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RRAGD-Associated Autosomal Dominant Kidney Hypomagnesemia with Cardiomyopathy: A Review on the Clinical Manifestations and Therapeutic Options

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Keywords
Tubulopathy · Hypomagnesemia · Hypokalemia · Cardiomyopathy · *RRAGD*

Abstract
Background: A hereditary condition primarily affecting the kidneys and heart has newly been identified: the *RRAGD*-associated autosomal dominant kidney hypomagnesemia with cardiomyopathy (ADKH-*RRAGD*). This disorder is characterized by renal loss of magnesium and potassium, coupled with varying degrees of cardiac dysfunction. These range from arrhythmias to severe dilated cardiomyopathy, which may require heart transplantation. Mutations associated with *RRAGD* significantly disrupt the non-canonical branch of the mechanistic target of rapamycin complex 1 pathway. This disruption hinders the nuclear translocation and transcriptional activity of the transcription factor EB a crucial regulator of lysosomal and autophagic function. ***Summary:*** All identified *RRAGD* variants compromise kidney function, leading to hypomagnesemia and hypokalemia of various severity. The renal phenotype for most of the variants (i.e., S76L, I221K, P119R, P119L) typically manifests in the second decade of life occasionally preceded by childhood symptoms of dilated cardiomyopathy. In contrast, the P88L variant is associated to dilated cardiomyopathy manifesting in adulthood. To date, the T97P variant has not been linked to cardiac involvement. The most severe manifestations of ADKH-*RRAGD*, particularly concerning electrolyte imbalance and heart dysfunction requiring transplantation in childhood appear to be associated with the S76L, I221K, P119R variants. ***Key Messages:*** This review

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aimed to provide an overview of the clinical presentation for ADKH-*RRAGD,* aiming to enhance awareness, promote early diagnosis, and facilitate proper treatment. It also reports on the limited experience in patient management with diuretics, magnesium and potassium supplements, metformin, or calcineurin and SGLT2 inhibitors.

Introduction

Evidence for a functional interdependence between the kidneys and the heart derived not only from the so-called "cardiorenal syndromes" where dysfunction of one organ hampers the proper function of the other. This connection is also evident in hereditary conditions such as Anderson-Fabry disease [1], autosomal dominant polycystic kidney disease (ADPKD) [2] and mitochondropathies [3].

A newly identified hereditary condition, known as *RRAGD*-associated Autosomal Dominant Kidney Hypomagnesemia with Cardiomyopathy (ADKH-*RRAGD*), is characterized by renal magnesium and potassium wasting, accompanied by varying degrees of heart dysfunction, ranging from arrhythmias to severe dilated cardiomyopathy that may require heart transplantation. *RRAGD* variants have been pinpointed as the genetic culprits [4].

The pathophysiology associated with mutations in *RRAGD* involves the mechanistic target of rapamycin complex 1 (mTORC1), a pivotal serine/threonine kinase governing various cellular processes including growth, metabolism, proliferation, and survival [5]. mTORC1 activates both canonical and non-canonical pathways [6, 7], promoting anabolism in nutrient-rich conditions by phosphorylating canonical substrates such as S6 kinase (S6K) and 4E-binding protein 1 (4E-BP1) [8–11].

Concurrently, mTORC1 inhibits catabolic processes by phosphorylating key components involved in initiating autophagy, such as ULK1 [5]. Notably, mTORC1 phosphorylates its non-canonical substrate, the transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy, influencing its nucleocytoplasmic shuttling and activity [12–14]. The importance of mTORC1 in nutrient sensing has been demonstrated to be crucial in maintaining kidney physiology [15]. Rag GTPases, including RagA, RagB, RagC, and RagD, regulate mTORC1 activity by forming heterodimers, thus controlling its activation state [16].

Recent studies have revealed a non-canonical mTORC1 signaling pathway mediated by RagD and its paralog, RagC, which specifically inhibits the activity of the transcription factors TFEB and TFE3 [7]. Genetic studies suggest that mutations in the gene encoding RagD (S76L, T97P, P119L, I221K) are linked to kidney tubulopathy and cardiomyopathy [4]. This study highlights for the first time the significant role of RagD in the regulation of renal electrolyte balance and cardiac function in human disease physiology. Another study identified a novel *RRAGD* mutant, P88L [17], and demonstrated that all known disease-causing mutations in *RRAGD* lead to protein autoactivation, independently of folliculin (FLCN) [18], the GTPase-activating protein (GAP) for RagC/D. Expression of these auto-activated RagD mutants significantly impacts on the non-canonical mTORC1 pathway, resulting in constitutive TFEB phosphorylation by mTORC1, hindering its nuclear translocation and transcriptional activity. Interestingly, it was shown that the auto-activated RagD mutants show minimal impact on canonical mTORC1 substrates, like S6K phosphorylation [17]. Additionally, these mutations inhibit the lysosomal/autophagic response to lysosomal injury and mitochondrial stress, emphasizing their relevance in kidney and heart functions [17]. In ADKH-*RRAGD* disease, TFEB inhibition seems to be the primary driver, underscoring the importance of the non-canonical mTORC1 signaling pathway in these conditions. Thus, strategies aimed at restoring TFEB function could represent promising therapeutic avenues in the future. Figure 1 illustrates how RagD activity is regulated under both physiological and mutated conditions, and it highlights the resulting impacts on mTORC1 signaling.

Summary of the Clinical Presentation and Treatment of the Largest Families Affected by *RRAGD* Mutations

The P88L RRAGD *Family*

The clinical presentation of the P88L *RRAGD* family has been previously documented [17]. We identified 8 affected individuals who exhibited a similar kidney phenotype but variable heart involvement. All affected members belong to two branches of the same family, with only female siblings being affected (Fig. 2a). The founder could not be identified, and whether the potential founders' deaths were related to kidney or heart issues remains unknown. Data spanning three generations, including information from individuals in the second, fourth, and sixth decades of life, were collected from this large family.

All children of this family were incidentally diagnosed as part of the family screening. Each child was born at term and birth weight was within a normal range.

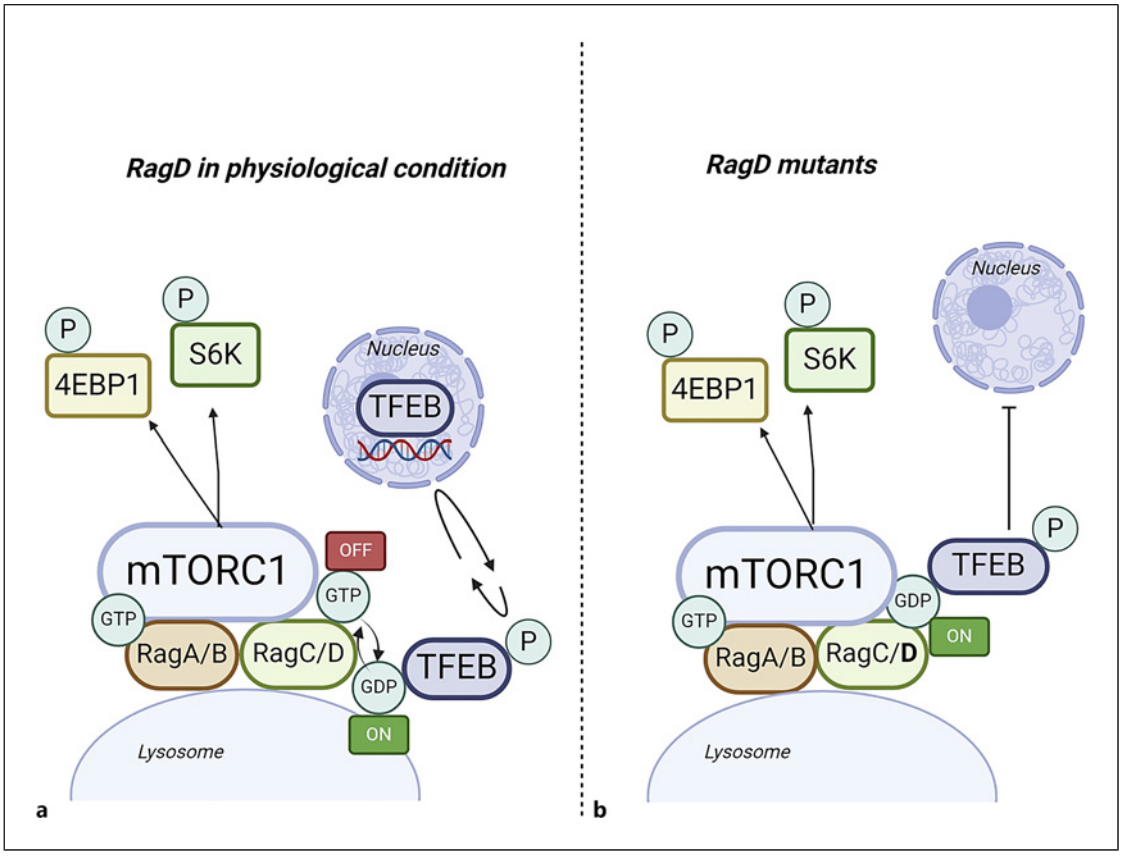

Fig. 1. Regulation of RagD activity in physiological or mutated conditions. **a** RagD in physiological conditions: in nutrient-rich environments, mTORC1 is recruited to the lysosome via Rag-dependent mechanisms, facilitating mTORC1 activity toward S6K and 4E-BP1. This recruitment also activates the GAP activity of FLCN toward RagC/D, promoting their GDP-loading. The resulting RagA/B GTP-RagC/D-GDP heterodimers facilitate the recruitment of TFEB to mTORC1. Conversely, during nutrient deprivation, RagA/B-GDP; RagC/D-GTP heterodimers lead to mTORC1 inactivation and facilitate TFEB nuclear translocation. TFEB binds to its target genes, thereby regulating various pathways and cellular functions such as autophagy and lysosomal biogenesis. **b** RagD mutations: mutations in RagD significantly disrupt the non-canonical mTORC1 pathway, resulting in constitutive phosphorylation of TFEB by mTORC1. This impedes TFEB's nuclear translocation and transcriptional activity. Notably, auto-activated RagD mutants have minimal impact on canonical mTORC1 substrates, such as S6K phosphorylation. Furthermore, these mutations hinder the lysosomal/autophagic response to lysosomal injury and mitochondrial stress, underscoring their relevance in kidney and heart functions.

Psychomotor development and growth progressed without any notable issues. At time of first visit, the patients IV.5, IV.6, IV.1 presented a slightly lower height as calculated by the height-SDS −1.25, −2.73, and −1.36 at age 18, 11, and 15 years old, respectively. Two (IV.5 and IV.6) of the 3 children in the family presented with nephrocalcinosis and renal stones made of calcium phosphate (IV.5) and calcium oxalate (IV.6).

P88L *RRAGD* family presented with slight hypokalemic metabolic alkalosis and hypomagnesemia that never required hospitalization even in association with other potential causes of electrolyte imbalance, such as diarrhea or fever. In children, the heart phenotype was limited to ventricular arrhythmia in the form of frequent bigeminy in only 1 patient (IV.5). However, clinical history data of the other patients revealed the presence of ventricular bigeminy even before the development of major heart problems. Significant heart problems were diagnosed in adulthood in this family, encompassing dilated cardiomyopathy (DCM) (III.2), myocardial infarction (III.5), and sudden cardiac death (III.10) reflecting the broad spectrum of the cardiac phenotype. Patients III.2 and III.5 were not receiving potassium or magnesium supplementation until being screened. Patient III.10 was diagnosed with hypokalemia at 6 years old and had been on potassium supplements since then.

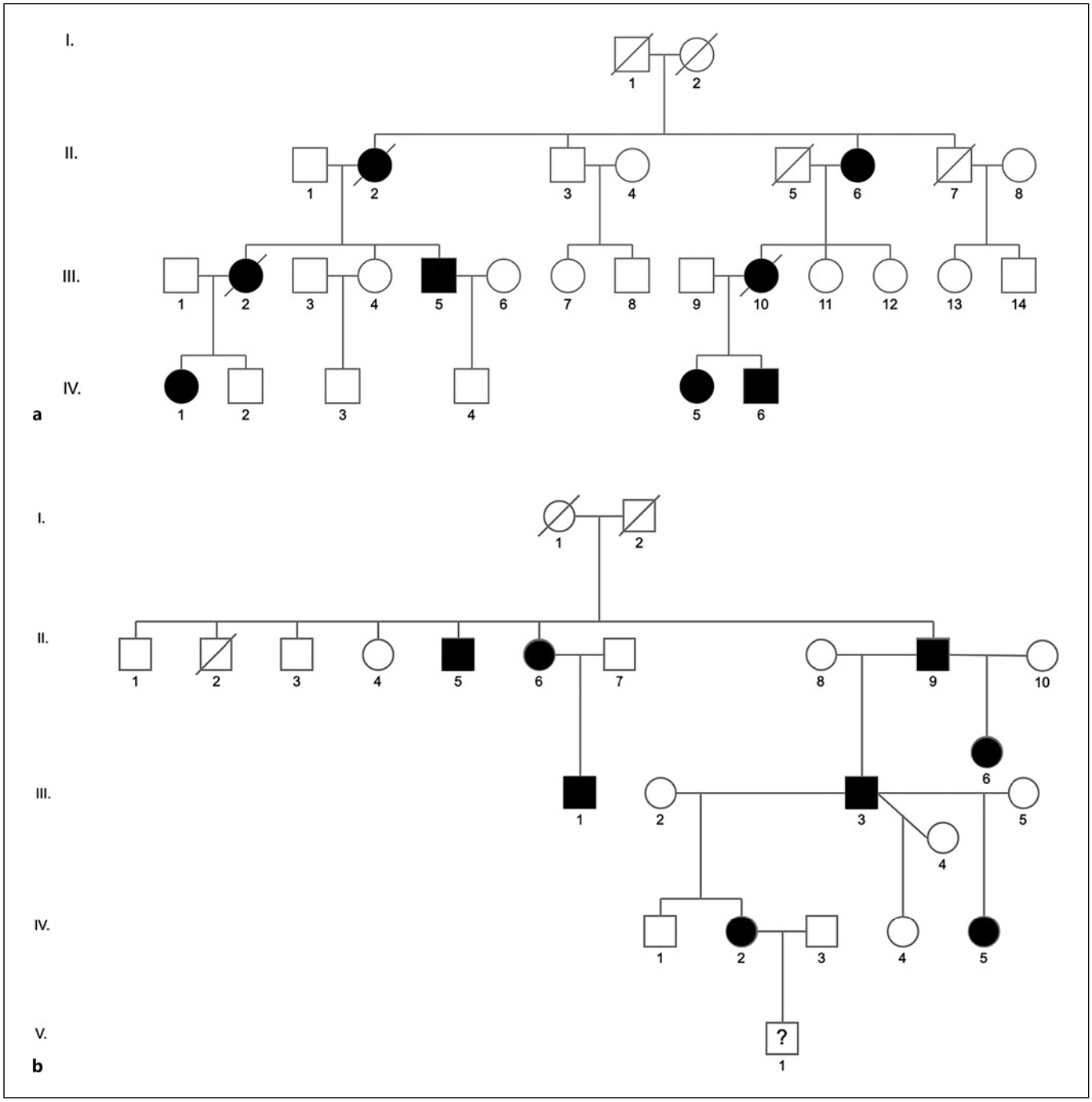

Fig. 2. a Pedigree of the P88L *RRAGD* family as modified from [17]. **b** Pedigree of the T97P *RRAGD* family as modified from [4]. In black affected members of the families.

Heart failure secondary to DMC required the installation of an implantable cardioverter-defibrillator in patient III.2. She was treated with the mineral corticoid receptor antagonists, spironolactone and eplerenone, and ACE inhibitors for the HFrEF. This treatment was associated with an increase in serum potassium levels, but no episodes of hypotension or fainting were reported. In addition, because of ankle swelling, she was successfully treated by furosemide with no significant worsening of the electrolyte homeostasis. Altogether, this scenario suggests

that the salt-losing phenotype was not so severe in patient III.2 as compared to other salt-losing tubulopathies like Bartter syndrome [19]. Due to the worsening of heart failure with reduced ejection fraction, patient III.2 underwent heart transplantation at the age of 43.

The oldest affected patients in this family were about 60 years old (II.2 and II.5). Similarly, to all the family members, they presented with a normal eGFR, suggesting that the P88L *RRAGD* variant is not associated with overall age-dependent worsening of kidney function. Only patient II.2 developed DCM requiring implantable cardioverter-defibrillator. Finally, she died for the complication of a metastatic cholangiocarcinoma. Whether gallbladder and bile duct involvement are affected by gain-of-function variants of *RRGAD* require future investigation. In the P88L family, cholelithiasis requiring surgery was observed in 4/8 patients.

All adult patients in the P88L family presented with a mild hypokalemic metabolic alkalosis associated with hypermagnesuric hypomagnesemia. No alterations in serum or urine calcium levels were detected. None of the female patients (II.2, II.5, III.2, III.10) presented with major complications during pregnancy, neither related to the gestation or the labor. Beside kidney and heart involvement, 3/8 of the patients showed sensorineural hypoacousia, suggesting the inner ear as a potential additional target of *RRAGD* dysfunction (II.2, II.5, and III.5).

The T97P RRAGD *Family*

The clinical presentation of the T97P *RRAGD* family was previously described in Schlingmann KP et al. [4]. We identified 8 individuals affected by severe and symptomatic hypomagnesemia, unresponsive to oral magnesium supplements (Fig. 2b). To date, no heart involvement has been observed in the T97P *RRAGD* family thus far. It was not possible to identify the founder since generation I was no longer living. The cause of death for these potential founders, and whether it was related to renal or cardiac conditions, remains undetermined. Nonetheless, this extensive family study spanned three generations, with data ranging from the age of 2 (patient IV.2) to 61 (patient II.9). Salt-losing nephropathy was detected in both males and females.

The index patient (III.3) initially exhibited muscular cramps complicated by tetany and muscular fatigue starting from the age of 20. There were no reports of polyuria or polydipsia. Early tooth erosions were described. Blood pressure (BP) consistently remained on the lower side of the range (90/60 mm Hg). Laboratory examinations revealed low serum levels of magnesium (0.46 mmol/L) and potassium (3.5 mmol/L), and metabolic alkalosis (s[HCO_3^-]: 35 mmol/L). Kidney function remained unaffected, with no evidence of proteinuria, kidney stones, or nephrocalcinosis. Cardiac assessments conducted up to the age of 50 revealed no irregularities, with sustained left ventricular contractility and an ejection fraction of 78%. Cardiac stress test was normal at both clinical and electrical levels. Note that this III.3 patient was treated with metformin (850 mg bid) in a context of type 2 diabetes (HbA1c level: 7.2%). Serum levels of magnesium (0.38 mmol/L) slightly decreased after a 4-week exposure to metformin (0.30 mmol/L), with *restitutio statu quo ante* (0.37 mmol/L) 4 weeks after metformin withdrawal. No diarrhea was reported.

The index patient's father (II.9) and paternal aunt (II.6) and uncle (II.5) displayed a similar muscular phenotype, characterized by hypomagnesemia-related tetany. Multiple cardiac evaluations were normal. More specifically, the echocardiogram of patient II.9 at 66 years old showed a normal left ventricular morphology, with no hypertrophy or dilation and an ejection fraction of 65%. The ejection fraction of patient II.6 reached 71%, with no abnormalities during the cardiac stress test at the age of 49. Note that BP levels were low (90/60 mm Hg). The patient's cousin (III.1) started to complain about muscular cramps at the age of 10 years. Additionally, polyuria was explored by a water restriction test, which showed no response to arginine-vasopressin administration. From the age of 21 years old, patient III.1 presented with recurrent formation of calcium-rich kidney stones. No nephrocalcinosis was detectable. BP levels were low (90/60 mm Hg), and laboratory results indicated hypomagnesemia (0.42 mmol/L), hypokalemia (3.4 mmol/L), and metabolic alkalosis ([HCO_3^-]: 28 mmol/L). Kidney function was normal, with no proteinuria. Patient III.1 exhibited no cardiac symptoms. As complication of nephrolithiasis, patient III.6 presented an obstructive pyelonephritis at the age of 22.

The index patient (II.9) has 4 children with 3 different spouses: 2 of them also presented with hypomagnesemia. One of the daughters (IV.2) experienced tetany at the age of 16 years, with low BP levels (<90/60 mm Hg) and recurrent symptomatic BP drops. Laboratory tests showed hypomagnesemia (0.56 mmol/L), hypokalemia (3.4 mmol/L), and metabolic alkalosis ([HCO_3^-]: 28 mmol/L). Kidney function was preserved, with no proteinuria, no kidney stones, or nephrocalcinosis. At the age of 22, she gave birth to a boy (with a birth weight of 2.385 g) after an uncomplicated 35-week pregnancy. The child's electrolyte and genotype are unknown. At the age of 23, she underwent a cardiac MRI in a context of asymptomatic diffuse alterations of the terminal phases at

EKG: MRI images were normal, with no signs of myocarditis or infiltrative diseases. The patient (IV.4) had asymptomatic hypomagnesemia (0.62 mmol/L) detected at the age of 4 years, as part of the familial screening. It is worth noting that serum magnesium levels were in the normal range at the age of 2 years. Another family member (III.6) also showed strictly normal magnesium levels at 3 months of age, but later developed symptomatic hypomagnesemia with cramps and tetany when she turned 12 years. All family members who tested negative for the T97P *RRAGD* mutation did not display any kidney or heart abnormalities, and there were no cases of sudden death within the T97P *RRAGD* family.

The S76L RRAGD *Patients*

A Belgian Patient

The clinical presentation of the Belgian S76L *RRAGD* patient has been previously described in Schlingmann KP et al. [4]. The patient first experienced chest pain and dyspnea at the age of 14 years in a context of a mildly reduced ejection fraction (EF: 50%). The ischemia stress tests and the cardiac MRI were within the normal range. The patient consistently presented with low blood pressure (90/60 mm Hg) with hypomagnesemia (0.42 mmol/L) and borderline hypokalemia (3.5 mmol/L) with normal kidney function and no proteinuria. The patient was treated by perindopril and bisoprolol. At the age of 35, the patient experienced a cardiogenic shock in the context of a pneumonia, which requires the implantation of a Boston defibrillator.

A subsequent echocardiogram at the age of 36 revealed DCM with an LV EF of 45% that required treatment with sacubitril/valsartan, spironolactone, bumetanide, and bisoprolol, and later with dapagliflozin and apixaban. The therapy was well tolerated with no major modifications of serum electrolytes and BP levels.

The patient's father passed away at the age of 33 due to a myocardial infarction, which was associated with untreated hypercholesterolemia and poorly controlled type 2 diabetes mellitus. However, since the paternal grandfather and uncle died for sudden death at the age of 26 years and 19 years, respectively, one may speculate that they might be carriers of the S76L *RRAGD* variant. No electrolyte imbalance or cardiac abnormalities were found in the patient's mother.

An Italian Patient

The Italian 7 years old girl was born full-term from non-consanguineous parents with a normal birth weight (2,750 g) and presented at 1 year old with failure to thrive, polyuria, and polydipsia. Despite normal psychomotor development, laboratory findings showed normal kidney function and serum levels of electrolytes, including calcium. Potassium levels were in the low-normal range (3.5 mM), while serum magnesium was not measured at that time. In the following 2 years, she continued to grow poorly. At 3 years old, she experienced bilateral carpopedal spasms in the context of recurrent episodes of vomiting and diarrhea. At that time, she presented with hypocalcemia (1.68 mM) and hypomagnesemia (0.29 mM). Despite supplemental therapy with magnesium salt (magnesium citrate), severe hypomagnesemia required hospital admission to appropriately manage vomiting and diarrhea. Hypokalemia (2.5 mM) was also observed. Genetic testing identified the S76L *RRAGD* variant. The corrected QT interval was prolonged during episodes of gastrointestinal decompensation and remained borderline prolonged (460–470 ms) in a steady state. Her serum magnesium levels usually ranged between 0.37 and 0.45 mM, and serum potassium levels were around 3.0 mM. Eye examination, abdominal ultrasound, and echocardiography were unremarkable, as was a cardiac stress test. Renal ultrasound showed no abnormalities. At 5.5 years old, her blood pressure was normal, while height-SDS was −3.2 and weight-SDS −4.1. Growth hormone deficiency was ruled out via an arginine-stimulation test. The patient had mild hypercalciuria (urinary calcium/creatinine ratio: 0.41 mg/mg); sodium fractional excretion, plasmatic aldosterone, renin activity, and ACTH were unremarkable. To limit polyuria, she was started on indomethacin that was successful in reducing urine volume. Cardiac ultrasound confirmed normal left ventricular morphology and function (EF: 65%). No renal stones or nephrocalcinosis were found. Treatment included potassium chloride (2 mEq/kg/day), magnesium sulfate (300 mg/kg/day), indomethacin 2 mg/kg/day.

Two Spanish Patients

The S76L *RRAGD* variant was also identified in two monozygotic twin sisters from Spain [20]. Their clinical presentation, including a salt-losing phenotype during childhood and DCM necessitating heart transplantation by their 40s, was similar to the Italian patient. Unlike the other cases, these Spanish patients exhibited nephrocalcinosis. Data from single patients carrying I221K, P119R/L, and S76W variants of *RRAGD* have been described previously [4]. The major points are summarized in Table 1.

Treatment of RRAGD – *Associated Hypomagnesemia*

Potassium and magnesium salt supplementation remain the cornerstone of ADKH-*RRAGD* treatment. KCl, K-citrate, and K-gluconate are commonly used for

Table 1. Main genotype/phenotype characteristics

RRAGD variants	P88L	T97P	S76L	S76W	I221K	P119R	P119L
Patients	8 (1)	8 (1)	6 (5)	1 (1)	1 (1)	2 (2)	1 (1)
Polyhydramnios	No	1/8	Yes	No	Yes	No	No
Polyuria	2/8	2/8	Yes	Yes	Yes	Yes	Yes
Hypomagnesemia	MI	MO/SE	MO/SE	MO	MO	MO/SE	MI
Hypokalemia	MI	MI	MI	MI/MO	MI	MI	MI
Nephrocalcinosis	3/8	No	Yes[a]	Yes	Yes	Yes	Yes
Renal stone	3/8	1/8	NO	–	–	–	–
DCM in childhood	No	No	Yes	No	Yes	Yes	Yes
DCM in adulthood	2/8	No	Yes[a]	No	–	–	–
Heart Tr. in childhood	–	No	Yes	No	Yes	–	–
Heart Tr. in adulthood	1/8	No	Yes[a]	No	–	Yes	–
SNHL	3/8	–	–	No	–	–	–
CKD development	No	No	No	No	No	No	No

The top row reports the, so far known, causative variants of ADKH-*RRAGD*. Hypomagnesemia has been defined as MI (mild 0.58–0.71 mM); MO (moderate 0.41–0.57 mM); SE (severe <0.40 mM); hypokalemia has been defined as MI (mild 3.5–3.0 mM); MO (moderate 2.5–2.9 mM); SE (severe <2.5 mM). DCM, dilated cardiomyopathy; heart Tr. heart transplantation; SNHL, sensorineural hearing loss. [a]The finding has been reported only in the Spanish family described in de Frutos F et al. [20].

treating hypokalemia, while different magnesium salt are used for hypomagnesemia, including $MgCl_2$, Mg sulfate, magnesium gluconate, dehydrated magnesium aspartate, and magnesium citrate. The choice of magnesium salts also depends on patient palatability and gastrointestinal tolerance. The salt-losing phenotype does not exacerbate when RAS inhibitors are used for heart failure management. ACE inhibitors, AT-1 receptor antagonists (with or without sacubitril), and mineralcorticoid receptor antagonists have been administered without significant blood pressure effects. Furthermore, furosemide or bumetanide usage did not worsen hypomagnesemia, suggesting a milder salt-losing. ACE inhibitors, antagonists of receptor AT-1 of angiotensin II (alone or in association with sacubitril), and mineralcorticoid receptor antagonists have been administered in these patients with no major effect on BP effect. On the same line, when heart failure progresses, *RRAGD* patients seem to be not protected by the development of edema. In this clinical context, the use of furosemide or bumetanide, when needed, was not associated with the worsening of hypomagnesemia, although we cannot rule out that hypomagnesemia is linked to a dysfunction of the thick ascending limb of Henlé's loop. All together, these observations suggest that the salt-losing component in RRAGD patients is milder than Gitelman or Bartter syndromes. The use of SGLT2 inhibitors prescribed for the management of heart failure was safe for the Italian P88L *RRAGD* II-5 and the Belgian S76L *RRAGD* patients, with no major impact on electrolyte plasma levels. Whether this class of drugs significantly ameliorates hypomagnesemia as suggested in diabetics [21, 22] requires further clinical investigations.

One of the Italian patients with overt polyuria in early ages was responsive to indomethacin administration. This seems an effective approach when polyuria is present, mainly in young children, similarly to what is classically done in other congenital tubulopathies. Finally, some of these patients required heart transplantation and were exposed to calcineurin inhibitors, including tacrolimus. When used in patient P88L III-2, tacrolimus did not worsen serum magnesium in condition of stable GFR (Fig. 3). However, since CNI-related hypomagnesemia varies on patient's status, this requires a further investigation on a larger number of patients.

Discussion

In order to increase the awareness on a novel clinical entity characterized by K^+ and Mg^{2+} wasting associated with heart abnormality, we report on the clinical histories of 23 patients from 11 families affected by gain-of-function variants of *RRAGD* gene in Europe. *RRAGD*-related kidney disease is associated with early alterations in renal magnesium and potassium handling that manifest around 2 years old, potentially leading to renal stones

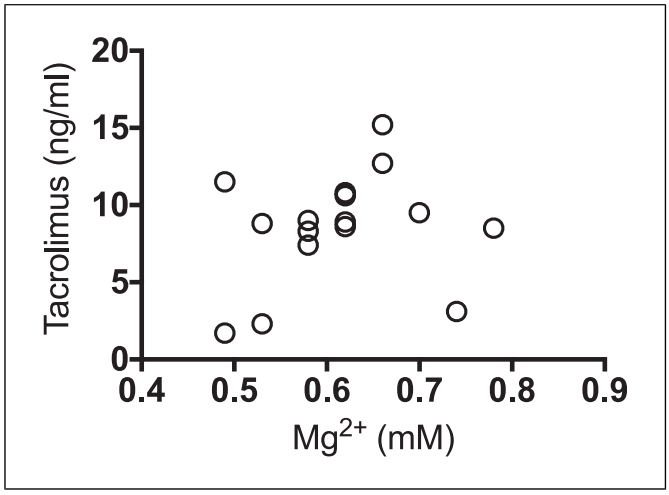

Fig. 3. Correlation between serum (Mg^{2+}) and tacrolimus in the first months of renal transplantation from patient III.2 carrying the P88L *RRAGD* variant was not statistically significant (*p* value 0.44). Only data corresponding to a serum creatinine in the normal range (0.8–1.2 mg/dL) were considered to rule out the influence of renal failure on Mg^{2+} handling.

and nephrocalcinosis. Renal calcium loss can be present, although this is not univocally present.

The majority of the patients described manifest symptoms of tubulopathy between the first and second decade of life. However, polyhydramnios and preterm delivery have been described for patients carrying the I221K- and S76L/W-*RRAGD* variants [4]. These patients, as well as the S76L *RRAGD*-carrying Italian girl described above, presented with polyuria during childhood. This suggests that the salt-losing phenotype could be more severe with the variants I221K- and S76L/W-*RRAGD.*

On the cardiologic point of view, it seems that two phenotypes can manifest in childhood. Indeed, some patients present with few (bigeminy, P88L *RRAGD*) or no signs of heart involvement (T97P- and S76W-*RRAGD,* follow-up limited up to 19 years old for the S76W*)*, while, for others, a symptomatic heart failure due to primary DCM occurs already in the first years of life and requires heart transplantation in the first and second decades of life (S76L, P119A, P119L, and I221K-*RRAGD*) [4].

In this report, we collected data from 3 generations of patients. Even the oldest individuals (sixth decade), there is no observed impairment in eGFR, suggesting that this condition does not affect the overall renal function. However, more data will be necessary to assess this point in patients with severe nephrocalcinosis.

The heart abnormality is often associated with the kidney phenotype, but apparently this is not always the case, as proven in the T97P *RRAGD* family described here. Longer observation and close cardiologic follow-up will further elucidate this finding. On the experimental models, the T97P *RRAGD* variant leads to cardiomyocyte dysfunction similarly to all other known variants described so far [17]. Compensatory mechanisms and/or milder alterations in the human heart could account for the unique kidney-limited phenotype seen in T97P *RRAGD* family.

A recent genomic sequencing study involving pediatric patients with DCM unveiled germline mutations in the *RRAGC* gene, affecting amino acids Ser75, Thr90, Tyr115, and Pro118. Experiments carried out on fibroblasts derived from individuals harboring the *RRAGC* Thr90Asn mutation demonstrated an augmentation in cell size and the cytosolic sequestration of TFEB. However, information regarding the canonical mTORC1 signaling remains elusive [23]. These findings parallel those observed with *RRAGD* mutations [17]. Of important note is that, when required, heart transplantation is neither associated with an amelioration nor worsening of hypomagnesemia or hypokalemia *per se*.

The severity of the electrolyte imbalance varies among patients. For a genotype/phenotype study, we will definitely need more patients/data. However, so far, common potassium and magnesium supplementations seem to control patients' symptoms. The tubulopathy component can be as severe as the most common Gitelman or Bartter syndrome, as seen in the S76L *RRAGD* young girl described here for the first time. As for the above-mentioned tubulopathies, indomethacin was effective for the management of polyuria. In the majority of the patients reported so far, RAS inhibitors did not worsen the salt-losing phenotype when administered for the management of heart failure. Finally, extrarenal and cardiac signs of disease involve the inner ear with the development of sensorineural hearing loss (SNHL) and tooth erosions. Since SNHL did not require any acoustic device, it is not known how much frequent is this sign among ADKH-*RRAGD* patients. Both the burden and the mechanisms underlying SNHL and tooth erosions require further investigation. In conclusion, the impact of *RRAGD*-related tubulopathy and cardiomyopathy requires careful evaluation, particularly among patients with DCM who test negative for commonly associated genes. Routine laboratory screenings often overlook magnesium levels; thus, assessing hypomagnesemia in these patients could prompt an extension of genetic diagnosis to include the *RRAGD* gene, either through targeted tubulopathy panels or whole exome sequencing.

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Conflict of Interest Statement

A.B. is cofounder of CASMA Therapeutics, Inc. and advisory board member of Avilar Therapeutics.

There are no other potential conflict of interest for the other coauthors.

Author Contributions

F.T. and F.J. designed and drafted the manuscript. I.S., A.B., B.R., F.E., G.F., I.V., and A.I. wrote the manuscript.

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