ERKNet
The European
Rare Kidney Disease
Reference Network

european
society for
paediatric
nephrology

WELCOME TO

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 19 October 2021

Topic: Claudin Related Disorders

Speaker: Gema Ariceta (Barcelona, Spain)

Moderator: Elena Levtchenko (Leuven, Belgium)

ERKNet
The European
Rare Kidney Disease
Reference Network

Claudin-related Disorders

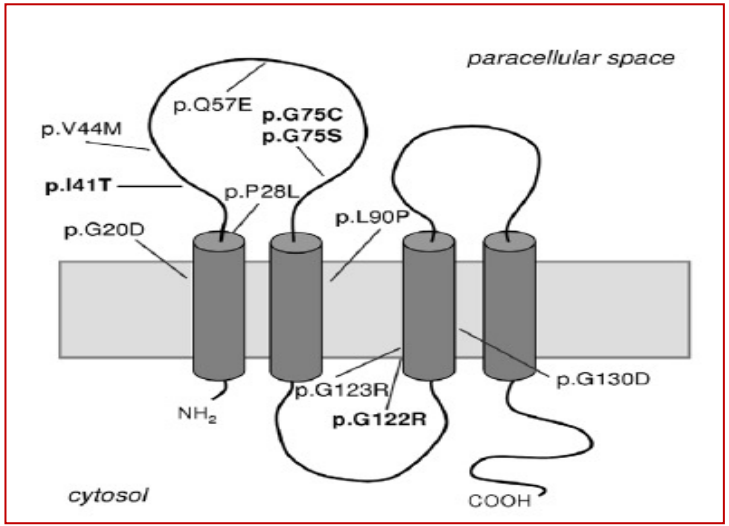
Gema Ariceta
Pediatric Nephrology,
University Hospital Vall d‘ Hebron
Barcelona, Spain

Disclosures

- Nothing to declare

Introduction

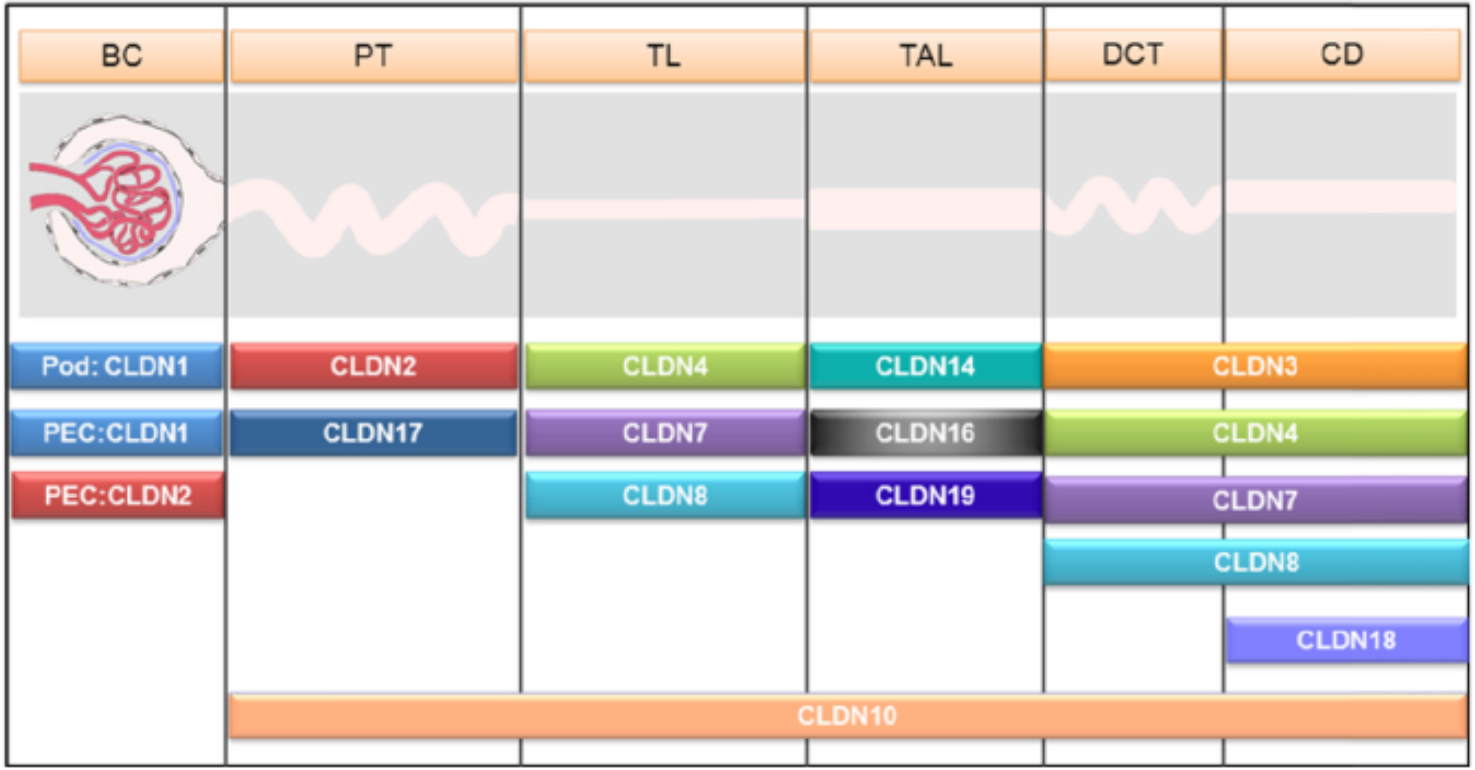
- **Tubular paracellular transport is tightly regulated and can be highly specific to each nephron segment**
- The permeability characteristics of the paracellular junction to various solutes are determined by claudins. **Claudins** are key integral proteins expressed at the **tight junctions** of epithelial and endothelial cells.
- Interactions between claudins with themselves and other claudin family members, within the same plasma membrane (cis) or with the adjacent epithelial cell (trans), create **pores** or **barriers** to ions and other small molecules.



Structure of CLDN19 and locations of different mutations observed in Spain.

Yu ASL. JASN 2015; Claverie-Martin F et al. Plos One, 2013; Prot-Bertoye C, Houillier P. Genes 2021

Expression profile of claudin genes along the nephron of the kidney



Gong Y, Hou J. Pflugers Arch. 2017

Physiologic role of claudins in the mammalian renal tubule

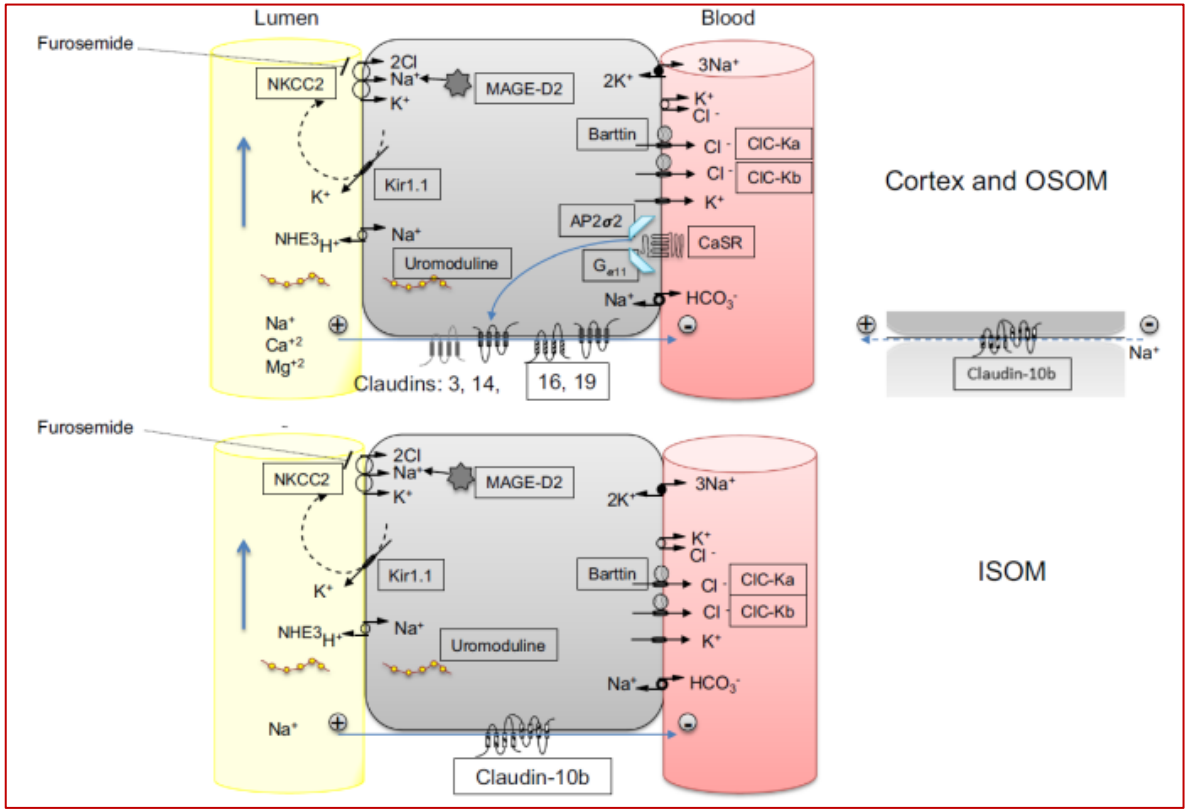
Claudin	Tubule Localization	Permeability Properties[a]	Physiologic Role[a]
2	PT, tDL[18,43]	Na^+, K^+, Ca^{2+}, and H_2O[25,26,29,44] pore	PT Na^+ and fluid reabsorption[46,62]
3	tAL, TALH, DCT, CD[18]	Nonselective barrier[107]	Unknown
4	tAL, CD[18]	Na^+ barrier and Cl^- pore[45,87,108]	Facilitates aldosterone-sensitive distal electrogenic Na^+ reabsorption?[96]
7	tDL, DCT, CD[85,109]	Cl^- barrier[85,110] or Cl^- pore?[45]	Renal salt reabsorption[86]
8	tDL, DCT, CD[18,109]	Na^+, K^+, and H^+ barrier[88,89] and Cl pore[108]	Facilitates distal electrogenic Na^+ reabsorption?
10a	PT, TALH, CCD[27,63]	Cl^- pore[63]	PT Cl^- reabsorption?
10b	TALH, MCD[27,63]	Na^{2+} pore[63]	Increases Na^+ permeability
14	TALH[81]	Na^+ [81] or Na^+ and Ca^{2+} barrier[82]	Mediates CaSR inhibition of TALH Ca^{2+} and Mg^{2+} reabsorption[81–83]
16	tAL, TALH[70,111]	Na^+ [112] or Ca^{2+} and Mg^{2+} pore[74,75,113]	TALH reabsorption of divalent cations[72,76]
17	PT > tAL, TALH, DCT[64]	Cl^- pore[64]	PT Cl^- reabsorption?
18	TALH, CD[73]	Na^+ and H^+ barrier[114]	Unknown
19	tAL, TALH[71,111]	Cl^- barrier[77]	TALH reabsorption of divalent cations[73]

PT, proximal tubule; tDL, thin descending limb; tAL, thin ascending limb; DCT, distal convoluted tubule; CD, collecting duct; CCD, cortical collecting duct; MCD, medullary collecting duct.

[a]Question marks indicate speculative conclusions that have not been studied experimentally or for which multiple studies came to different conclusions.

Modified from Yu ASL. JASN 2015

TAL



Vargas Poussou R. Pediatr Nephrol 2021

Claudins and kidney disease

3 claudins (10b, 16 and 19) have been recognized as cause of rare autosomal recessive human syndroms:

CLDN10b	CLDN16 CLDN19	CLDN14
• HELIX Syndrome	• FHHNC 1 • FHHNC 2	• hypercalciuria • kidney stones

Prot-Bertoye C, Houillier P. Genes 2021

Claudin 10b & Helix syndrome

The human *CLDN10* gene is located on chromosome 13q32 and contains five exons. There are two claudin 10 splice variants that encode two main claudin 10 isoforms: claudin 10a and claudin 10b

The specific effect of claudin 10b is to increase the paracellular permeability to Na^+.

Helix syndrome (OMIM # 617671) is a rare AR salt-losing tubulopathy, described in 2017, caused by *CLDN10b* loss-of-function mutations, that lead to lower paracellular Na^+ permeability in the TAL, sweat glands and salivary glands

HELIX syndrome phenotype

Hypohidrosis	100%
Electrolyte imbalance	94%
Hypolacrimia	100%
Ichthyosis	86%
Xerostomia	100%
Hypokalemia	38%
Hypermagnesemia	88%
eGFR <60	25%
Nephrolithiasis	18%
Hyperaldosteronism without hyperreninism	some patients

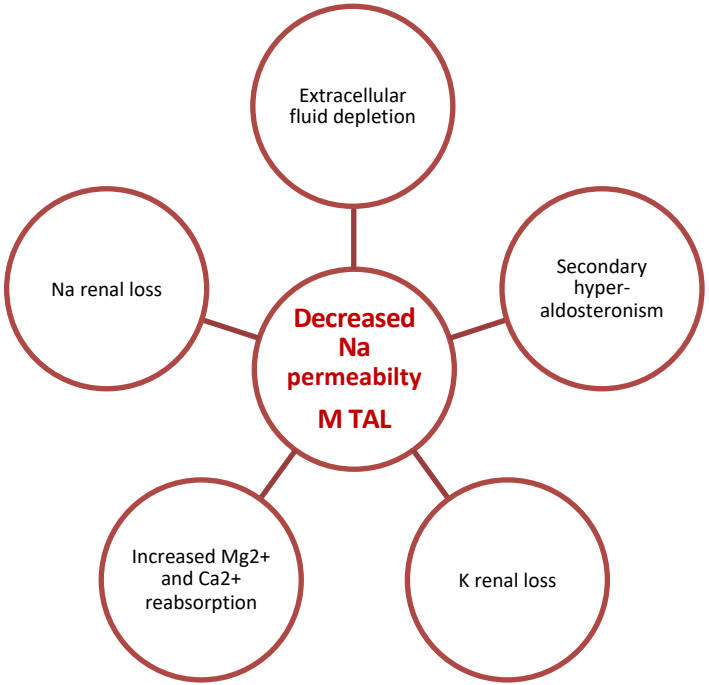
Modified from Prot-Bertoye C, Houillier P. Genes 2021
Vargas-Poussou R. Pediatr Nephrol 2021

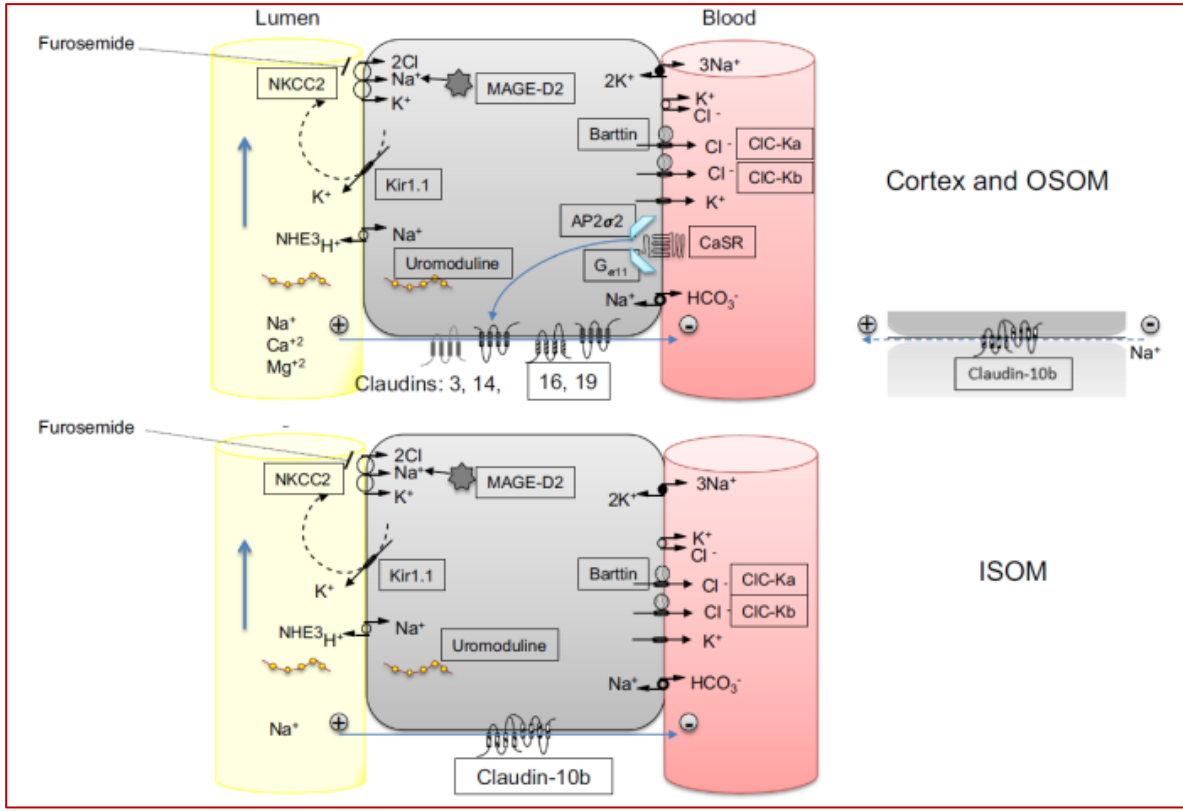
HELIX syndrome

H	**H**ypohidrosis
E	**E**lectrolyte imbalance
L	hypo**L**acrimia
I	**I**chthyosis
X	**X**erostomia

Modified from Prot-Bertoye C, Houillier P. Genes 2021

HELIX syndrome pathogenesis at the TAL





Prot-Bertoye C, Houillier P. Genes 2021

Vargas Poussou R. Pediatr Nephrol 2021

QUESTION

What of the following manifestations is not characteristic of Helix syndrome?

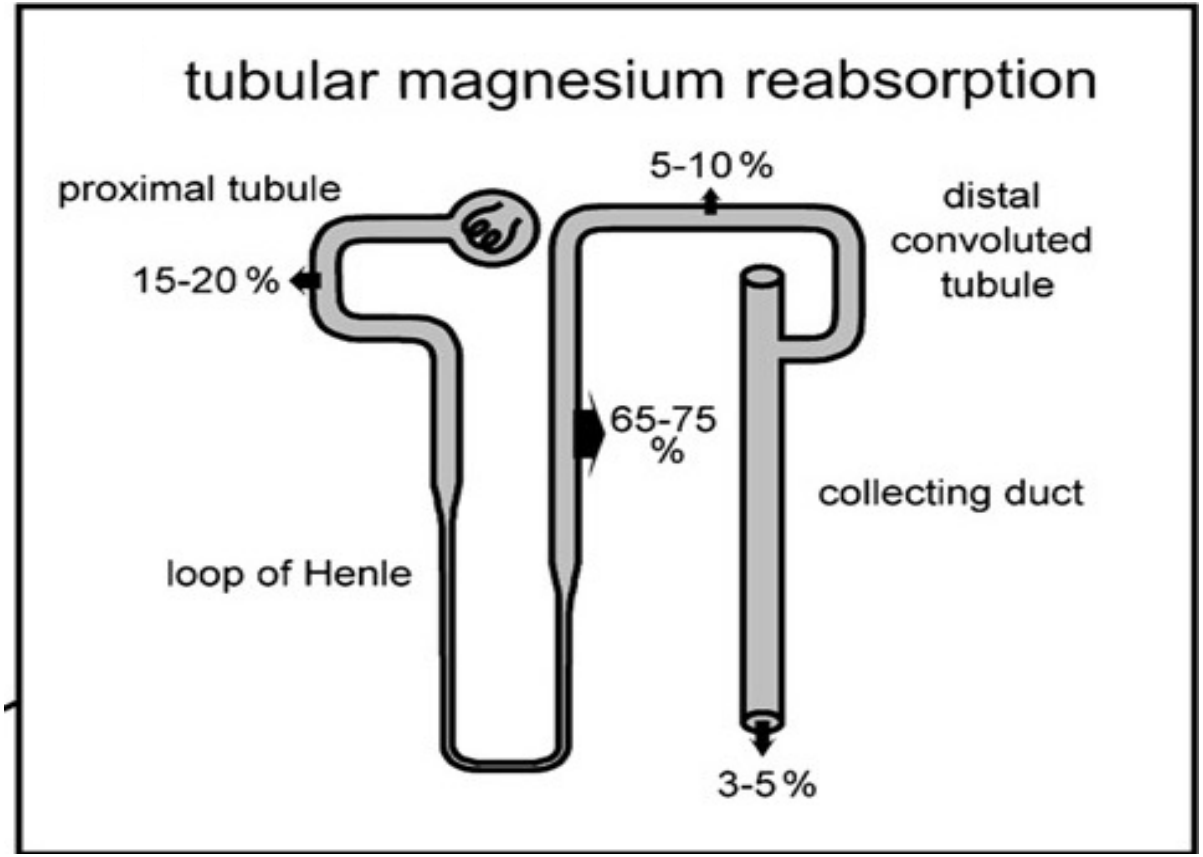
1. Hypohidrosis
2. Hypolacrimia
3. Hyperkalemia
4. Hypermagnesemia
5. All above

ANSWER

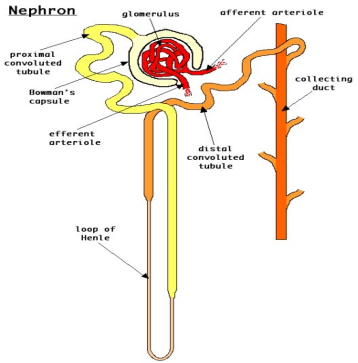
What of the following manifestations is not characteristic of Helix syndrome?

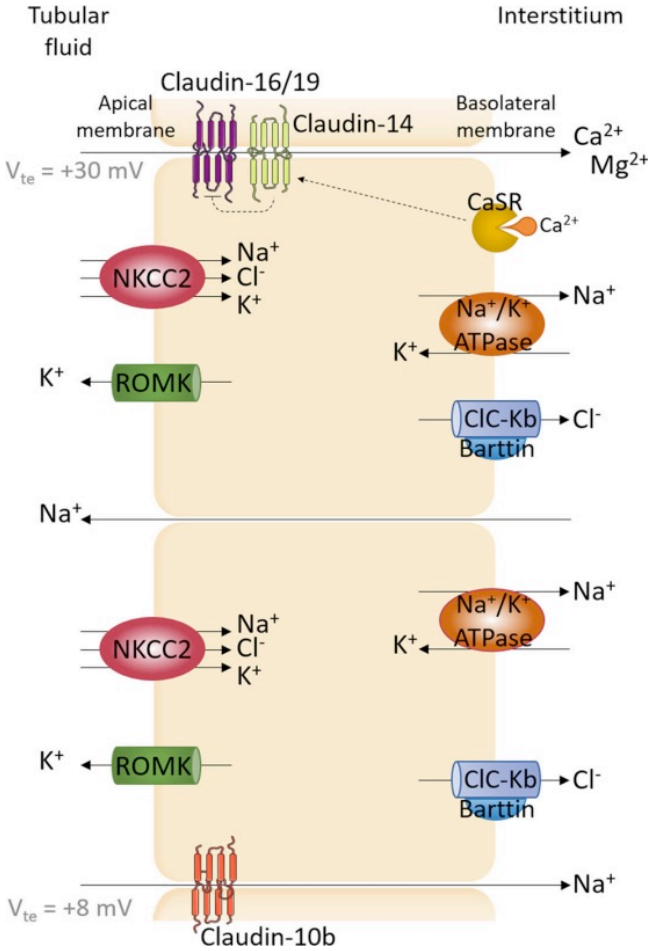
1. Hypohidrosis
2. Hypolacrimia
3. Hyperkalemia
4. Hypermagnesemia
5. All above

Patients present with hypokalemia due secondary hyperaldosteronism caused by salt wasting and extracelular fluid depletion


tubular magnesium reabsorption
proximal tubule
5-10 %
distal convoluted tubule
15-20 %
65-75 %
collecting duct
loop of Henle
3-5 %

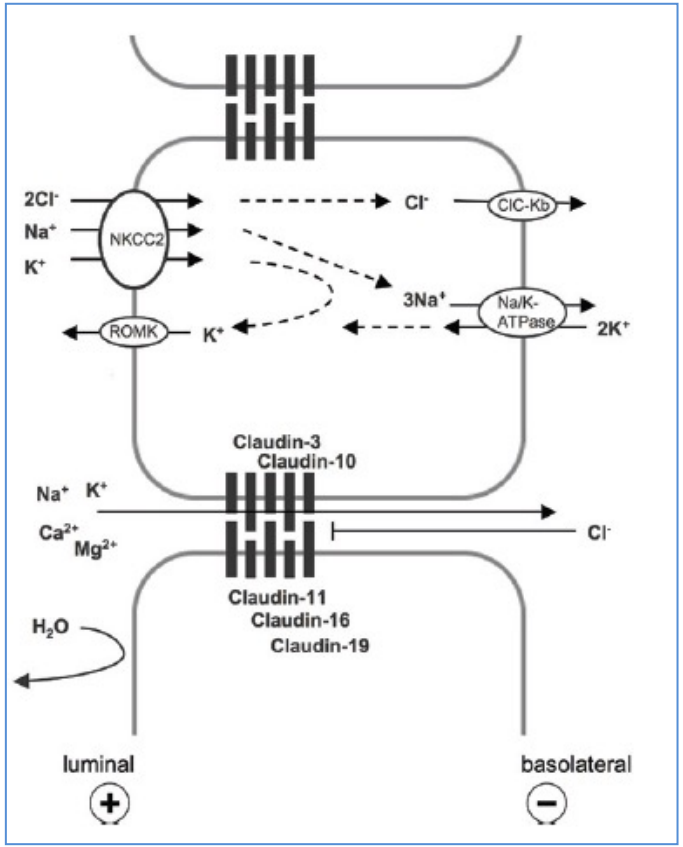
Ca2+ and Mg2+ reabsorption at the TAL





Vall-Palomar M et al. Pediatr Nephrol, 2021

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.

Familial Hypomagnesemia with hypercalciuria & nephrocalcinosis (FHHNC)

It is a rare autosomal recessive , with an incidence of <1/1.000,000, described by Michelis-Castrillo et al in 1972. It is characterized by severe urinary Mg wasting, associated with hypercalciuria and progression to CKD

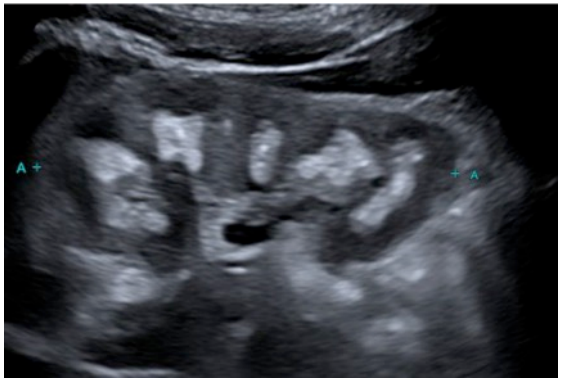
- Polyuria, polydipsia
- UTI
- Hyperuricemia
- Hypomagnesemia
- Severe hypermagnesiuria
- Severe hypercalciuria
- Bilateral nephrocalcinosis
- Kidney stones
- Low citrate in urine
- Incomplete DRTA
- Hyperparathyroidism
- CKD

- High fractional urinary excretion of Mg

is found while Mg serum level is inappropriately low.

- Hypomagnesemia may be overlooked in patients with advanced CKD.

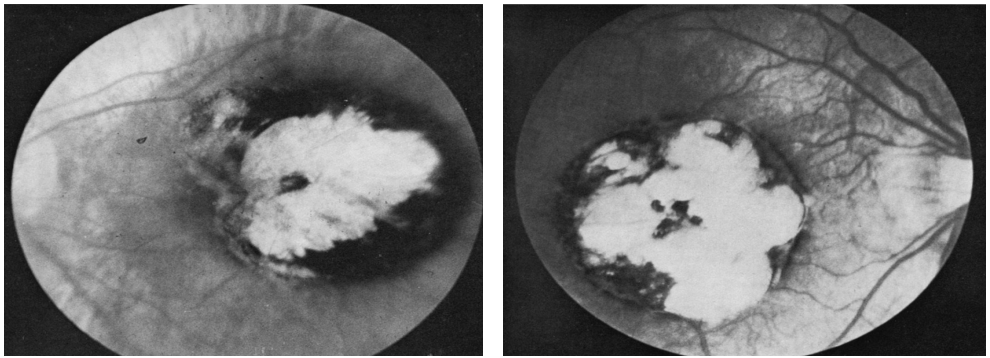
nephrocalcinosis



Familial Hypomagnesemia with hypercalciuria & nephrocalcinosis (FHHNC)

± Ocular phenotype

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

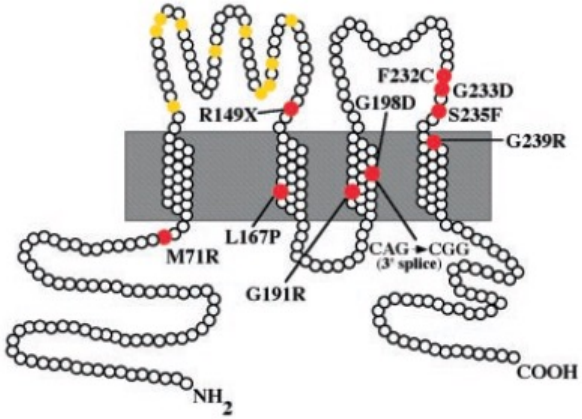


Maier et al. (1979) *Helv Paediatr Acta* 34

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

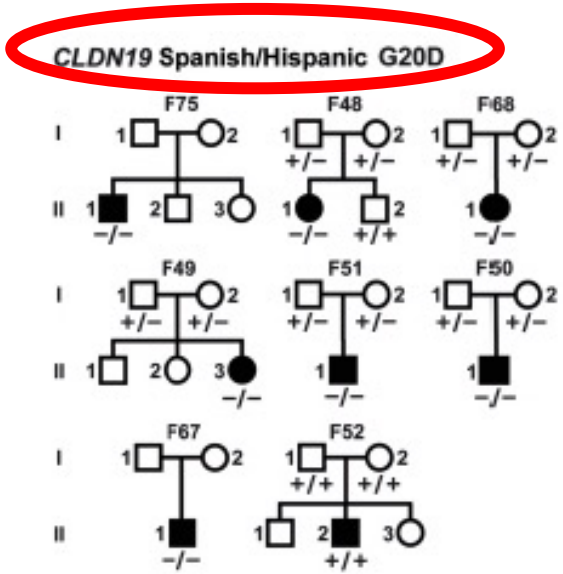
David B. Simon,[1,2*] Yin Lu,[1,2*] Keith A. Choate,[1,2] Heino Velazquez,[2] Essam Al-Sabban,[3] Manuel Praga,[4] Giorgio Casari,[5] Alberto Bettinelli,[6] Giacomo Colussi,[7] Juan Rodriguez-Soriano,[8] David McCredie,[9] David Milford,[10] Sami Sanjad,[11] Richard P. Lifton[1,2†]

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

FHHNC: clinical manifestations

Clinical symptoms	Laboratory findings	Radiological findings	Extrarenal manifestations
Polyuria/Polydipsia	Hypomagnesemia	Medullary nephrocalcinosis	Horizontal nystagmus
Feeding difficulties	Hypercalciuria	Nephrolithiasis	Myopia magna**
Vomits	Hypermagnesiuria	Renal cysts	Macular colobomata**
Failure to thrive	Hyperuricemia	Bilateral slipped capital femoral epiphysis	Macular degeneration**
Abdominal pain	Elevated serum creatinine		Pigmentary retinitis**
Enuresis	Hyperparathyroidism		Macular scar**
UTI	Metabolic acidosis		Strabismus**
Rickets	Sterile leukocyturia		Astigmatism**
Cramps	Hypocitraturia		Amelogenesis imperfecta
Tremors			Chondrocalcinosis
Gait instability			
Seizures			

*** in patients with CLDN19 mutations*

Vall-Palomar M et al. Pediatr Nephrol, 2021

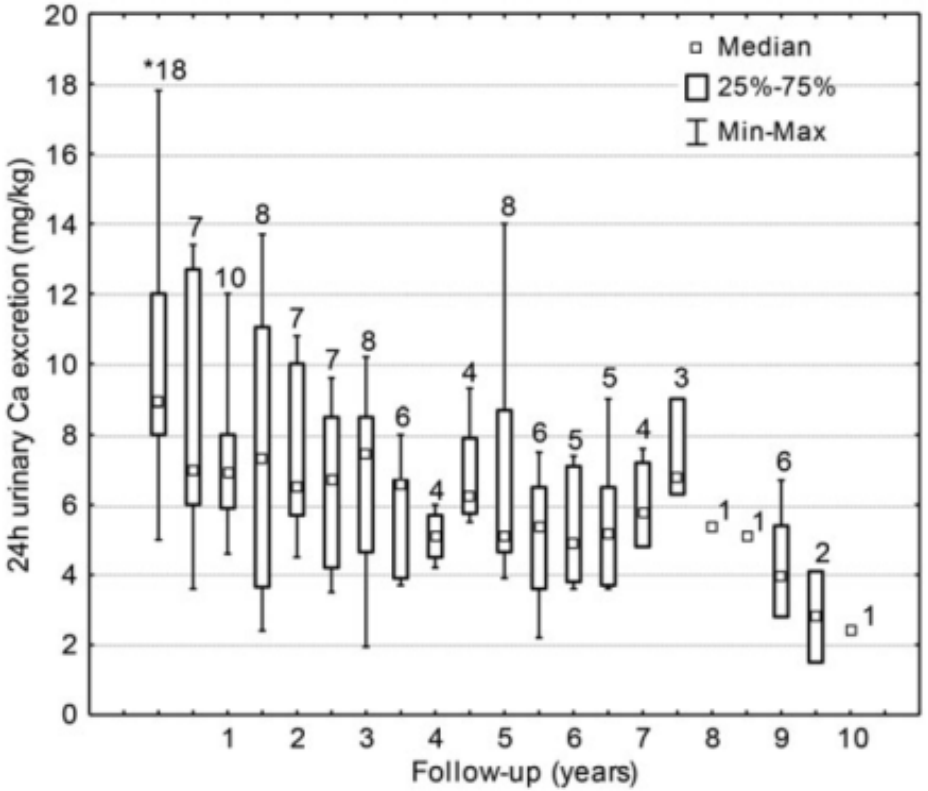
Urinary and plasmatic values of Ca y Mg in FHHNC

Parameter	Described in patients with FHHNC	Normal values
Serum Mg	0.6 ± 0.3 mmol/L 1.1 ± 0.2 mg/dL	0.70–1.1 mmol/L 1.8–2.3 mg/dL
Urinary Mg	FEMg 6-26% UMg/Cr 0.8–1.2 mmol/mmol UMg/Cr 0.17–0.26 mg/mg	FEMg < 4% UMg/Cr 0.89–1.07 mmol/mmol UMg/Cr 0.19–0.23 mg/mg
Urinary Ca	VCa 0.25 ± 0.15 mmol/kg/day VCa 10 ± 6 mg/kg/day UCa/Cr 0.5–2.5 mmol/mmol UCa/Cr 0.18–0.88 mg/mg	VCa < 0.1 mmol/kg/day VCa < 4 mg/kg/day UCa/Cr < 1.4 mmol/mmol UCa/Cr < 0.5 mg/mg

FEMg fractional excretion of Mg, *UMg/Cr* urinary Mg/creatine, *VCa* urinary Ca excretion in 24 h, *UCa/Cr* urinary Ca/creatinine

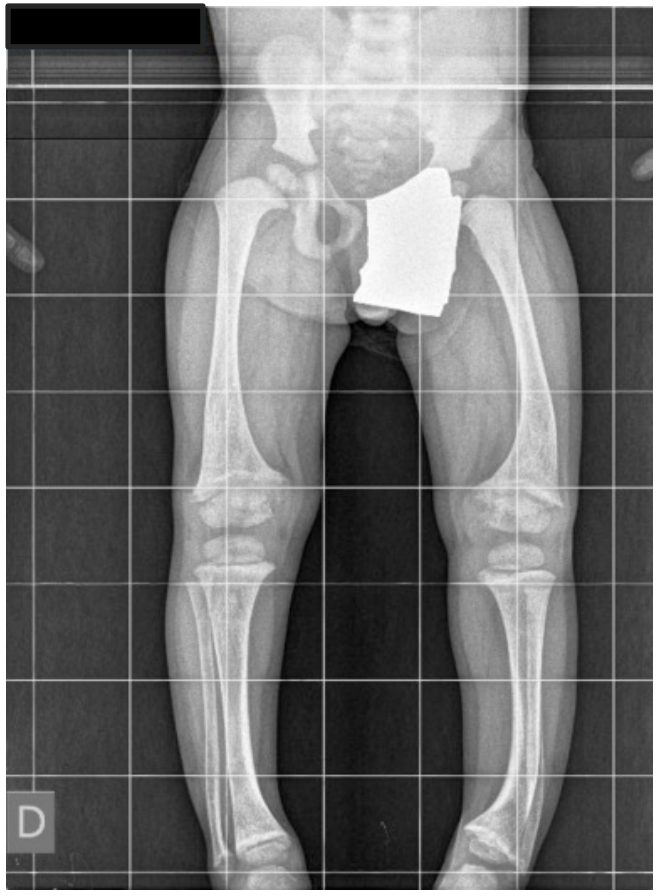
Vall-Palomar M et al. Pediatr Nephrol, 2021

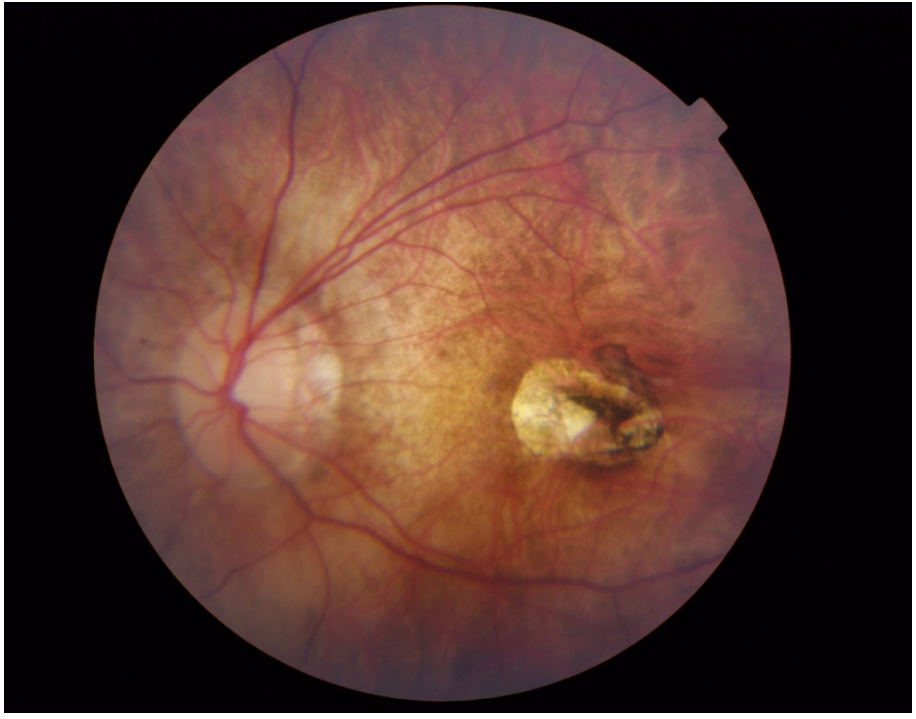
Calciuria in 24 patients with FHHNC (French series)



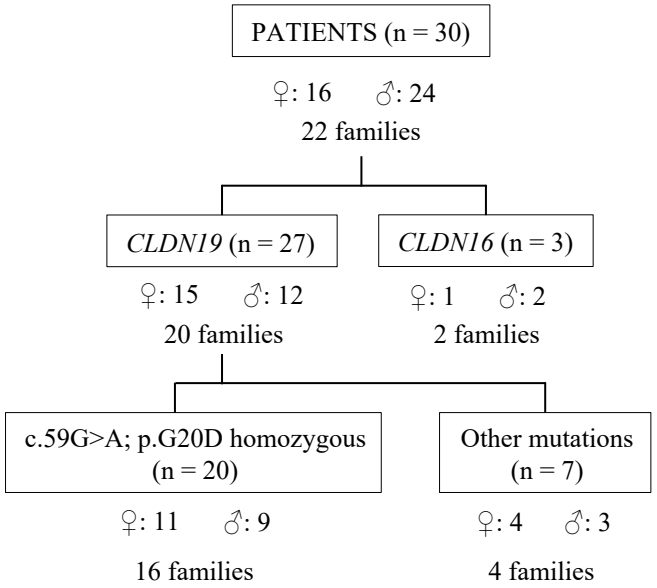
Godron et al. cJASN, 2012; 7: 81-909

Extrarrenal manifestions in FHHNC

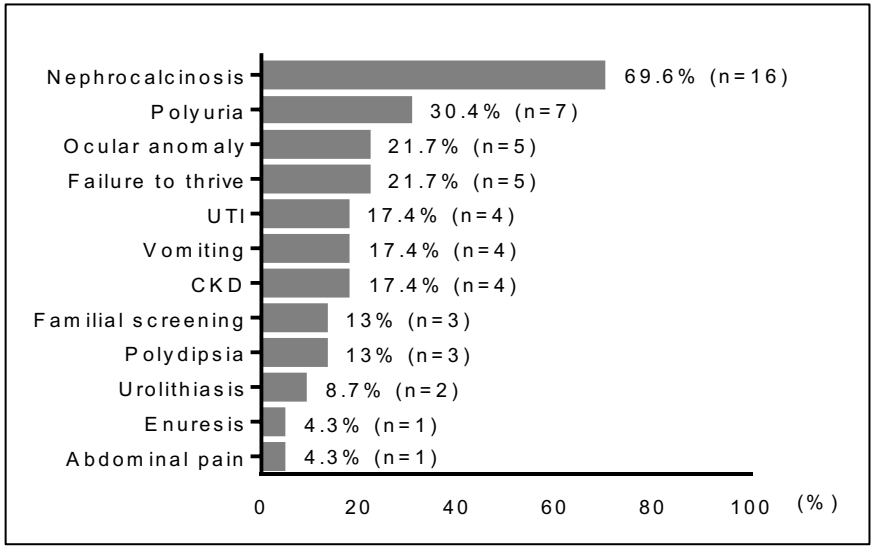




FHHNC: our contemporary experience in Spain (30 patients)



Clinical picture at diagnosis



Vall-Palomar M et al. J Nephrology, 2021

FHHNC: ocular phenotype in *CLDN19* patients

- 60% myopia magna, macular coloboma ± nystagmus
- 20% mild myopia or astigmatism
- **20% without ocular involvement**

- Remarkably, no correlation between ocular impairment and progression to kidney failure was observed.

Vall-Palomar M et al. J Nephrology, 2021

QUESTION

What of the following manifestations is not required for the diagnosis of FHHNC?

1. Hypercalciuria
2. Macular coloboma
3. Increased FEMg
4. Nephrocalcinosis
5. All are required

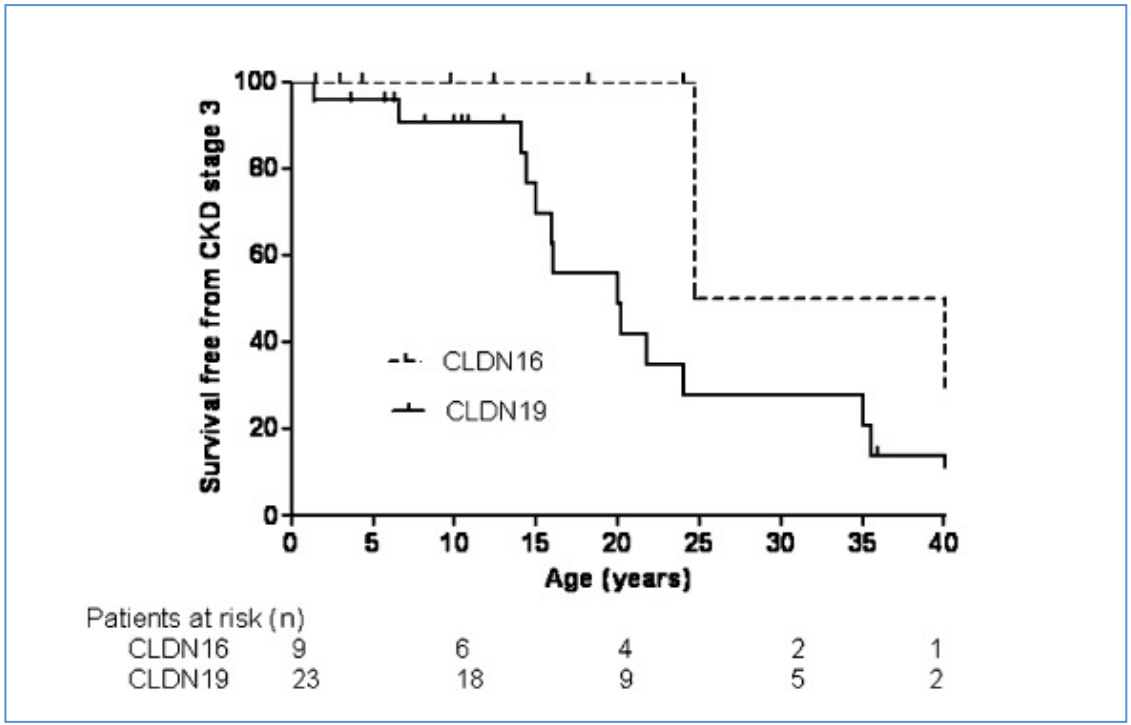
ANSWER

What of the following manifestations is not required for the diagnosis of FHHNC?

1. Hypercalciuria
2. Macular coloboma
3. Increased FEMg
4. Nephrocalcinosis
5. All are required

Macular coloboma is limited to some patients with *CLDN19* mutations. Patients with *CLDN16* mutations do not exhibit severe ocular anomalies

Outcome and genotype in 24 patients with FHHNC (French series)



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

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)

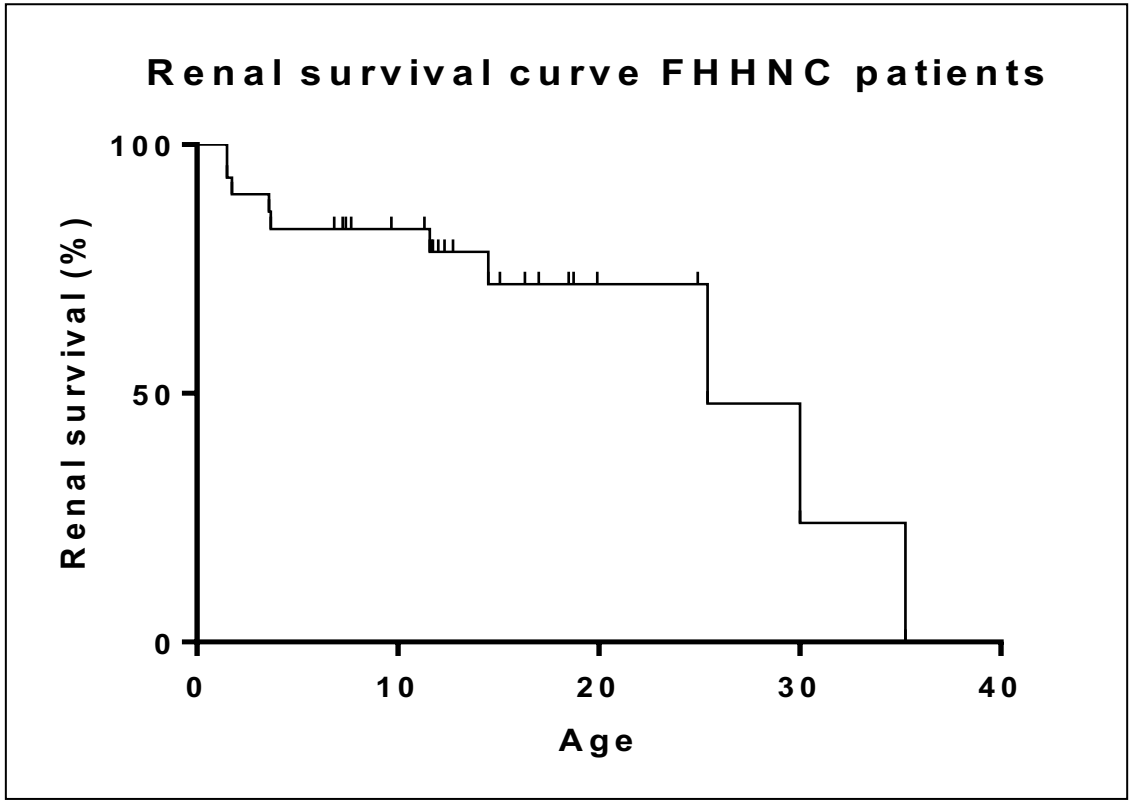
Renal survival *md* 25.4 years

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

More severe phenotype in females:

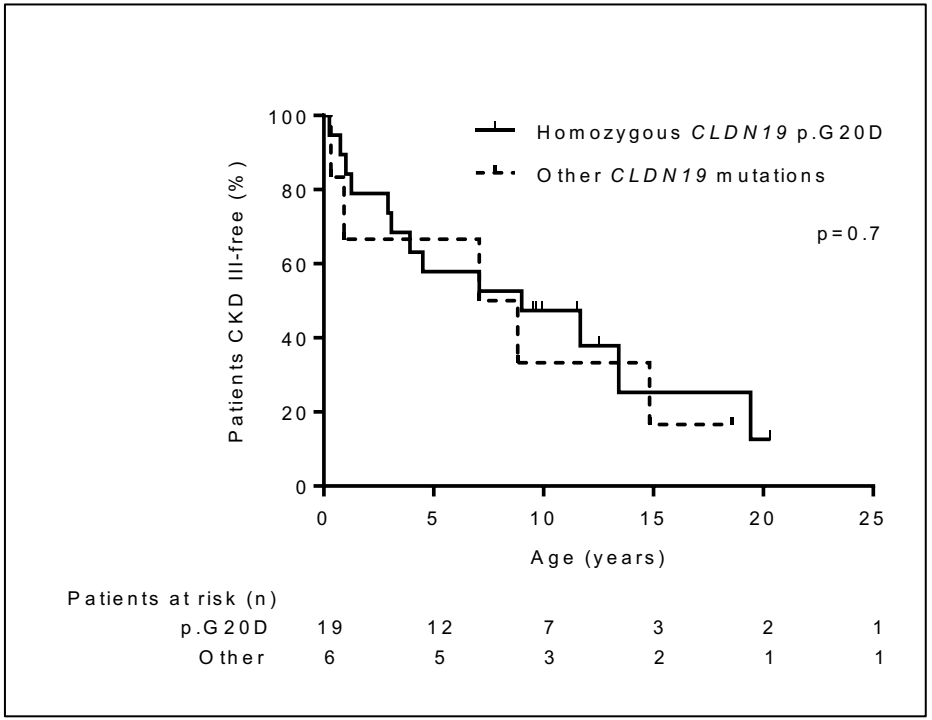
(80% females in the subgroup with ESKD vs. 40% females in the subgroup not requiring renal replacing therapy)

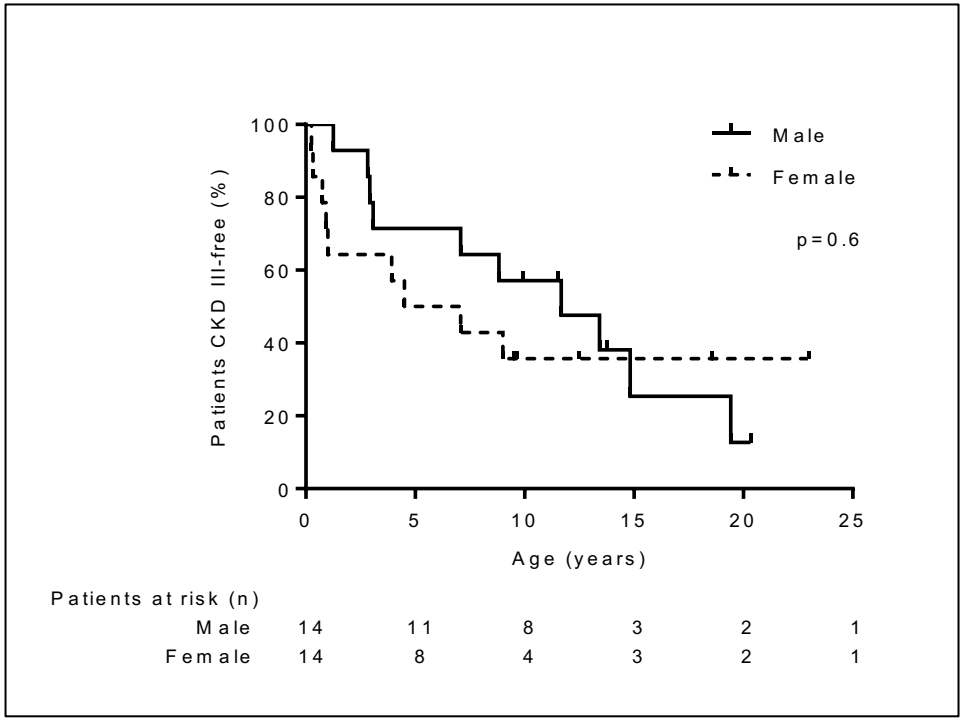
73% with ocular involvement



Vall-Palomar M et al. J Nephrology, 2021

FHHNC outcome in Spain: CKD 3 free survival (30 patients)





Vall-Palomar M et al. J Nephrology, 2021

Factors associated with faster CKD progression in FHHNC patients

CLDN19 ? (vs *CLDN16*) gene mutations

Female gender

Higher PTH levels

Higher urinary excretion of Mg and Ca

Others?

Konrad et al. JASN, 2008

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

Vall-Palomar M et al. J Nephrology, 2021

Variability of disease severity occurs in FHHNC siblings with *CLDN19* mutations

	Família 1		Família 2		Família 3		Família 4		Família 5		Família 6		Família 7	
Pacient	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
Sexe	H	D	D	H	H	H	D	D	D	D	D	D	H	H
Edat diagnòstic[a]	9,2	0,3	3,6	1,6	8,6	5,2	5,1	1,9	0,9	0,3	< 1	2	3,9	0,8
Motius diagnòstic	PU AO	CF	CF	PU	-	AO CKD	-	PU PD NC CD	ITU	CKD NC	NC	-	PU PD ITU NC	-
eGFR diagnòstic	60	46	85,5	90	67	55	78	63	56	64	N/D	N/D	0,9[b]	0,5[b]
Edat actual[a]	18,5	9,1	18,5	17	15,1	11,7	9,7	7,3	12,9	9,3	45,9	36,3	11,3	10,4
eGFR actual	47	N/A	61,5	27	87	54	79	41	N/A	N/A	N/A	N/A	22,4	N/A
Edat FR[a]	N/A	1,5	N/A	N/A	N/A	N/A	N/A	N/A	1,5	1,8	29,9	25,4	N/A	3,6
Anomalies ocular	MM CM	M AS	M	N M	MM	MM	-	-	-	-	MM CM N	M AS	CM A	M

H: Home; D: Dona; M: Miopia; AS: Astigmatisme; MM: Miopia magna; CM: Coloboma macular; N: Nistagme; CKD: *Chronic Kidney Disease*; CF: Cribratge familiar; CD: Creixement deficient; NC: Nefrocalcinosi; PU: poliúria; PD: Polidípsia; AO: Anomalies oculars; ITU: Infecció del tracte urinari; eGFR: *Estimated glomerular filtration rate;* FR: Fallida renal

N/A: No aplica; N/D: No determinat.

[a]Edat expressada en anys, [b]Creatinina sèrica expressada en mg/dL.

Vall-Palomar M et al. J Nephrology, 2021

Treatment of FHHNC: supportive

Oral Mg supplements:

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

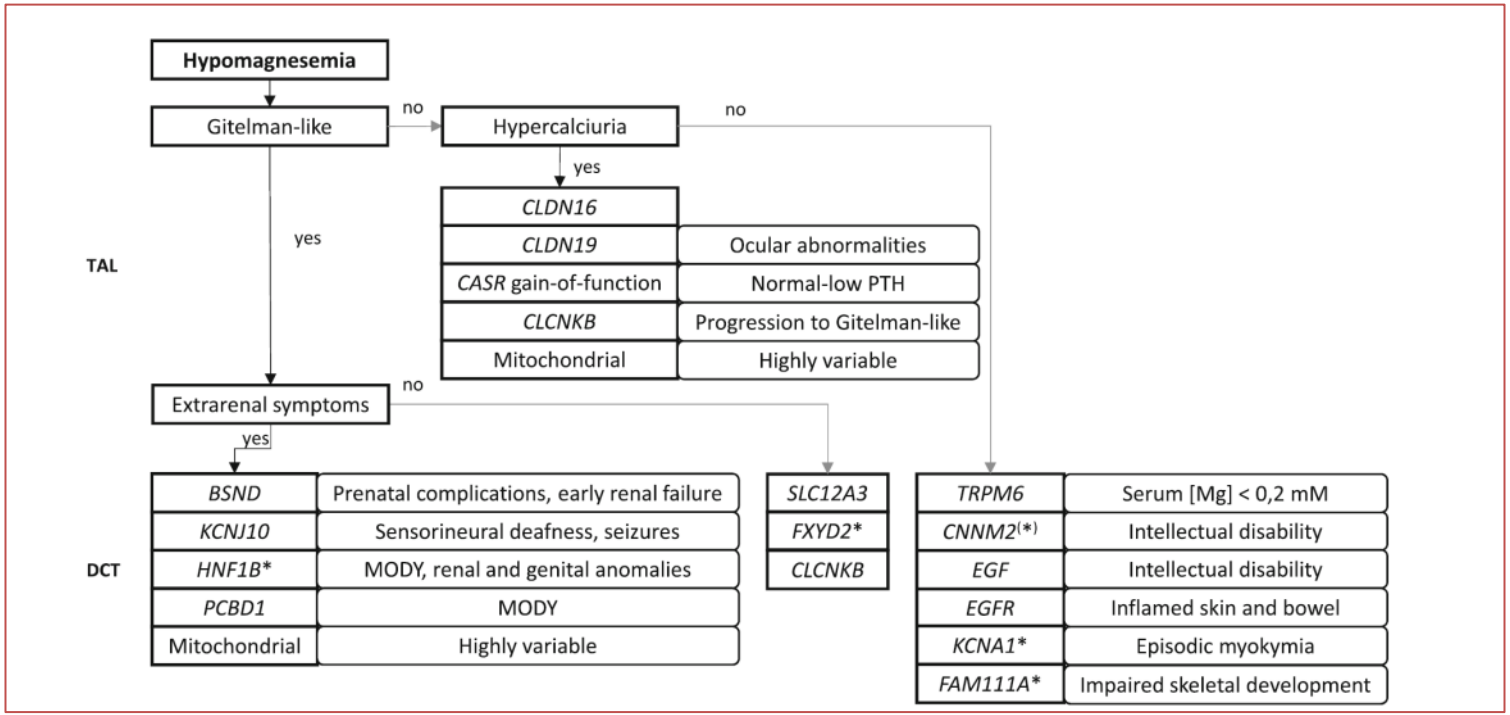
Thiazides: to reduce hypercalciuria

Citrate (caution with serum K^+)

Avoid acquired renal damage (dehydration, drugs,…)

Kidney transplant (carriers can be donors)

Diagnostic flowchart for a suspected genetic cause of hypomagnesemia



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

Next Webinars

ERKNet
The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

ERA
LEADING EUROPEAN NEPHROLOGY

WGIKD
Working Group on Inherited Kidney Disorders

IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

ESPN/ERKNet Virtual Workshop on Fundamentals in pediatric Dialysis

Date: **20/21 Oct 2021**

Speaker: **Various Speakers, organized by the ERKNet Paediatric CKD & Dialysis Working Group and the ESPN Dialysis Working Group**

Topic: **Fundamentals in pediatric dialysis**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **26 Oct 2021**

Speaker: **Paola Romagnani**

Topic: **Stem cells in the kidney**

ERA/ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **02 Nov 2021**

Speaker: **Karl Peter Schlingmann**

Topic: **Genetic cause of nephrolithiasis and nephrocalcinosis**

Subscribe the ERKNet and IPNA Newsletter and don`t miss Webinars!