Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

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Disclosures

- Nothing to declare

Introduction: Mg 2^+

2nd most abundant intracellular cation	4th most abundant cation overall
essential metabolic modulator: cofactor >600 enzymes (ATP)	enhances resistance of DNA and RNA against oxidative stress
participates at cell cycle control and cell proliferation process	crucial for nerve conduction and cardiac contractility

Symptoms of hypomagnesemia (Mg <1.7 mg/dL; < 0.70 mM)

- muscle cramps, paresthesias
- hyperreflexia (Chvostek and Trousseau's signs)
- seizures
- ataxia
- depression, fatigue, coma
- arrhythmia (prolonged QT Interval)
- hypertension
- chondrocalcinosis
- failure to thrive (in children)
- basal ganglia calcifications
- intellectual disability
- coma, death

Mg balance

Diet (360 mg)
chocolate, cocoa
nuts, peanuts, green vegetables

120 mg

Intestine

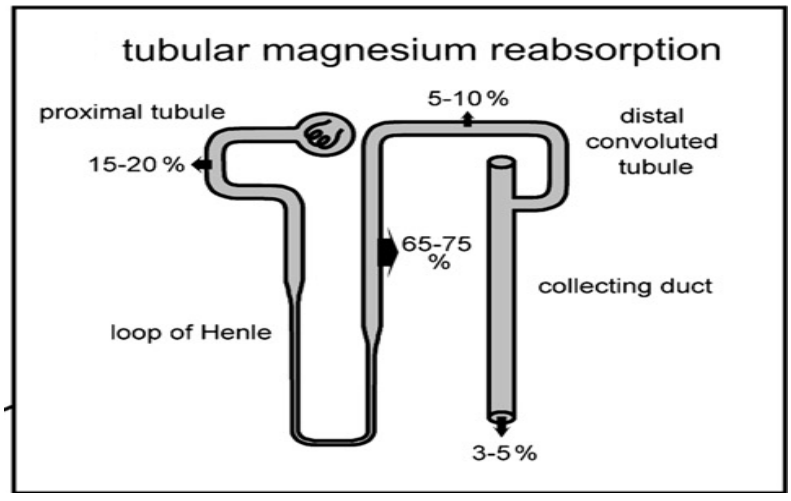
20 mg

Blood (1%)
1.8-2.3 mg/dL
0.70-1.1 mM

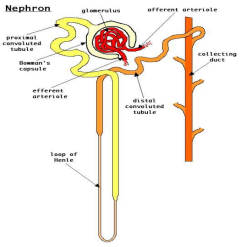
Kidney
(100 mg)

Muscle
(39%)

Bone
(60%)



The kidney regulates Mg body balance by variation of Mg excretion in urine
~0.5% of total filtered Mg in the presence of hypomagnesemia
≤80% of total filtered Mg in the presence of hypermagnesemia

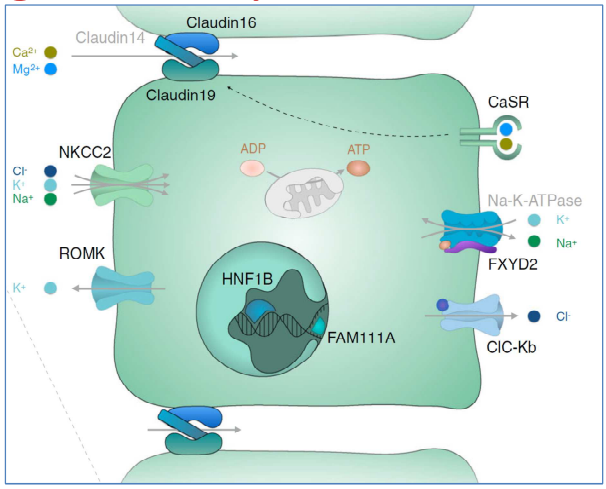


Mg reabsorption at the TAL

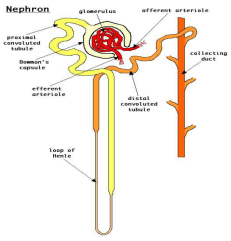
PRO-URINE

BLOOD

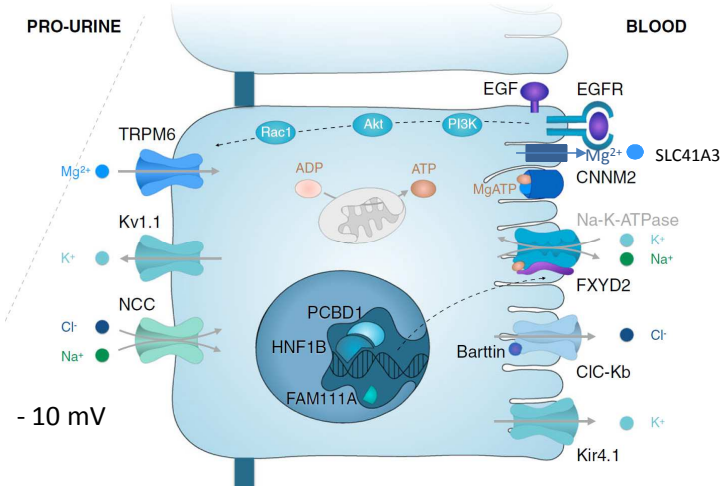
+ 8 mV



Modified from Viering DHHH et al. Pediatr Nephrol, 2017; 32: 1123-1135



Mg reabsorption at the DCT



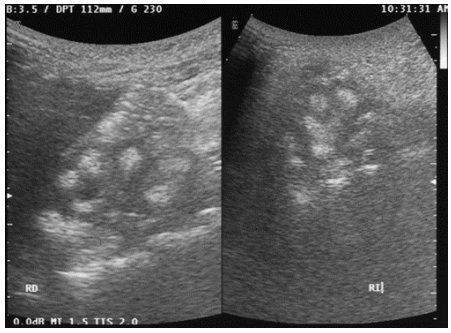
Modified from Viering DHHH et al. Pediatr Nephrol, 2017; 32: 1123-1135; Baaij JHF et al. Sci Rep. 2016; 6: 28565.

Familial Hypomagnesemia with hypercalciuria & nephrocalcinosis (FHHNC)

FHHNC was described by Michelis-Castrillo et al in 1972
Autosomal recessive. Age of diagnosis: 5-25 y

- Polyuria, polydipsia
- UTI
- Hyperuricemia
- Hypomagnesemia
- Severe hypermagnesiuria
- Severe hypercalciuria
- Bilateral nephrocalcinosis
- Kidney stones
- Low citrate in urine
- Incomplete DRTA
- Hyperparathyroidism
- CKD

Renal phenotype

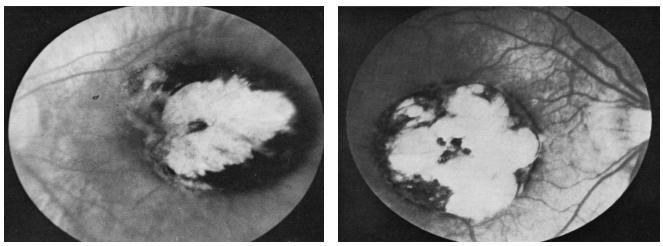


42% family members with kidney stones and hypercalciuria

Familial Hypomagnesemia with hypercalciuria & nephrocalcinosis (FHHNC)

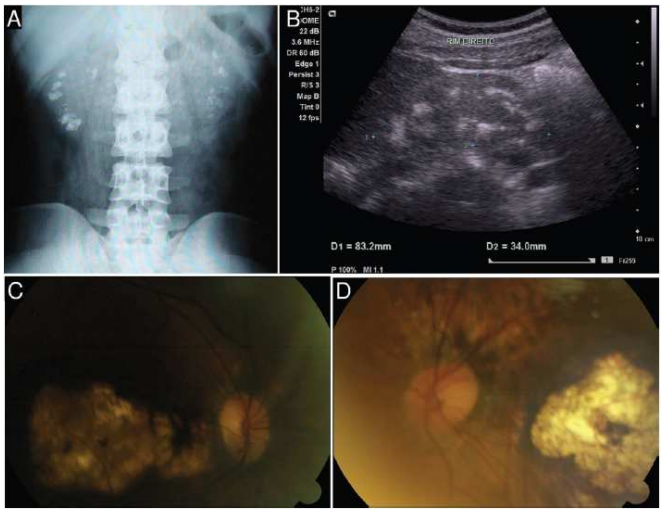
± Ocular phenotype

- Reduced visual ability
- Macular Colobomata
- Retinopathy
- Nystagmus
- Severe Myopia

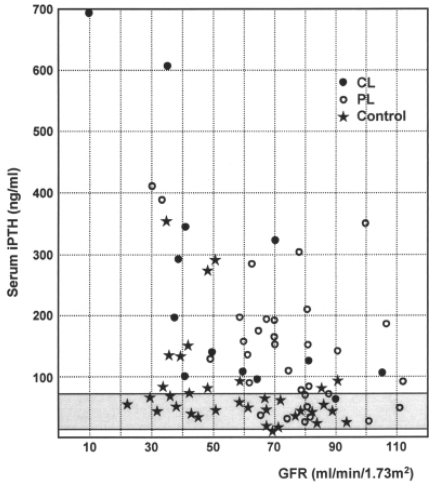


Maier et al. (1979) *Helv Paediatr Acta* 34

Patients with FHHNC and advanced CKD may not present with hypomagnesemia . PTH increases even before the onset of CKD



Haisch L et al. JASN, 2011

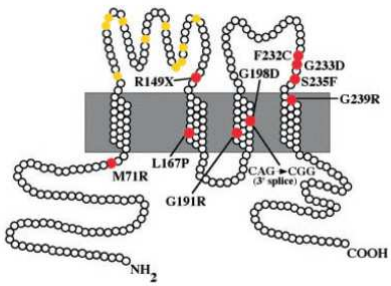


Konrad et al. JASN, 2008

Paracellin-1, a Renal Tight Junction Protein Required for Paracellular Mg^{2+} Resorption

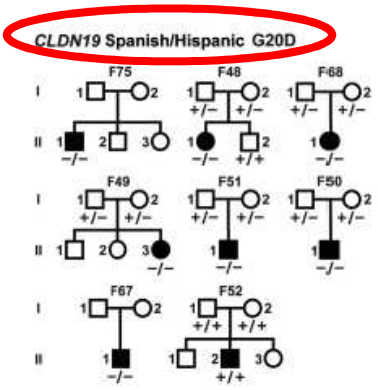
David B. Simon,[1,2]* Yin Lu,[1,2]* Keith A. Choate,[1,2] Heino Velazquez,[2] Essam Al-Sabban,[3] Manuel Praga,[4] Giorgio Casari,[5] Alberto Bettinelli,[6] Giacomo Colussi,[7] Juan Rodriguez-Soriano,[8] David McCredie,[9] David Milford,[10] Sami Sanjad,[11] Richard P. Lifton[1,2]†

www.sciencemag.org SCIENCE VOL 285 2 JULY 1999



Mutations in the Tight-Junction Gene Claudin 19 (*CLDN19*) Are Associated with Renal Magnesium Wasting, Renal Failure, and Severe Ocular Involvement

Martin Konrad, André Schaller, Dominik Seelow, Amit V. Pandey, Siegfried Waldegger, Annegret Lesslauer, Helga Vitzthum, Yoshiro Suzuki, John M. Luk, Christian Becker, Karl P. Schlingmann, Marcel Schmid, Juan Rodriguez-Soriano, Gema Ariceta, Francisco Cano, Ricardo Enriquez, Harald Jüppner, Sevcan A. Bakkaloglu, Matthias A. Hediger, Sabina Gallati, Stephan C. F. Neuhauss, Peter Nürnberg, and Stefanie Weber *Am. J. Hum. Genet.* 2006;79:949–957.

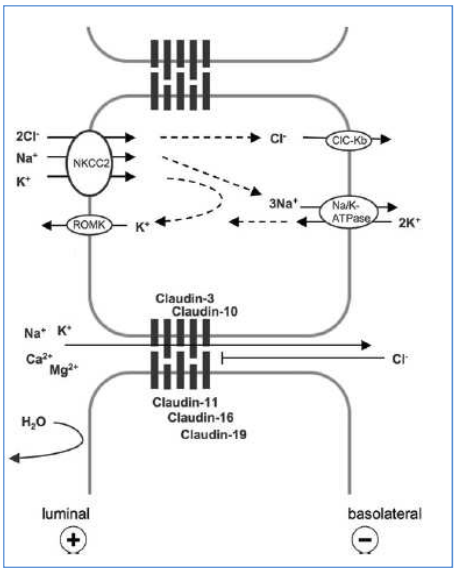


CLDN19 Spanish mutation p.G20D (c.59G>A)

	gene	chromosome	protein
FHHNC 1	*CLDN16*	3q27-29	Paracellin-1 (Claudin-16)
FHHNC 2	*CLDN19*	1p34.2	Claudin-19

Simon DB et al. Science, 1999; 285: 103-6
Konrad M et al. Am J Hum Genet, 2006; 79:949-957

Claudin-16 / Claudin- 19 complex



Claudin-16 increases paracellular permeability to Na^+ while Claudin-19 decreases paracellular permeability to Cl^-, leading to a lumen-positive voltage to drive Ca2+ and Mg2+ reabsorption

Hou J et al. J Clin Invest, 2008; Haisch L et al. JASN, 2011.

Treatment of FHHNC: supportive

Oral Mg supplements:

Aim: to avoid symptoms of hypomagnesemia, but Mg2+ persists low

Thiazides: to reduce hypercalciuria

Citrate (caution with serum K^+)

Avoid acquired renal damage (dehydration, drugs,…)

Kidney transplant cures FHHNC

Disease carriers can be donors

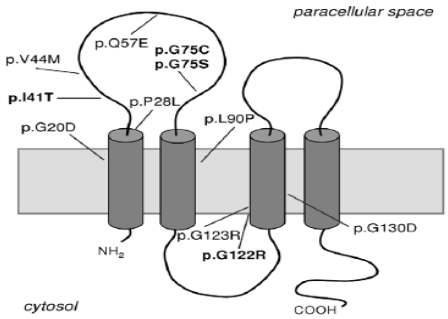
OPEN ACCESS Freely available online

PLOS ONE

Claudin-19 Mutations and Clinical Phenotype in Spanish Patients with Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

Félix Claverie-Martín[1*], Víctor García-Nieto[2], Cesar Loris[3], Gema Ariceta[4], Inmaculada Nadal[5], Laura Espinosa[6], Ángeles Fernández-Maseda[7], Montserrat Antón-Gamero[8], África Avila[9], Álvaro Madrid[10], Hilaria González-Acosta[1], Elizabeth Córdoba-Lanus[1], Fernando Santos[11], Marta Gil-Calvo[12], Mar Espino[13], Elena García-Martinez[8], Ana Sanchez[14], Rafael Mulev[15], for the RenalTube Group

PLoS ONE 8(1): e53151. doi:10.1371/journal.pone.0053151



31 patients (27 families)

87% ocular involvement

22% Kidney transplant

61% CKD

100% *CLDN19* mutations

23/31 homozygous pG20D

2/31 heterozygous pG20D

Outcome and genotype in FHHNC (Spanish contemporary series, n = 30)

Age at diagnosis 3.7±4.7 y.

At 4 y. 5/30 (17%) ESKD

Overall, 10/30 (33%) ESKD (9 KT)

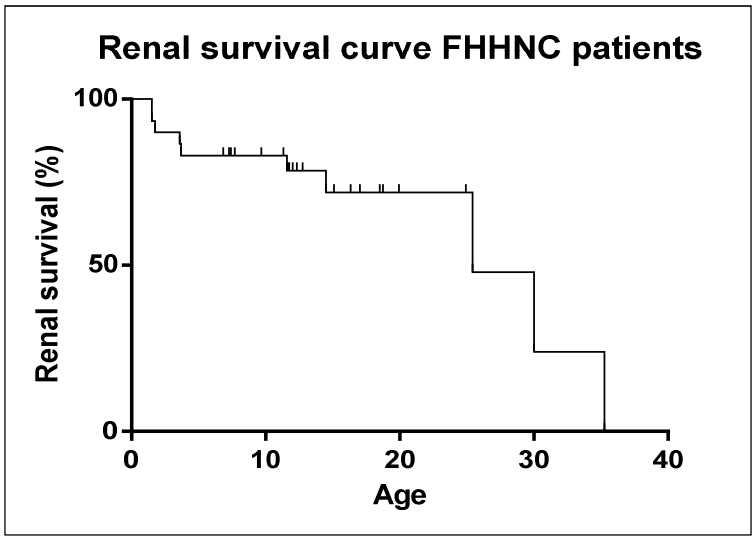
Renal survival *md* 25.4 years

63% CKD 4-18 y.
30% CKD >18y.

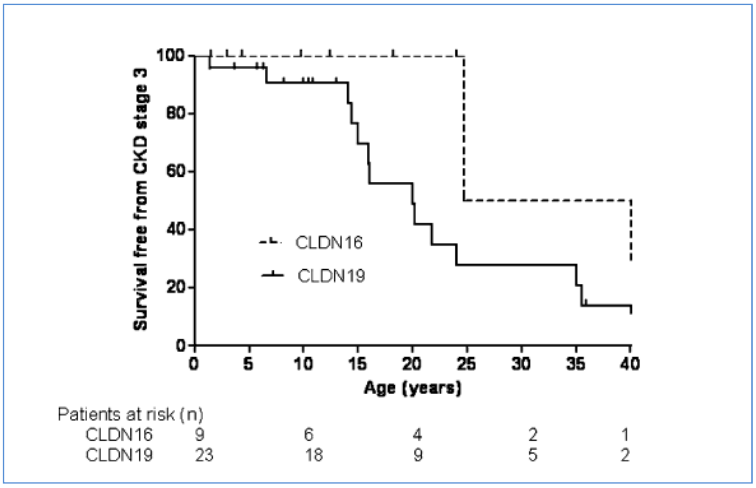
More severe phenotype in females:

(80% females in the subgroup with ESKD vs. 40% females in the subgroup not requiring renal replacing therapy)

73% with ocular involvement



Outcome and genotype in FHHNC (French series)

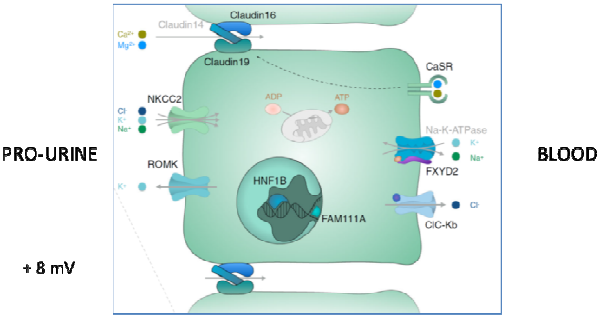


Godron et al. cJASN, 2012; 7: 81-909

Differential diagnosis of FHHNC

Hypercalciuric hypomagnesemias

- **Autosomal dominant hypocalcemia (ADH)** hypocalcemia, hypercalciuria, kidney stones, normal/inappropriately low PTH; hypomagnesemia (50%) . It is caused by gain-of-function mutations in the CaSR
- **Bartter Syndrome type 5** (CaSR)
- **Bartter Syndrome** (by disturbing the lumen-positive potential)



Non-hypercalciuric hypomagnesemia

TAL

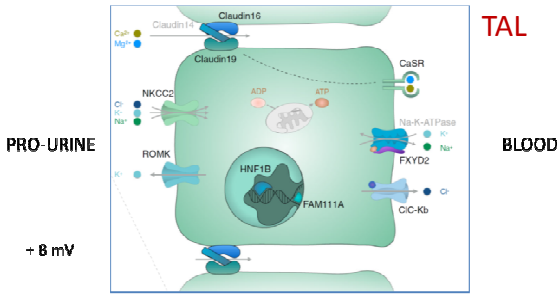
- **Bartter Syndrome (type 3, type 4)** mutations in *CLCNKB* and *BSND* (interferes the generation lumen-positive potential)

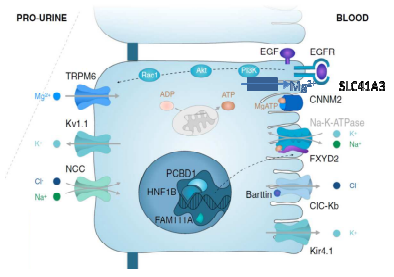
DCT

- **Gitelman Syndrome** mutations in *SLC12A3* (NCC)
- **Isolated dominant hypomagnesemia** mutations in *FXYD2* (γ subunit of the Na+/K+-ATPase) and *KCNA1* (Kv1.1)
- **EAST Syndrome** mutations in *Kir4.1*
- **Isolated recessive hypomagnesemia** mutations in *EGF* gene

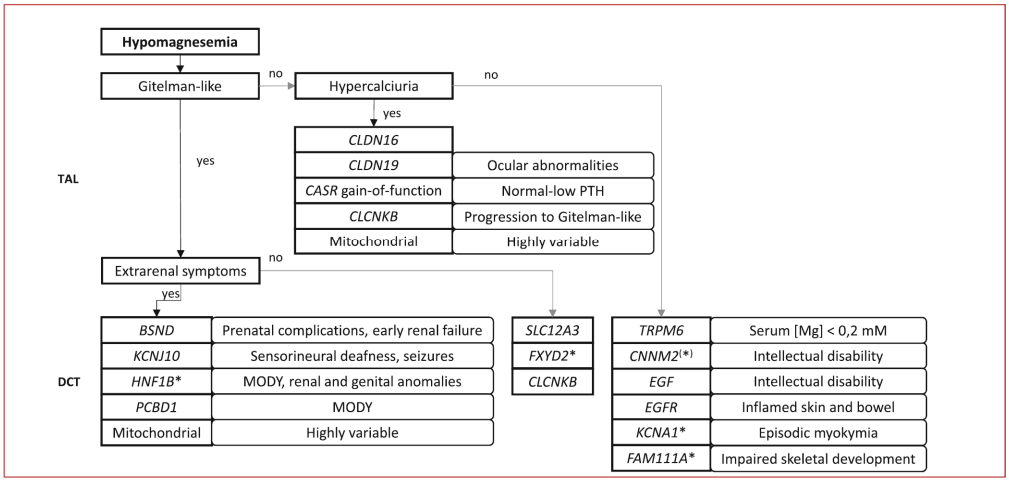
Other

HNF1B nephropathy
Mitochondrial diseases
Other causes





Diagnostic flowchart for a suspected genetic cause of hypomagnesemia



Viering DHHH et al. Pediatr Nephrol, 2017; 32: 1123-1135

Frequent causes of hypomagnesemia

Drug	Mechanism
Proton pump inhibitors (omeprazole)	Reduced TRPM6 expression
Diuretics (furosemide, thiazides)	Effect on NKCC2, NCC
Cisplatin	Reduced TRPM6 expression
Immunosuppresants (CsA, tacrolimus)	Reduced TRPM6 expression
Anti-EGF receptors (cetuximab, panitumumab)	Reduced TRPM6 expression
Antimicrobials	Induced Fanconi Syndrome

Blanchard A et al, Kidney Int, 2017; 91:24-33

Thank you for your attention

Next Webinar June 12th

Dr. Roser Torra

Renal involvement in Tuberous Sclerosis Complex