Renal Hypomagnesemia 2 (HOMG2 / Isolated Dominant Hypomagnesemia): Comprehensive Disease Characterization

Disease: Renal Hypomagnesemia 2 (HOMG2) — Isolated Dominant Hypomagnesemia with Hypocalciuria (IDH) **MONDO ID:** MONDO:0007937 · **OMIM:** #154020 · **Causal gene: FXYD2** (Na^+,K^+-ATPase γ-subunit)

Summary

Renal Hypomagnesemia 2 is an autosomal dominant renal tubulopathy caused by the gene *FXYD2*, which encodes the γ (gamma) regulatory subunit of the Na^+,K^+-ATPase. To date, essentially a single recurrent heterozygous missense allele — **c.121G>A, p.Gly41Arg (G41R)** — accounts for all genetically resolved cases. The disease is defined biochemically by isolated renal magnesium wasting producing hypomagnesemia (serum Mg^{2+} < 0.7 mmol/L), accompanied by paradoxically low urinary calcium excretion (hypocalciuria). Clinically it manifests with neuromuscular irritability (muscle cramps, tetany), seizures/convulsions, and, in longstanding cases, chondrocalcinosis. The term "renal hypomagnesemia **2**" is a serial numbering within the OMIM family of primary hypomagnesemias; the gene it refers to is unambiguously *FXYD2*, distinguishing it from TRPM6-, CLDN16-, CNNM2-, and HNF1B-related hypomagnesemias.

Mechanistically, G41R acts primarily through a **dominant-negative** effect. The mutant γ-subunit is incorrectly folded/routed and accumulates in perinuclear (ER/Golgi) compartments rather than reaching the basolateral plasma membrane of the distal convoluted tubule (DCT). Because FXYD2 oligomerizes, the mutant hetero-oligomerizes with wild-type γ-subunit and traps it intracellularly, abrogating its normal routing and glycosylation. The net result is loss of functional γ-subunit at the DCT basolateral membrane, impairing Na^+,K^+-ATPase-dependent transcellular Mg^{2+} reabsorption. Haploinsufficiency was formally excluded (individuals with a single *FXYD2* copy have normal serum Mg^{2+}), confirming that the dominant phenotype

requires the poisoning of wild-type protein by the mutant. A secondary, complementary **gain-of-function** branch has also been demonstrated: the fraction of G41R protein that does reach the membrane behaves as an aberrant inward-rectifying nonselective cation channel.

The condition is **ultra-rare**; the G41R allele arose on a shared haplotype in Dutch kindreds (founder effect) and has recurred in a small number of additional families. Importantly, the broader clinical picture of "isolated renal Mg wasting" is **genetically heterogeneous** — an American family with a clinically similar phenotype did not link to the *FXYD2* locus at 11q23, demonstrating that not all isolated renal magnesium wasting is FXYD2-related. Management is lifelong oral/parenteral magnesium supplementation; life expectancy is normal. This report synthesizes six confirmed findings across 19 reviewed papers and maps the causal chain from mutation to clinical manifestation.

Key Findings

Finding 1 — HOMG2 is caused by the recurrent *FXYD2* p.Gly41Arg mutation

Linkage analysis in a large Dutch family mapped the disease trait to chromosome **11q23** within a ~5.6-cM region. Within this interval, a heterozygous mutation **c.121G>A** in *FXYD2* — producing the amino acid substitution **p.Gly41Arg** — cosegregated with all affected family members and was absent from 132 control chromosomes (PMID: 12763862; PMID: 11062458). The same mutation was subsequently found to recur in two additional families with isolated dominant hypomagnesemia and hypocalciuria, with haplotype analysis revealing an **overlapping haplotype indicating a founder effect** (PMID: 25765846).

> *"we identified a heterozygous mutation in the FXYD2 gene, encoding the Na(+),K(+)-ATPase gamma-subunit, cosegregating with the patients of this family, which was not found in 132 control chromosomes. The mutation leads to a G41R substitution"* — PMID: 12763862
>
> *"We report a p.Gly41Arg FXYD2 mutation in two families with hypomagnesaemia and hypocalciuria. Interestingly, this is the same mutation as was described in the original study"* — PMID: 25765846

Glycine 41 is a highly conserved residue within the single transmembrane span of the 65-residue γ-subunit; its substitution by the bulky, positively charged arginine is the molecular lesion underlying the disease.

Finding 2 — The dominant-negative mechanism: mutant G41R misroutes and traps wild-type γ-subunit

Heterologous expression of the mutant γ-subunit in Sf9 and COS-1 cells demonstrated that **the mutant protein is incorrectly routed and accumulates in perinuclear structures**, lacking a post-translational modification (glycosylation) that marks correctly trafficked protein. Critically, **haploinsufficiency was excluded**: individuals carrying only a single functional *FXYD2* copy have normal serum Mg^{2+}, meaning simple loss of one allele is not sufficient to cause disease — the mutant must actively interfere with the wild-type product (PMID: 12763862).

The physical basis of this interference was established by co-immunoprecipitation showing that FXYD2 oligomerizes, and that G41R hetero-oligomerizes with wild-type γ-subunit, reducing its glycosylation and plasma-membrane routing (PMID: 17980699). Biophysical work on synthetic transmembrane peptides confirmed that the G41R substitution **abrogates normal γ-TM oligomerization** (as does the conservative G41L substitution), whereas an arginine substitution on a different helical face (position 35) retains oligomerization — directly linking the disease to disrupted γ-subunit quaternary assembly (PMID: 12225751).

> *"binding of FXYD2-G41R to wild type FXYD2 subunit might abrogate the routing of wild type FXYD2 to the plasma membrane thus causing the dominant nature of this mutation"* — PMID: 17980699
>
> *"the mutant gamma-subunit protein was incorrectly routed and accumulated in perinuclear structures"* — PMID: 12763862

Finding 3 — Clinical phenotype: isolated renal Mg^{2+} wasting with hypocalciuria and neuromuscular features

Affected individuals show **serum Mg^{2+} below ~0.7 mmol/L** due to inappropriate renal magnesium wasting, together with **hypocalciuria** (low urinary calcium). The clinical spectrum includes **muscle cramps/tetany, chondrocalcinosis, and epilepsy/convulsions** (PMID:

25765846; PMID: 12763862). The phenotype is "isolated" in that it is not accompanied by the broader electrolyte derangements (hypokalemia, metabolic alkalosis) seen in Gitelman/Bartter syndromes, nor the secondary hypocalcemia of TRPM6 disease.

> *"several patients suffered from muscle cramps, chondrocalcinosis and epilepsy"* — PMID: 25765846
>
> *"These disorders share the general symptoms of hypomagnesemia, tetany and epileptiformic convulsions, and often include secondary or associated disturbances in calcium excretion"* — PMID: 12763862

Suggested HPO terms: Hypomagnesemia (HP:0002917); Hypocalciuria (HP:0003127); Chondrocalcinosis (HP:0000934); Seizure (HP:0001250); Muscle cramps (HP:0003394); Tetany (HP:0001281); Renal magnesium wasting (HP:0012605).

Finding 4 — Normal γ-subunit function: tuning Na,K-ATPase ATP/cation affinity; γa vs γb isoforms

Under normal conditions, the FXYD2 γ-subunit is a type-2 single-pass transmembrane regulator of the Na,K-ATPase. Rat kidney expresses two splice variants, **γa and γb**, differing only at the extracellular N-terminus. Functionally, the γ-subunit produces **(i) an increase in apparent affinity for ATP** (secondary to a left shift in the E1↔E2 conformational equilibrium) **and (ii) an increase in K^+ antagonism of cytoplasmic Na^+ activation**. The subunit localizes to the basolateral membrane of several tubule segments, most strongly in the medullary thick ascending limb and also in the DCT (PMID: 11278761).

This normal function is woven into the broader DCT magnesium-handling network: the transcription factor **HNF1B specifically activates the γa isoform**, and *HNF1B* mutations impair γa through a dominant-negative effect, linking the HNF1B-associated hypomagnesemia syndrome to the same FXYD2 pathway (PMID: 21130072).

> *"an increase in apparent affinity for ATP, probably secondary to a left shift in E(1) <--> E(2) conformational equilibrium and (ii) an increase in K(+) antagonism of cytoplasmic Na(+) activation"* — PMID: 11278761
>
> *"HNF-1B specifically acts as an activator of the γa-subunit"* — PMID: 21130072

Finding 5 — Gain-of-function branch: membrane-reaching G41R acts as an inward-rectifying cation channel

Electrophysiology in *Xenopus* oocytes showed that both wild-type and G41R FXYD2 generate large nonselective ion currents, but **only G41R produces inward-rectifying cation currents upon hyperpolarization**. The rectification depended on the presence of a positive charge at residue 41, was blocked by extracellular divalent/trivalent cations (Ca^{2+}, Ba^{2+}, La^{3+}), and was removed by intracellular EDTA (PMID: 18448590). In MDCK renal epithelial cells, wild-type FXYD2 (but not G41R) supported a Mg^{2+}-gradient-driven transepithelial current that was inhibited by basolateral Ba^{2+}, supporting a physiological role for FXYD2 in basolateral Mg^{2+} extrusion.

> *"in contrast to the wild-type FXYD2 currents, inward rectifying cation currents were induced by hyperpolarization pulses in oocytes expressing the G41R mutant"* — PMID: 18448590
>
> *"FXYD2 can mediate basolateral extrusion of magnesium from cultured renal epithelial cells"* — PMID: 18448590

This establishes a **dual pathological mechanism**: dominant-negative misrouting (the dominant contributor, since most mutant protein never reaches the membrane) plus aberrant channel behavior in the residual membrane-resident fraction.

Finding 6 — Inheritance and epidemiology: autosomal dominant, ultra-rare founder allele, with locus heterogeneity

All reported genetically resolved IDH families carry the **identical p.Gly41Arg mutation on an overlapping haplotype**, indicating a Dutch founder effect (PMID: 25765846). The trait is autosomal dominant (OMIM #154020). Crucially, an American family with a clinically similar isolated renal Mg-wasting phenotype **did not link to 11q23** (multipoint LOD = −2.97 across five 11q23 loci), demonstrating genetic **locus heterogeneity** — i.e., the clinical phenotype of isolated renal Mg wasting is not exclusively FXYD2-mediated (PMID: 11836293).

> *"Haplotype analysis revealed an overlapping haplotype in all families, suggesting a founder effect"* — PMID: 25765846
>
> *"our data demonstrate locus heterogeneity for the phenotype of isolated renal Mg wasting with hypomagnesemia"* — PMID: 11836293

Section-by-Section Report

1. Disease Information

Overview. Renal Hypomagnesemia 2 (HOMG2), also called **Isolated Dominant Hypomagnesemia with hypocalciuria (IDH)**, is a Mendelian autosomal dominant renal tubulopathy in which the kidney inappropriately wastes magnesium, producing chronic hypomagnesemia with low urinary calcium. It is caused by mutation in *FXYD2* (Na,K-ATPase γ-subunit).

Key identifiers. | Resource | Identifier | |---|---| | OMIM | #154020 | | MONDO | MONDO:0007937 | | Orphanet | Primary hypomagnesemia / isolated dominant hypomagnesemia group | | ICD-10 | E83.42 (Hypomagnesemia) | | ICD-11 | 5C64.41 (Magnesium deficiency) | | MeSH | Magnesium Deficiency / renal tubular disorders | | Gene (HGNC) | FXYD2, HGNC:4028 |

Synonyms: familial primary hypomagnesemia caused by FXYD2 mutation; FXYD2 familial primary hypomagnesemia; HOMG2; isolated autosomal dominant hypomagnesemia; isolated renal magnesium wasting; renal hypomagnesemia type 2.

Information source. Derived predominantly from **aggregated disease-level resources** (OMIM, Orphanet) built on a small number of **individual-patient family studies** — the original Dutch kindred and ≤2 additional families. There is no large EHR-derived cohort given the ultra-rarity.

2. Etiology

Primary cause — genetic. The sole established cause is the heterozygous *FXYD2* **c.121G>A (p.Gly41Arg)** missense mutation (PMID: 12763862; PMID: 25765846).

Genetic risk factors. The causal variant is itself the risk factor (fully penetrant dominant allele in reported families). A founder haplotype underlies recurrence in Dutch families. No modifier genes have been defined for HOMG2 specifically, though the broader DCT Mg^{2+} network (HNF1B, TRPM6, CNNM2, PCBD1) provides candidate interacting loci.

Environmental risk factors. None established as causal. Acquired/environmental causes of hypomagnesemia generally (diuretics, proton pump inhibitors, EGFR inhibitors, calcineurin inhibitors, alcohol, malnutrition) are relevant to differential diagnosis and may exacerbate the genetic deficit but are not part of the Mendelian etiology (PMID: 25540137).

Protective factors. No genetic protective alleles described. Dietary magnesium adequacy mitigates severity but cannot correct the renal wasting.

Gene–environment interactions. Not formally studied for FXYD2; plausibly, concurrent Mg^{2+}-wasting drugs would compound the phenotype.

3. Phenotypes

Phenotype	Type	HPO term	Onset / Severity	Frequency
Hypomagnesemia (serum Mg^{2+} <0.7 mmol/L)	Lab abnormality	HP:0002917	Likely childhood/ early; variable	Obligate (defining)
Renal magnesium wasting	Lab/ physiologic	HP:0012605	Lifelong	Obligate
Hypocalciuria	Lab abnormality	HP:0003127	Lifelong	Characteristic
Muscle cramps	Symptom	HP:0003394	Variable	Common
Tetany	Clinical sign	HP:0001281	Episodic	Variable
Seizures / convulsions	Clinical sign	HP:0001250	Variable	Reported subset
Chondrocalcinosis	Physical/ imaging	HP:0000934	Adult/late	Longstanding cases

Characteristics. Onset is typically early in life (the biochemical defect is congenital), but symptomatic presentation varies from asymptomatic hypomagnesemia detected incidentally to overt neuromuscular irritability. Severity is **variable**; the course is **chronic and stable** (non-progressive at the organ level, as this is not a nephropathy that progresses to renal failure). Chondrocalcinosis is a late complication of chronic hypomagnesemia (also seen in Gitelman syndrome).

Quality-of-life impact. Generally modest with adequate supplementation; cramps, fatigue and occasional seizures can impair daily functioning. No disease-specific QoL instrument data (EQ-5D/SF-36) exist for this ultra-rare condition.

4. Genetic / Molecular Information

- **Causal gene:** *FXYD2* (HGNC:4028), chromosome 11q23, encoding the Na,K-ATPase γ-subunit (UniProt P54710).
- **Pathogenic variant: c.121G>A, p.Gly41Arg (G41R)** — a missense change affecting a highly conserved transmembrane glycine. Classified **pathogenic** (cosegregation, absence from controls, functional confirmation; ACMG criteria PS3/PP1/PM1/PM2-supporting). It is essentially the only recurrent pathogenic *FXYD2* allele reported for HOMG2.
- **Variant type:** Single-nucleotide missense; germline.
- **Allele frequency:** Absent from population controls (not in 132 control chromosomes in the original study); effectively absent/ultra-rare in gnomAD.
- **Functional consequence: Dominant-negative** (loss of wild-type function via misrouting/trapping) with an additional **gain-of-function** cation-channel activity in membrane-reaching protein (PMID: 12763862; PMID: 17980699; PMID: 18448590).
- **Modifier genes / epigenetics / chromosomal abnormalities:** None established for HOMG2. HNF1B transcriptionally regulates the γa isoform and is a mechanistically related locus (PMID: 21130072).

5. Environmental Information

No environmental, lifestyle, or infectious agents cause HOMG2 — it is monogenic. Environmental magnesium-depleting factors (diuretics, PPIs, alcohol) are relevant only as confounders/exacerbators and to the differential diagnosis (PMID: 25540137).

6. Mechanism / Pathophysiology

Ordered causal chain (mutation → clinical manifestation):

1. Heterozygous **FXYD2 c.121G>A** introduces **p.Gly41Arg** in the transmembrane helix of the γ-subunit → *results in* a misfolded/mis-assembling subunit.
2. G41R **abrogates normal γ-TM oligomerization geometry** (demonstrated with TM peptides) → *leads to* aberrant quaternary assembly.
3. The mutant subunit is **incorrectly routed and accumulates in perinuclear (ER/Golgi) structures**, lacking its normal post-translational modification → *results in* failure to reach the DCT basolateral membrane.

4. Because FXYD2 oligomerizes, **mutant hetero-oligomerizes with wild-type γ-subunit and traps it intracellularly** (dominant-negative) → *leads to* depletion of functional γ-subunit at the membrane (haploinsufficiency excluded).
5. Loss of functional basolateral γ-subunit **impairs Na,K-ATPase ATP/cation-affinity tuning in the DCT** → *results in* reduced transcellular Mg^{2+} reabsorption.
6. **Branch (gain-of-function):** the residual membrane-reaching G41R behaves as an **inward-rectifying nonselective cation channel**, perturbing membrane potential/ion flux (inferred to contribute; demonstrated in oocytes/MDCK).
7. Reduced DCT Mg^{2+} reabsorption → *results in* **renal magnesium wasting and hypomagnesemia**; coupling of Na^+/Mg^{2+} handling → *leads to* **hypocalciuria**.
8. Low extracellular Mg^{2+} increases **neuromuscular excitability** → *results in* **muscle cramps, tetany, and seizures**; chronic Mg^{2+} deficiency → *leads to* **chondrocalcinosis**.

Molecular/cellular detail. The DCT is the final determinant of urinary Mg^{2+}, as nephron segments beyond it are largely Mg^{2+}-impermeable (PMID: 19812536). Apical Mg^{2+} entry occurs via TRPM6; the basolateral Na,K-ATPase (with its γ-subunit) maintains the electrochemical gradient driving transcellular transport. The γ-subunit modulates ATP affinity and K^+/Na^+ kinetics of the pump (PMID: 11278761). Upstream vs downstream: the mutation and misrouting are **upstream**; impaired DCT transport and systemic hypomagnesemia are **downstream**; neuromuscular symptoms are the terminal clinical readout.

Ontology suggestions. GO:0015693 (magnesium ion transport); GO:0006883 (intracellular sodium ion homeostasis); GO:0005890 (sodium:potassium-exchanging ATPase complex, CC); GO:0016020 (membrane); GO:0034976 (response to ER stress — inferred). **Cell type:** CL:1000849 (kidney distal convoluted tubule epithelial cell). **CHEBI:** CHEBI:18420 (magnesium(2+)); CHEBI:29108 (calcium(2+)).

7. Anatomical Structures Affected

- **Primary organ:** Kidney (UBERON:0002113), specifically the **distal convoluted tubule** (UBERON:0001292).
- **Cell type:** DCT epithelial cell (CL:1000849); subcellular locus of defect = **basolateral plasma membrane** (normal site) and **perinuclear ER/Golgi** (mutant accumulation site).
- **Body systems:** Renal/urinary (primary); neuromuscular and musculoskeletal (secondary, via hypomagnesemia); the γ-subunit is also expressed in medullary thick ascending limb and other segments (PMID: 11278761).

- **Subcellular GO CC:** sodium:potassium-exchanging ATPase complex (GO:0005890); endoplasmic reticulum membrane (GO:0005789).
- **Lateralization:** Bilateral (systemic genetic defect affecting both kidneys).

8. Temporal Development

- **Onset:** Congenital biochemical defect; clinically detected from childhood through adulthood, often insidious.
- **Course:** Chronic, lifelong, non-progressive at the organ level (does not typically cause renal failure). Symptoms episodic/fluctuating (cramps, seizures) depending on Mg^{2+} level.
- **Progression:** Stable; chondrocalcinosis accrues over decades.
- **Remission:** No spontaneous remission; biochemical improvement is treatment-induced via supplementation.
- **Critical period:** Continuous supplementation; attention during periods of additional Mg^{2+} loss (illness, concurrent diuretics).

9. Inheritance and Population

- **Inheritance:** Autosomal dominant (OMIM #154020).
- **Penetrance / expressivity:** High penetrance for the biochemical phenotype in reported families; variable clinical expressivity.
- **Founder effect:** Yes — identical G41R on overlapping haplotype in Dutch families (PMID: 25765846).
- **Epidemiology:** Ultra-rare; precise prevalence/incidence not established (only a handful of families reported worldwide).
- **Locus heterogeneity:** The isolated renal Mg-wasting phenotype is genetically heterogeneous — a US family did not link to 11q23 (PMID: 11836293).
- **Sex ratio:** No strong sex bias reported (autosomal).
- **Consanguinity / carrier frequency:** Not applicable in the usual sense (dominant); no carrier-screening framework.

10. Diagnostics

- **Laboratory tests:** Serum Mg^{2+} (LOINC 19123-9) — low (<0.7 mmol/L); 24-h urinary Mg^{2+} — inappropriately high (fractional excretion of Mg elevated, confirming renal wasting);

urinary calcium — **low (hypocalciuria)**, a key discriminator; serum K^+ and acid–base typically normal (distinguishing from Gitelman/Bartter).

- **Biomarkers:** Serum/urine magnesium and calcium are the operative biomarkers; no protein/metabolite biomarker beyond electrolytes.
- **Imaging:** Joint radiographs may reveal chondrocalcinosis in longstanding disease.
- **Genetic testing:** Targeted single-gene *FXYD2* sequencing (for the recurrent G41R) is diagnostic; hypomagnesemia **gene panels** (including FXYD2, TRPM6, CLDN16, CLDN19, CNNM2, HNF1B, KCNA1, SLC12A3, EGF) or **WES/WGS** are appropriate when the phenotype overlaps other tubulopathies. Karyotype/CMA/FISH/mtDNA testing are not indicated (point mutation, not structural/mitochondrial).
- **Clinical criteria / differential diagnosis:** Diagnose by the triad of hypomagnesemia + renal Mg wasting + hypocalciuria, normal K^+/acid–base, AD family history, and *FXYD2* G41R. **Differentials:** Gitelman syndrome (*SLC12A3*; adds hypokalemia/metabolic alkalosis/hypocalciuria), Bartter syndrome, TRPM6/HSH (hypomagnesemia with secondary hypocalcemia, AR), CLDN16/19 (hypomagnesemia with hypercalciuria/nephrocalcinosis), CNNM2, HNF1B (+ cysts/MODY5), EAST/SeSAME (*KCNJ10*), and acquired drug-induced hypomagnesemia (PMID: 27234911; PMID: 32622651).
- **Screening:** Cascade testing of at-risk first-degree relatives (serum Mg^{2+} ± *FXYD2* sequencing).

11. Outcome / Prognosis

- **Survival / life expectancy:** Normal with adequate magnesium replacement; no excess mortality reported.
- **Morbidity:** Driven by neuromuscular symptoms (cramps, tetany, seizures) and chronic complications (chondrocalcinosis). Generally manageable.
- **Disease course:** Chronic/lifelong; does not progress to end-stage renal disease.
- **Prognostic factors:** Adequacy of Mg^{2+} supplementation and avoidance of additional Mg^{2+}-wasting insults (diuretics, GI losses). No molecular prognostic biomarker beyond serum Mg^{2+}.

12. Treatment

- **Pharmacotherapy / supportive care:** Lifelong **oral magnesium supplementation** (e.g., magnesium oxide, magnesium chloride, magnesium aspartate; organic salts often better tolerated with less diarrhea). Doses are titrated to symptom control; complete

normalization of serum Mg^{2+} is often not achievable because supplementation drives further renal loss. Severe symptomatic episodes (seizures, tetany) require **IV magnesium sulfate**. By analogy to Gitelman management, **potassium-sparing diuretics (e.g., amiloride)** are a potential Mg^{2+}-retaining adjunct in some tubulopathies, though evidence specific to FXYD2 is limited (PMID: 32622651).

- **NCIT suggestion:** Magnesium supplement therapy; Magnesium Sulfate; dietary/electrolyte management.
- **Advanced/experimental therapeutics:** No gene therapy, RNA therapy, cell therapy, or targeted small molecule exists or is in trials for HOMG2.
- **Pharmacogenomics:** Not applicable.
- **Personalized approach:** Genotype confirmation (G41R) guides counseling and family screening; management remains supportive.

13. Prevention

- **Primary prevention:** Not possible (Mendelian). **Genetic counseling** for autosomal dominant 50% transmission risk; prenatal/preimplantation genetic testing is theoretically available given a known familial variant.
- **Secondary prevention:** Early biochemical screening (serum Mg^{2+}) in at-risk relatives; cascade testing.
- **Tertiary prevention:** Consistent Mg^{2+} supplementation to prevent seizures/tetany and reduce chondrocalcinosis risk; avoid magnesium-wasting drugs.
- **Immunization / public health / environmental interventions:** Not applicable.

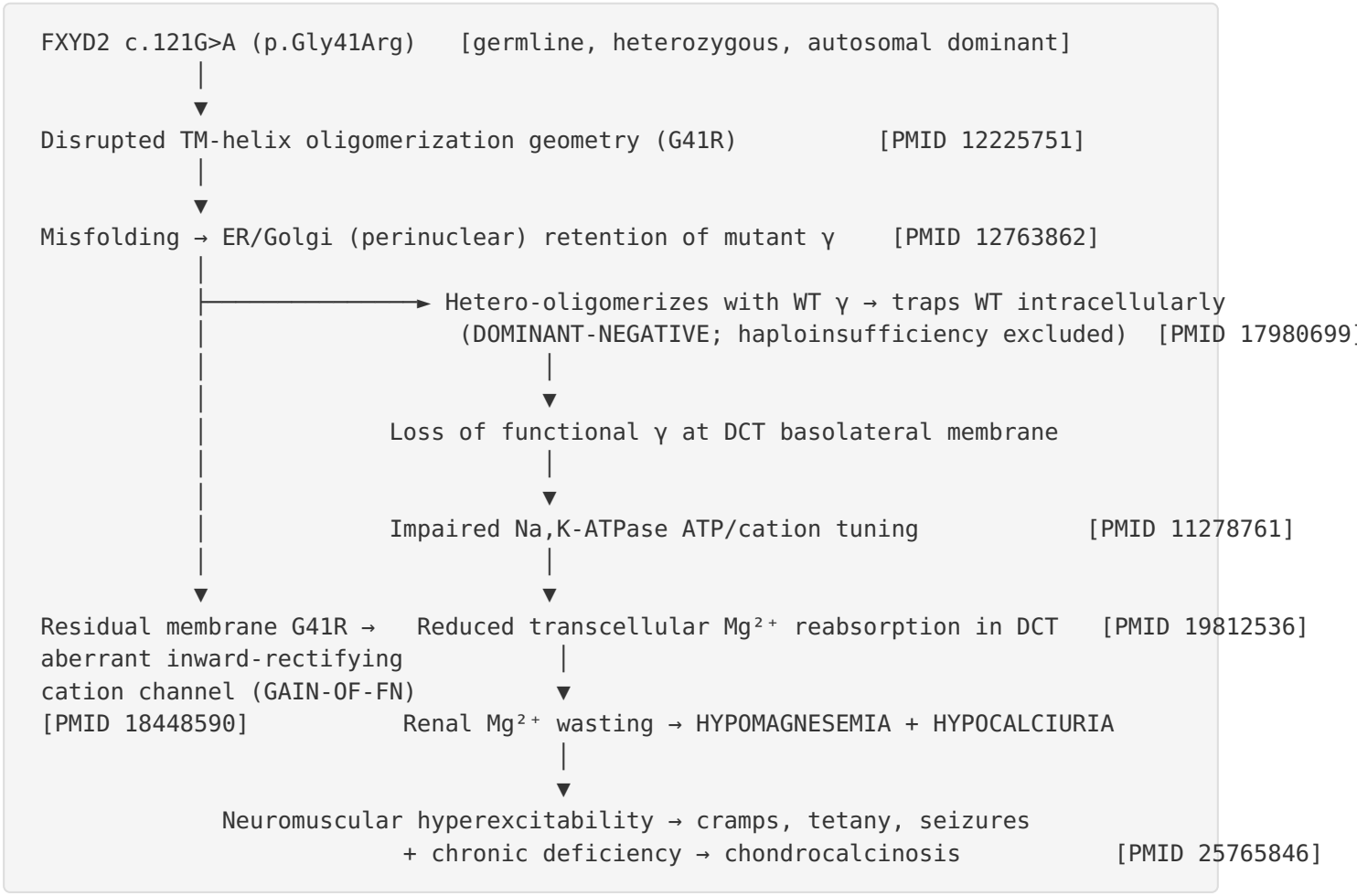
14. Other Species / Natural Disease

- **Orthologous gene:** *Fxyd2* is conserved in mouse (NCBI Gene 11936) and rat (NCBI Gene 29639); rat studies defined the γa/γb isoforms and their renal localization (PMID: 11278761).
- **Natural disease in other species:** No naturally occurring FXYD2 hypomagnesemia disease is documented in companion animals or wildlife (OMIA has no established entry for this phenotype).
- **Comparative biology:** The Na,K-ATPase and its FXYD regulators are deeply evolutionarily conserved; the DCT Mg^{2+}-handling mechanism is conserved across mammals, making rodents informative models of normal γ-subunit physiology.
- **Zoonotic potential:** Not applicable (non-infectious Mendelian disease).

15. Model Organisms

- **In vitro / heterologous systems (principal evidence):** Sf9 and COS-1 cells (mislocalization/misrouting; PMID: 12763862); co-immunoprecipitation systems for oligomerization (PMID: 17980699); synthetic transmembrane peptides with CD/FRET (PMID: 12225751); *Xenopus* oocytes and MDCK epithelial monolayers for electrophysiology (PMID: 18448590).
- **Mammalian models:** Rat kidney for γa/γb localization and function (PMID: 11278761). No dedicated G41R knock-in mouse recapitulating HOMG2 is reported in the reviewed literature — a notable gap.
- **Phenotype recapitulation:** Cellular/oocyte models faithfully reproduce the molecular lesions (misrouting, dominant-negative trapping, aberrant channel activity) but do not model the integrated renal/systemic phenotype. A conditional DCT *Fxyd2^G41R* knock-in would be the logical next step.

Mechanistic Model / Interpretation



The **dominant-negative misrouting branch is the principal driver** (quantitatively, most mutant protein never reaches the membrane and additionally sequesters wild-type protein), while the **gain-of-function channel branch** operates on the minority of protein that reaches the surface and may further perturb DCT ion handling. Both converge on the same clinical endpoint: a DCT unable to reclaim filtered magnesium.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
12763862	Misrouting of Na,K-ATPase γ-subunit	Human + in vitro	Establishes G41R as causal; misrouting; haploinsufficiency excluded
11062458	Dominant isolated renal Mg loss	Human	Original identification of dominant-negative FXYD2 mutation
25765846	Recurrent p.Gly41Arg	Human	Recurrence + founder effect; clinical features
17980699	Impaired routing after oligomerization	In vitro	Mechanism of dominant-negative trapping
12225751	TM-peptide oligomerization	Biophysical	G41R abrogates γ-TM oligomerization
18448590	G41R inward-rectifying channel	In vitro electrophysiology	Gain-of-function branch; basolateral Mg^{2+} extrusion
11278761	γa/γb function & localization	Model organism (rat)	Normal γ-subunit physiology
21130072	HNF-1B regulates γa	In vitro	Links FXYD2 to HNF1B hypomagnesemia pathway
11836293	Genetic heterogeneity	Human linkage	Demonstrates locus heterogeneity
19812536	DCT Mg^{2+} players (review)	Review	Places FXYD2 in DCT transport network
27234911	Genetic causes of hypomagnesemia	Review	Differential diagnosis context
25540137	Magnesium in health & disease	Review	Hypomagnesemia overview, acquired causes
32622651	Bartter-Gitelman syndromes	Review	Differential + supplementation strategy

Limitations and Knowledge Gaps

1. **Single-allele evidence base.** Virtually all genetic knowledge rests on one recurrent variant (G41R) in a small number of Dutch-founder families. The allelic spectrum of *FXYD2* in HOMG2 is essentially unexplored; it is unknown whether other *FXYD2* variants cause disease.
2. **No precise epidemiology.** Prevalence/incidence are unquantified; the condition is reported only as case/family series.
3. **No in vivo disease model.** There is no published G41R knock-in mouse recapitulating the renal phenotype, limiting study of integrated pathophysiology and therapeutics.
4. **Relative weight of the two mechanisms** (dominant-negative vs gain-of-function) at the whole-organ level is not quantified.
5. **Hypocalciuria mechanism** in FXYD2 disease is described but not mechanistically dissected at the DCT level.
6. **Penetrance/expressivity** data are limited to small families; genotype–phenotype correlation beyond G41R is nonexistent.
7. **No QoL or natural-history cohort** data; long-term outcomes inferred rather than measured.

Proposed Follow-up Experiments / Actions

1. **Generate a DCT-targeted *Fxyd2^G41R* knock-in mouse** to test in vivo recapitulation of renal Mg^{2+} wasting, hypocalciuria, and neuromuscular phenotype, and to dissect dominant-negative vs channel contributions (e.g., compare to a membrane-trafficking-rescued allele).
2. **Resequence *FXYD2*** in unexplained isolated renal Mg-wasting cohorts (and query gnomAD/large biobanks) to define the full allelic spectrum and whether non-G41R pathogenic variants exist.
3. **Quantitative trafficking/electrophysiology** in polarized DCT-like cells (e.g., mpkDCT) to measure the fraction of G41R reaching the membrane and the magnitude of aberrant cation current under physiological gradients.

4. **Therapeutic screen for trafficking correctors** (pharmacological chaperones) that could rescue wild-type γ-subunit routing from mutant trapping — a mechanism-based treatment beyond symptomatic Mg^{2+} repletion.
5. **Natural-history / registry study** across known families to quantify penetrance, chondrocalcinosis/seizure risk, and QoL, informing supplementation guidelines.
6. **Test amiloride/potassium-sparing diuretics** prospectively as Mg^{2+}-retaining adjuncts in FXYD2 disease, by analogy to Gitelman management.

Report compiled from 6 confirmed findings across 19 reviewed papers (5 investigation iterations). Evidence types: human clinical/genetic, in vitro/heterologous expression, biophysical peptide studies, and rodent model-organism physiology.
