster et al., 2000; Sweadner and Rael, 2000; Sweadner et al., 2000; Meij et al., 2000) and three in mouse (Jones et al., 2001). Mutation detection analysis of FXYD2 in the probands of the families with dominant renal hypomagnesemia yielded a G41R mutation which resulted in the replacement of a highly conserved amino-acid with a charged arginine residue within the single transmembrane domain of the protein. The mutation cosegregated with the disease in both families and was not found in 132 control chromosomes. Expression studies in both insect Sf9 cells and mammalian COS-1 cells showed that the normal routing to the plasma membrane of the mutant gamma-subunit is disturbed in both cell types (Figure 1). Moreover, in insect cells, when mutant gamma-subunit was coexpressed with the alpha- and beta-subunit of the Na+,K+-ATPase, normal routing of the alpha-subunit was disturbed as well, indicating that the mutation in the gamma-subunit affects the complete ATPase complex (Meij et al., 2000).

Figure 1. Na+,K+-ATPase gamma-subunit routing defect observed in both insect Sf9 cells (upper panels) and mammalian COS-1 cells (bottom panels), when comparing wild type (left) and mutant (right) expression (Meij et al., 2000).

Measurement of serum Mg$^{2+}$-concentration in two individuals with a heterozygous 11q23-ter deletion (including the FXYD2 gene as determined by FISH analysis) revealed that both individuals had normal serum Mg$^{2+}$-values, indicating that the loss of one FXYD2 gene copy is not sufficient to cause a Mg$^{2+}$-deficient phenotype. This strongly suggests that the hypomagnesemia in these patients is caused by a dominant negative effect rather than haploinsufficiency (Meij et al., 2000). The current hypothesis of the authors on how the FXYD2 mutation could influence tubular Mg$^{2+}$-reabsorption involves the putative Mg$^{2+}$-entry channel present in mouse distal convoluted tubule cells (mDCT) as described by Ritchie et al. (1996). When mDCT cells were cultured under K+-depleted conditions, apical entry of Mg$^{2+}$ was blocked in these cells. Meij et al (2000) suggest that the mutation in the gamma-subunit mimics this situation by inhibiting the routing of Na+,K+-ATPase complex to the plasma membrane, thus limiting the amount of K+-entry into the cell. Closing of the K+-sensitive apical Mg$^{2+}$-channel would then cause reduced Mg$^{2+}$-reabsorption and hypomagnesemia in the patients with dominant renal Mg$^{2+}$-loss (Figure 2).

Figure 2. Hypothetical model of the involvement of the Na+,K+-ATPase gamma-subunit in Mg$^{2+}$ reabsorption by DCT cells including putative K+-sensitive apical Mg$^{2+}$-entry and basolateral Mg$^{2+}$-extrusion mechanisms (Ritchie et al., 1996).

A) Wild type situation in which the apical Mg$^{2+}$-channel is open.
B) Putative effect of the Na+,K+-ATPase α-subunit mutation involves disturbed routing of
the Na+,K+-ATPase $\alpha\beta\gamma$-complex (1) leading to a decreased intracellular K+-concentration which closes the apical Mg$^{2+}$-channel (2). Additionally, reduced efflux of Na+ and decreased availability of intracellular Mg$^{2+}$ may also inhibit the basolateral Mg$^{2+}$-extrusion mechanism (3).

References


http://www.orpha.net/data/patho/GB/uk-HOMG.pdf