

mTOR-Activating Mutations in RRAGD Are Causative for Kidney Tubulopathy and Cardiomyopathy

Background: Over the last decade, advances in genetic techniques have resulted in the identification of rare hereditary disorders of renal magnesium and salt handling. Nevertheless, approximately 20% of all patients with tubulopathy lack a genetic diagnosis.

Methods: We performed whole-exome and -genome sequencing of a patient cohort with a novel, inherited, salt-losing tubulopathy; hypomagnesemia; and dilated cardiomyopathy. We also conducted subsequent in vitro functional analyses of identified variants of RRAGD, a gene that encodes a small Rag guanosine triphosphatase (GTPase).

Results: In eight children from unrelated families with a tubulopathy characterized by hypomagnesemia, hypokalemia, salt wasting, and nephrocalcinosis, we identified heterozygous missense variants in RRAGD that mostly occurred de novo. Six of these patients also had dilated cardiomyopathy and three underwent heart transplantation. We identified a heterozygous variant in RRAGD that segregated with the phenotype in eight members of a large family with similar kidney manifestations. The GTPase RagD, encoded by RRAGD, plays a role in mediating amino acid signaling to the mechanistic target of rapamycin complex 1 (mTORC1). RagD expression along the mammalian nephron included the thick ascending limb and the distal convoluted tubule. The identified RRAGD variants were shown to induce a constitutive activation of mTOR signaling in vitro.

Conclusions: Our findings establish a novel disease, which we call autosomal dominant kidney hypomagnesemia (ADKH-RRAGD), that combines an electrolyte-losing tubulopathy and dilated cardiomyopathy. The condition is caused by variants in the RRAGD gene, which encodes Rag GTPase D; these variants lead to an activation of mTOR signaling, suggesting a critical role of Rag GTPase D for renal electrolyte handling and cardiac function.

Keywords: Bartter syndrome; TRPM6; genetic renal disease; hypokalemia; hypomagnesemia; kidney stones; mTOR; magnesium; nephrocalcinosis; rag complex; salt wasting.