Hospital
Dr. Guillermo
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Benavente
Servicio de Salud
Concepción

Ministerio de
Salud

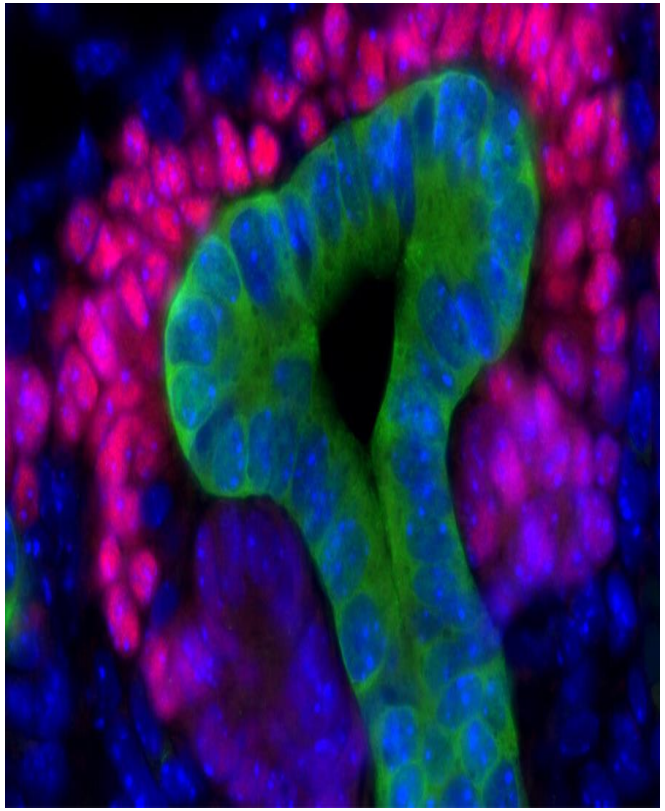
Bases genéticas de las anomalías congénitas renales y del tracto urinario (CAKUT)

M. Nicole Bascur Postel

Teaching Course Nefrología Pediátrica
Valdivia 26 y 27 de septiembre 2019

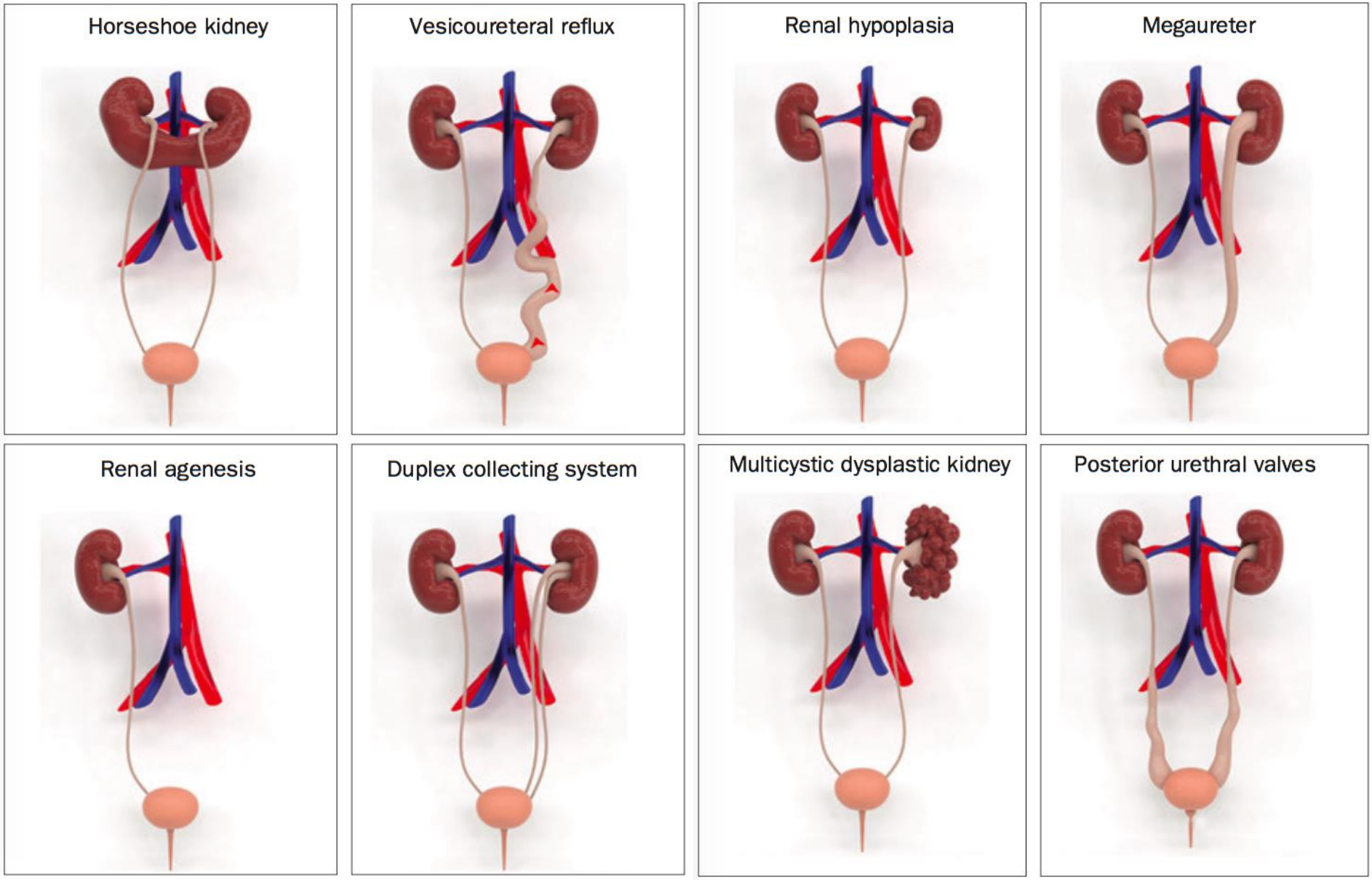
Epidemiología CAKUT

- 20-30 % de todas las malformaciones
- 1 en 500 RNV
- Europa - 41,3 % de los niños con TRR
- Registro Chileno de ERC Pediátrica- 53% pacientes

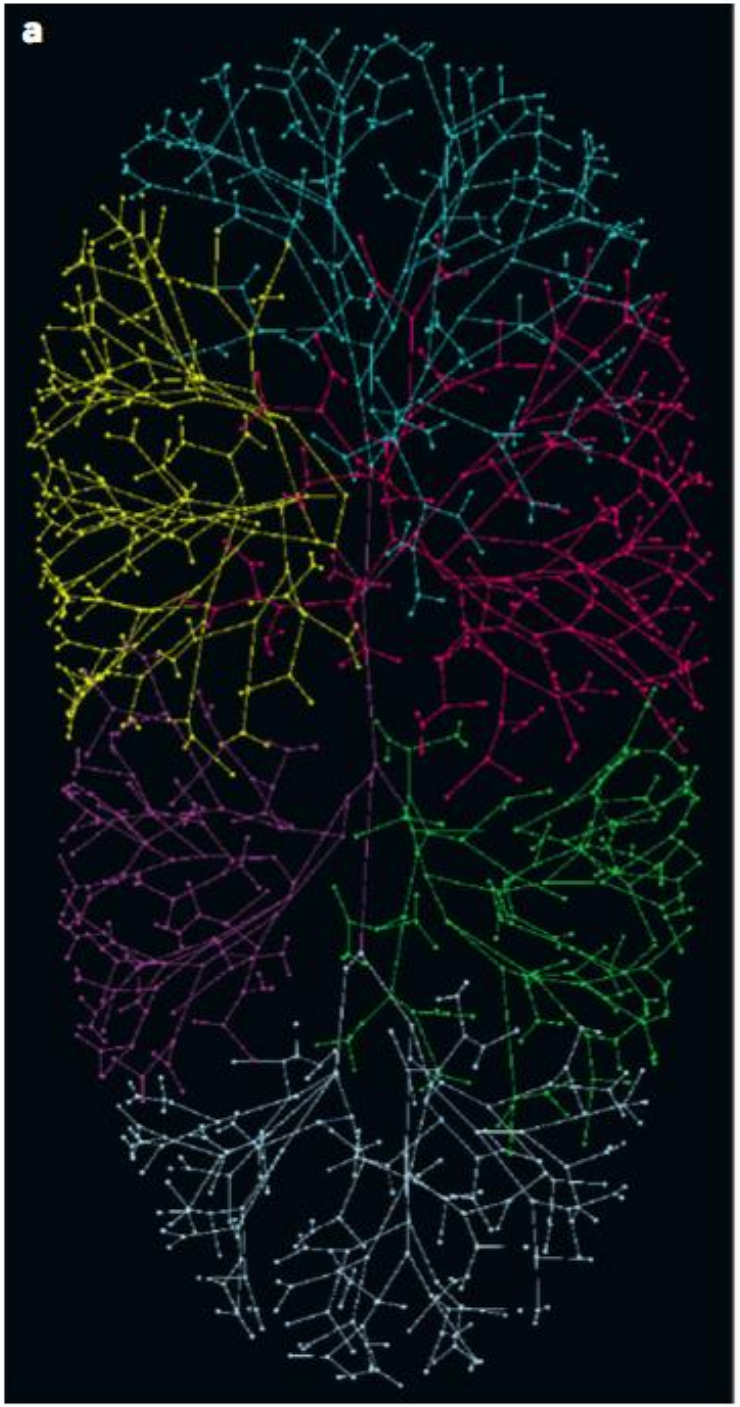


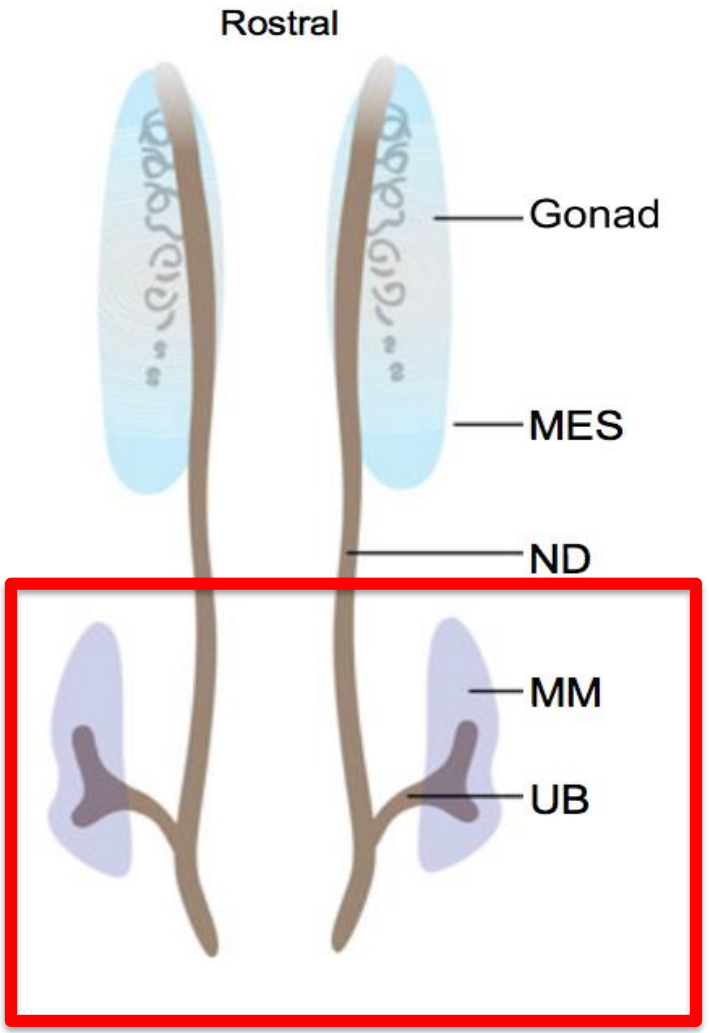
Pediatr Nephrol 29:2403–2410 (2014)

Registro de ERC Rama Nefrología Pediátrica 2017



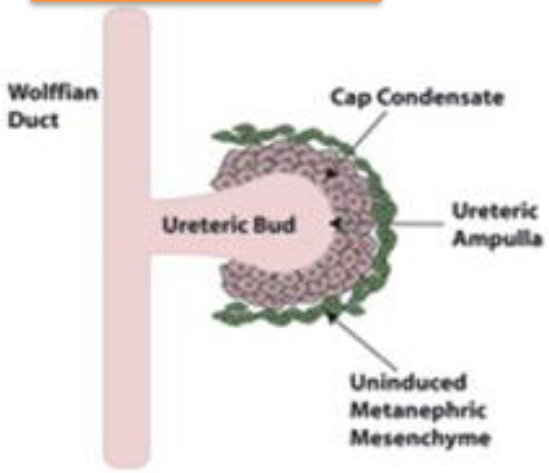
Nat Rev Nephrol. 2015 Dec;11(12):720-31



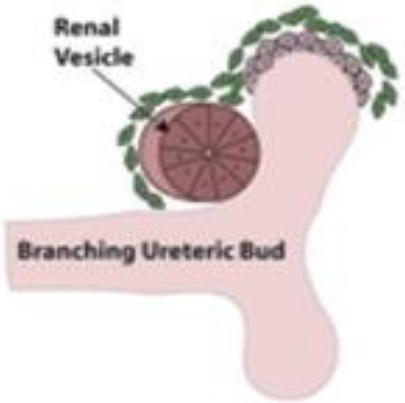


Development (2015) 142, 1937-1947

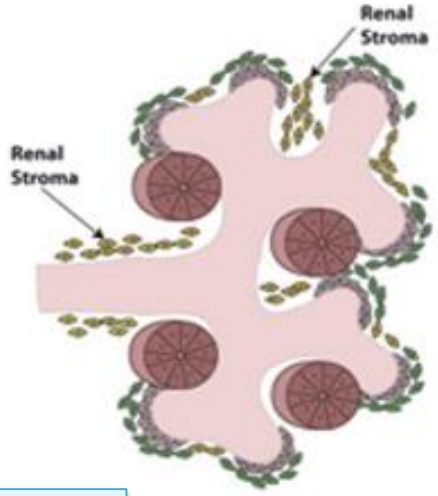
Inducción yema ureteral



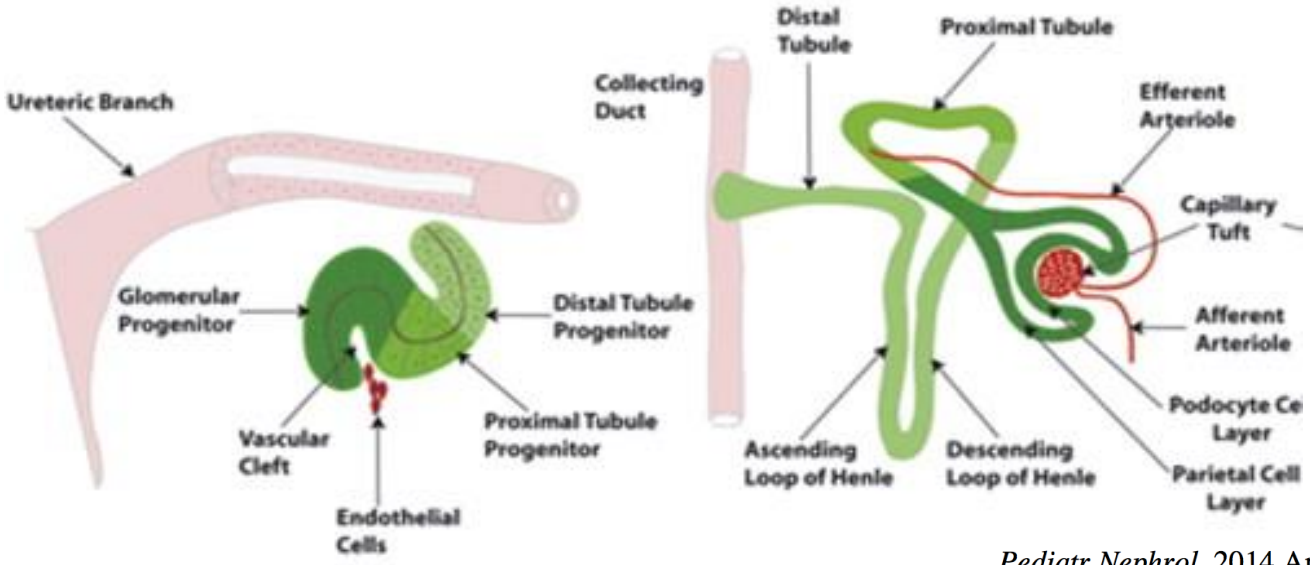
Transición mesénquimo epitelial



Morfogénesis de la ramificación renal

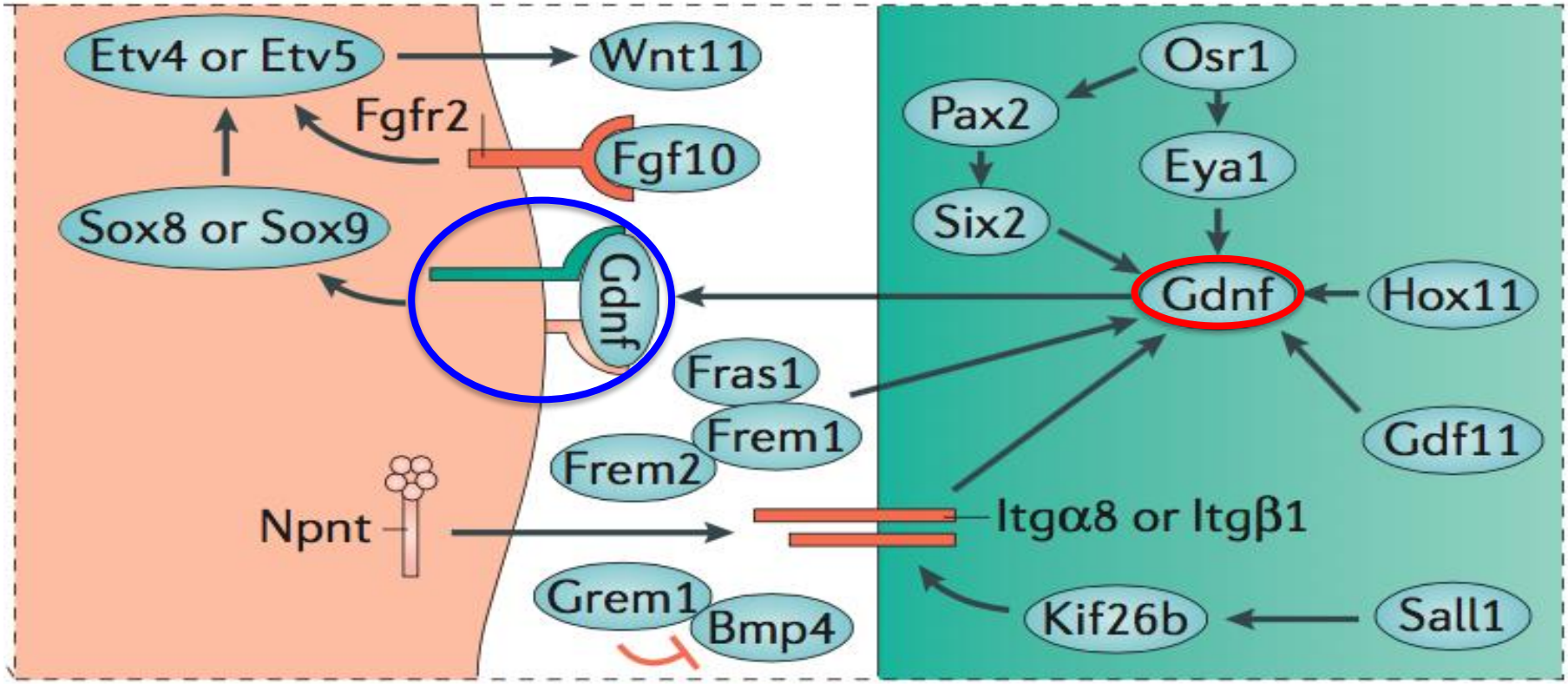


Desarrollo y elongación de nefrones (nefrogénesis)



Pediatr Nephrol. 2014 April ; 29(4): 695–704

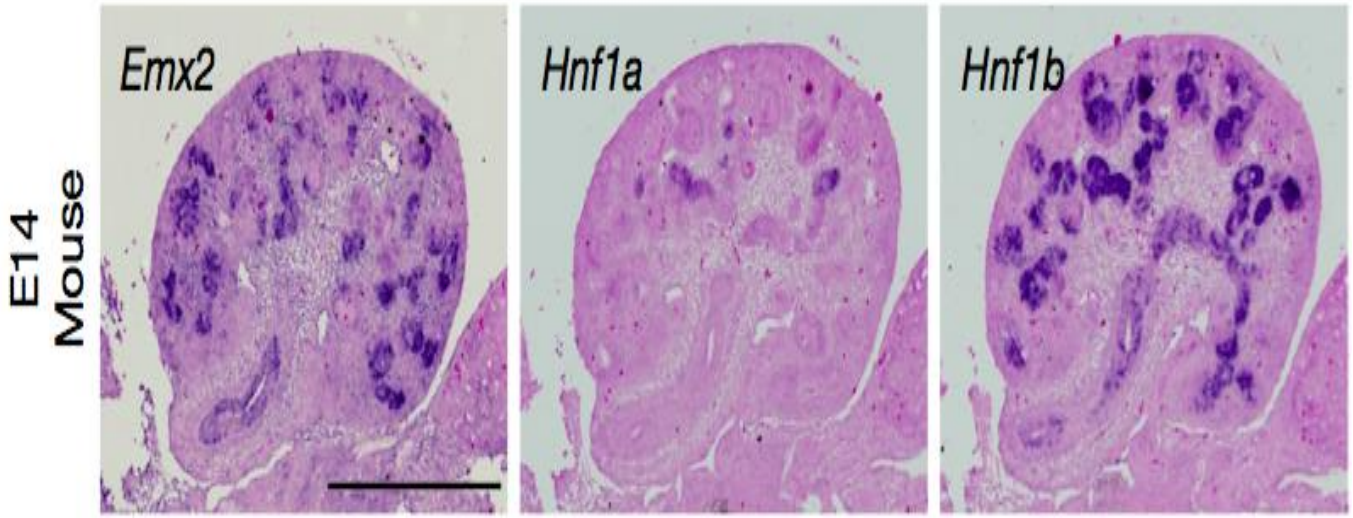
Inducción yema ureteral



Nat Rev Nephrol. 2016 Dec;12(12):754-767

Direct reprogramming of fibroblasts into renal tubular epithelial cells by defined transcription factors

Michael M. Kaminski[1], Jelena Tosic[1,2,3,4], Catena Kresbach[1], Hannes Engel[1], Jonas Klockenbusch[1], Anna-Lena Müller[1], Roman Pichler[1], Florian Grahammer[1], Oliver Kretz[1,5], Tobias B. Huber[1,6], Gerd Walz[1,6], Sebastian J. Arnold[1,2,6,7] and Soeren S. Lienkamp[1,6,7]

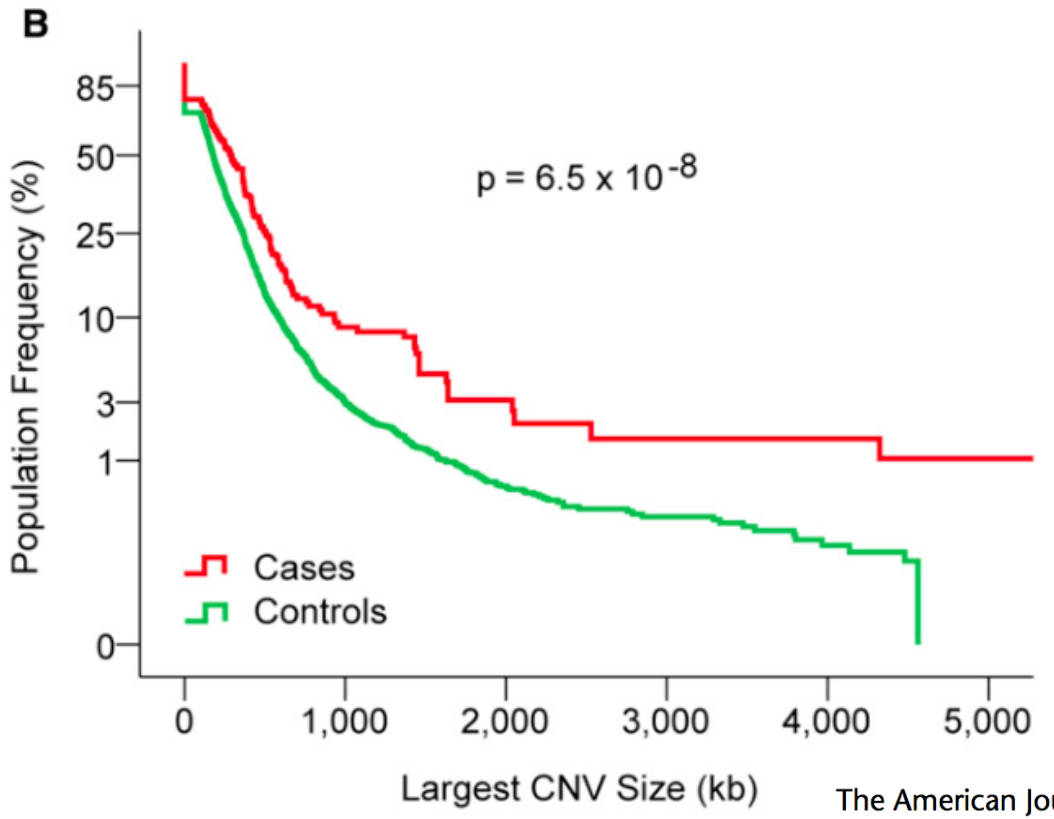


Generación de células tubulares ex vivo
Emx2, Hnf1b, Hnf4a and Pax8

Nat Cell Biol. 2016 Dec;18(12):1269-1280

Copy-Number Disorders Are a Common Cause of Congenital Kidney Malformations

Simone Sanna-Cherchi,[1,2] Krzysztof Kiryluk,[1] Katelyn E. Burgess,[1] Monica Bodria,[3] Matthew G. Sampson,[5] Dexter Hadley,[4] Shannon N. Nees,[1] Miguel Verbitsky,[1] Brittany J. Perry,[1] Roel Sterken,[1] Vladimir J. Lozanovski,[6] Anna Materna-Kiryluk,[7] Cristina Barlassina,[8,9] Akshata Kini,[4] Valentina Corbani,[10] Alba Carrea,[3] Danio Somenzi,[11] Corrado Murtas,[3] Nadica Ristoska-Bojkovska,[6] Claudia Izzi,[12] Beatrice Bianco,[11] Marcin Zaniew,[13] Hana Flogelova,[14] Patricia L. Weng,[1] Nilgun Kacak,[1] Stefania Giberti,[11] Maddalena Gigante,[15] Adela Arapovic,[16] Kristina Drnasin,[17] Gianluca Caridi,[3] Simona Curioni,[8] Franca Allegri,[18] Anita Ammenti,[19] Stefania Ferretti,[20] Vinicio Goj,[21] Luca Bernardo,[21] Vaidehi Jobanputra,[22] Wendy K. Chung,[23] Richard P. Lifton,[24] Stephan Sanders,[24] Matthew State,[24] Lorraine N. Clark,[25] Marijan Saraga,[16,26] Sandosh Padmanabhan,[27] Anna F. Dominiczak,[27] Tatiana Foroud,[28] Loreto Gesualdo,[15] Zoran Gucev,[6] Landino Allegri,[11] Anna Latos-Bielenska,[7] Daniele Cusi,[8] Francesco Scolari,[12] Velibor Tasic,[6] Hakon Hakonarson,[4,5] Gian Marco Ghiggeri,[3] and Ali G. Gharavi[1,*]



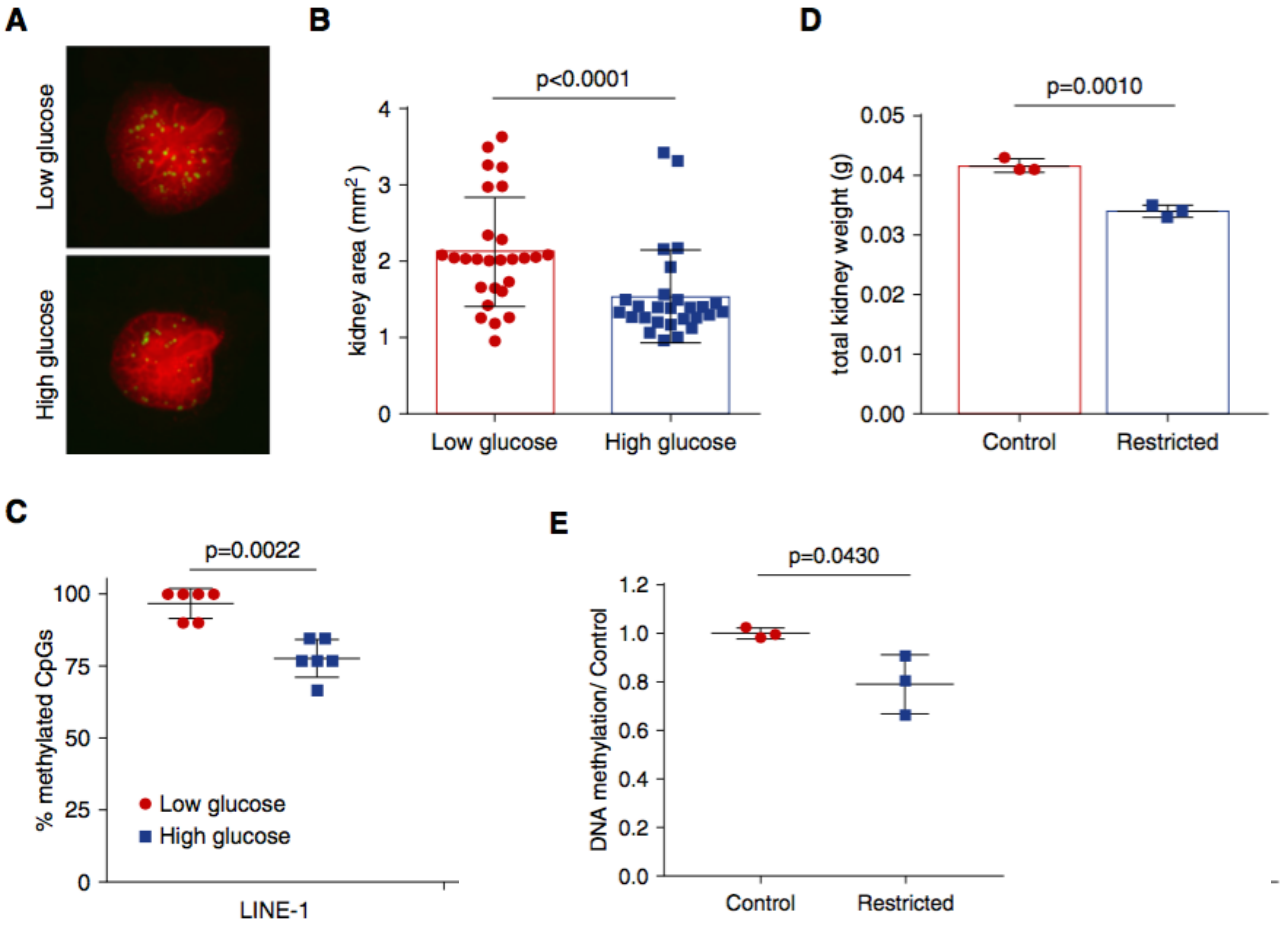
192 casos RHD (NA, Europa: Italia, Polonia, Macedonia, Croacia, República Checa)
4733 controles pareados por etnia

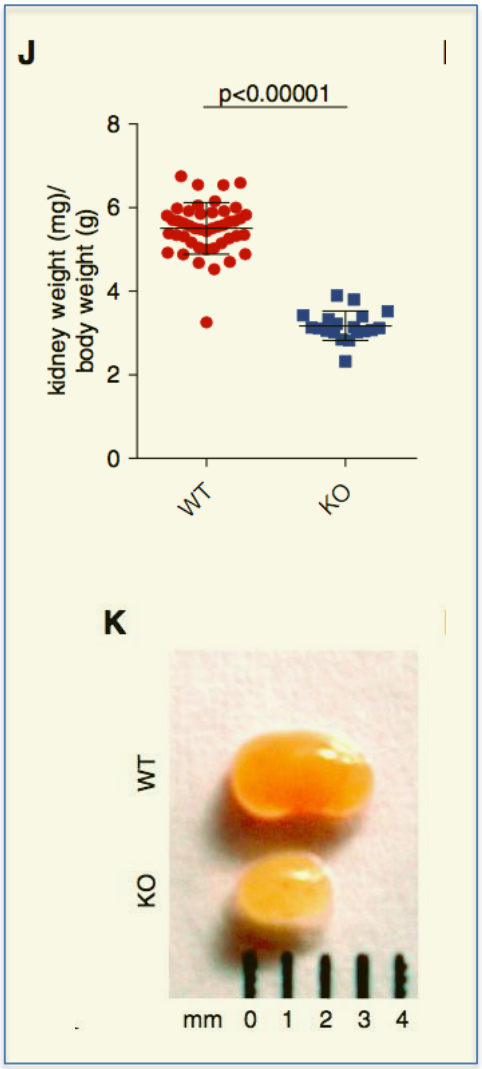
The American Journal of Human Genetics *91*, 987–997, December 7, 2012

BASIC RESEARCH www.jasn.org

DNA Methyltransferase 1 Controls Nephron Progenitor Cell Renewal and Differentiation

Nicola Wanner,[1] Julia Vornweg,[2,3] Alexander Combes,[4,5] Sean Wilson,[4] Julia Plappert,[2] Gesa Rafflenbeul,[2] Victor G. Puelles,[1] Raza-Ur Rahman,[6] Timur Liwinski,[6,7] Saskia Lindner,[2] Florian Grahammer,[1] Oliver Kretz,[1,8] Mary E. Wlodek,[9] Tania Romano,[10] Karen M. Moritz,[11] Melanie Boerries,[12,13,14] Hauke Busch,[14,15] Stefan Bonn,[6,16] Melissa H. Little,[5,17] Wibke Bechtel-Walz,[2] and Tobias B. Huber[1,2,18,19]

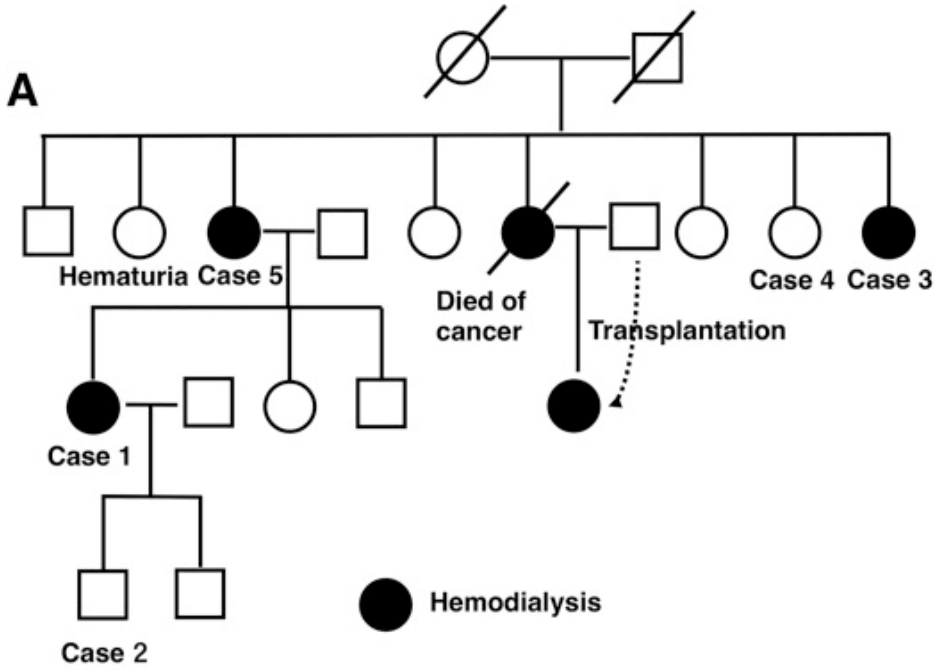




J Am Soc Nephrol **30:** 63–78, 2019

PAX2

- CAKUT aislado
- Displasia nervio óptico y malformaciones renales
- Autosómico dominante
- 10q24.31



PLoS One. 2015 Nov 16;10(11)

BASIC RESEARCH www.jasn.org

Mutations in *PAX2* Associate with Adult-Onset FSGS

Moumita Barua,* Emilia Stellacci,† Lorenzo Stella,‡ Astrid Weins,§ Giulio Genovese,*‖¶** Valentina Muto,† Viviana Caputo,†† Hakan R. Toka,*‡‡ Victoria T. Charoonratana,* Marco Tartaglia,† and Martin R. Pollak*

176 familias GEFS
85 individuos CAKUT
SECUENCIACIÓN EXOMA, Sanger

Table 2. Clinical features of FSGS families with *PAX2* mutation–associated disease

Family ID	Self-Reported Ethnicity	Ages at Disease Onset (yr)	Persons Affected (*n*)	Patients with ESRD (*n*)	Ages at Development of ESRD (yr)	Ultrasonography Findings	Diagnosis	Patients with Biopsy (*n*)
FG-BF	White	8	2	1	Unknown	Increased echogenicity	FSGS	1
FG-DO	African American	7–11	2	Unknown	Unknown	Unknown	Proteinuria	Unknown
FG-EQ	European	17–68	6	2	40, 58	Dilated renal pelvis, small kidneys	FSGS	2
FG-GE	Unknown	Unknown	2	1	Unknown	Slightly small kidney, calyceal diverticulum	Proteinuria	1
FG-IX	Middle Eastern	36	4	Unknown	Unknown	Unknown	FSGS	Unknown
FG-JO	East Indian	31–32	5	4	30–36	Unknown	FSGS	3
FG-KV	European American	15–24	3	1	42	Unknown	FSGS, undiagnosed PRS	3

J Am Soc Nephrol **25:** 1942–1953, 2014

Dominant *PAX2* mutations may cause steroid-resistant nephrotic syndrome and FSGS in children

Asaf Vivante[1,2] · Orna Staretz Chacham[3] · Shirlee Shril[1] · Ruth Schreiber[4] · Shrikant M. Mane[5] · Ben Pode-Shakked[2,6] · Neveen A. Soliman[7] · Irene Koneth[8] · Mario Schiffer[9] · Yair Anikster[6] · Friedhelm Hildebrandt[1]

Table 1 Four different heterozygous *PAX2* mutations detected in four different families with SRNS/FSGS

Family-Individual	Ancestry	Nucleotide alteration	Alteration in coding sequence[a]	Zygosity
AN10–21 (index family)	Arab	c.69-70InsG [b]	p.Val26Glyfs*28	Het
A4041–11	Egypt	c.254G > T	p.Gly85Val	Het
A4041–23	Egypt	c.254G > T	p.Gly85Val	Het
A4041–24	Egypt	c.254G > T	p.Gly85Val	Het
A5089–11	Europe	c.862-1G > A	Splice mutation	Het
A5089–21	Europe	c.862-1G > A [c]	Splice mutation	Het
A5281	Europe	c.275C > T	p.Thr92Met	Het

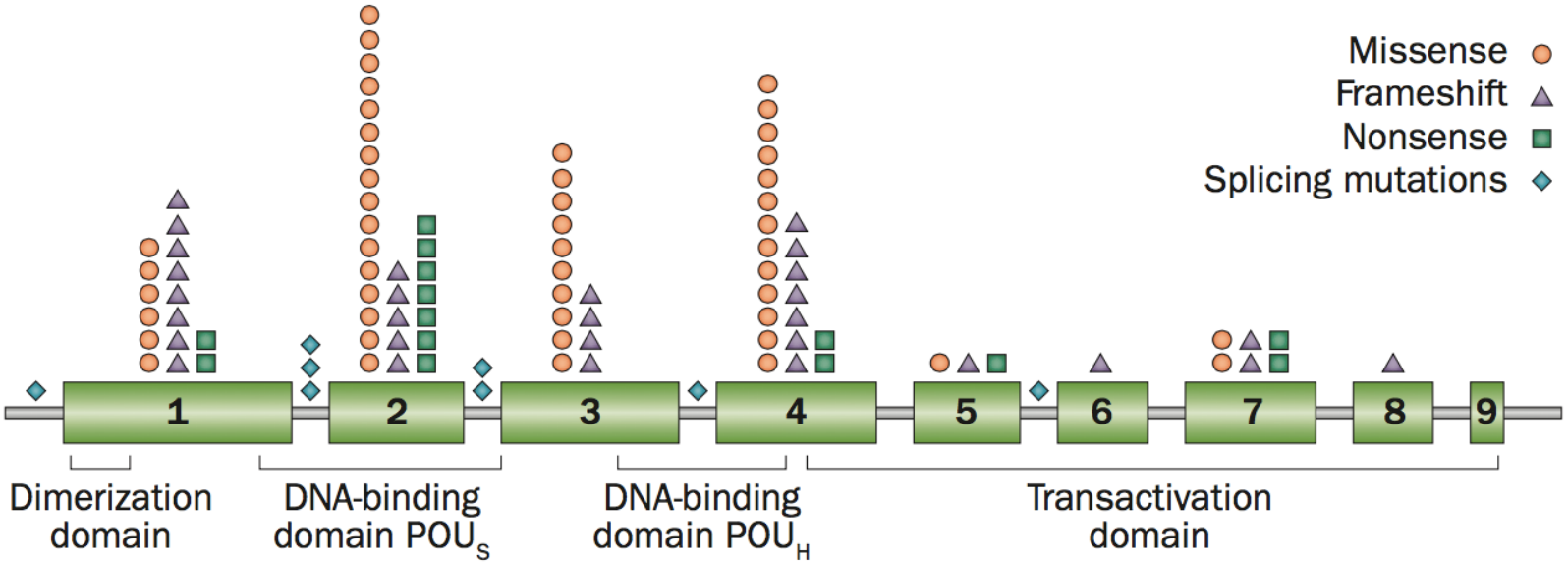
Family-Individual	SIFT/PP2	Presenting symptoms (age)	Renal histology	eGFR at presentation/ESRD age	Extra-renal phenotype
AN10–21 (index family)	Deleterious/1 (reported)	Elevated creatinine and proteinuria (2y)	FSGS	ESRD at age 4 years	Coloboma, cardiomyopathy, microcephaly
A4041–11	Deleterious/1 (novel)	Proteinuria and elevated creatinine (35y)	n/a	ESRD at age 39 years	–
A4041–23	Deleterious/1 (novel)	Proteinuria and elevated creatinine (13y)	FSGS	63 ml/min/1.73m^2	–
A4041–24	Deleterious/1 (novel)	Edema, proteinuria and elevated creatinine (10y)	FSGS	50 ml/min/1.73m^2	–
A5089–11	Obligatory splice[b] (novel)	Proteinuria and normal creatinine	n/a	n/a	–
A5089–21	Obligatory splice (novel)	Edema, proteinuria and elevated creatinine (20)	FSGS	ESRD at age 27	–
A5281	Deleterious/1 (novel)	HTN found on screening (18)	FSGS	n/a[d]	Cryptorchidism

Pediatr Nephrol. 2019 Sep;34(9):1607-1613

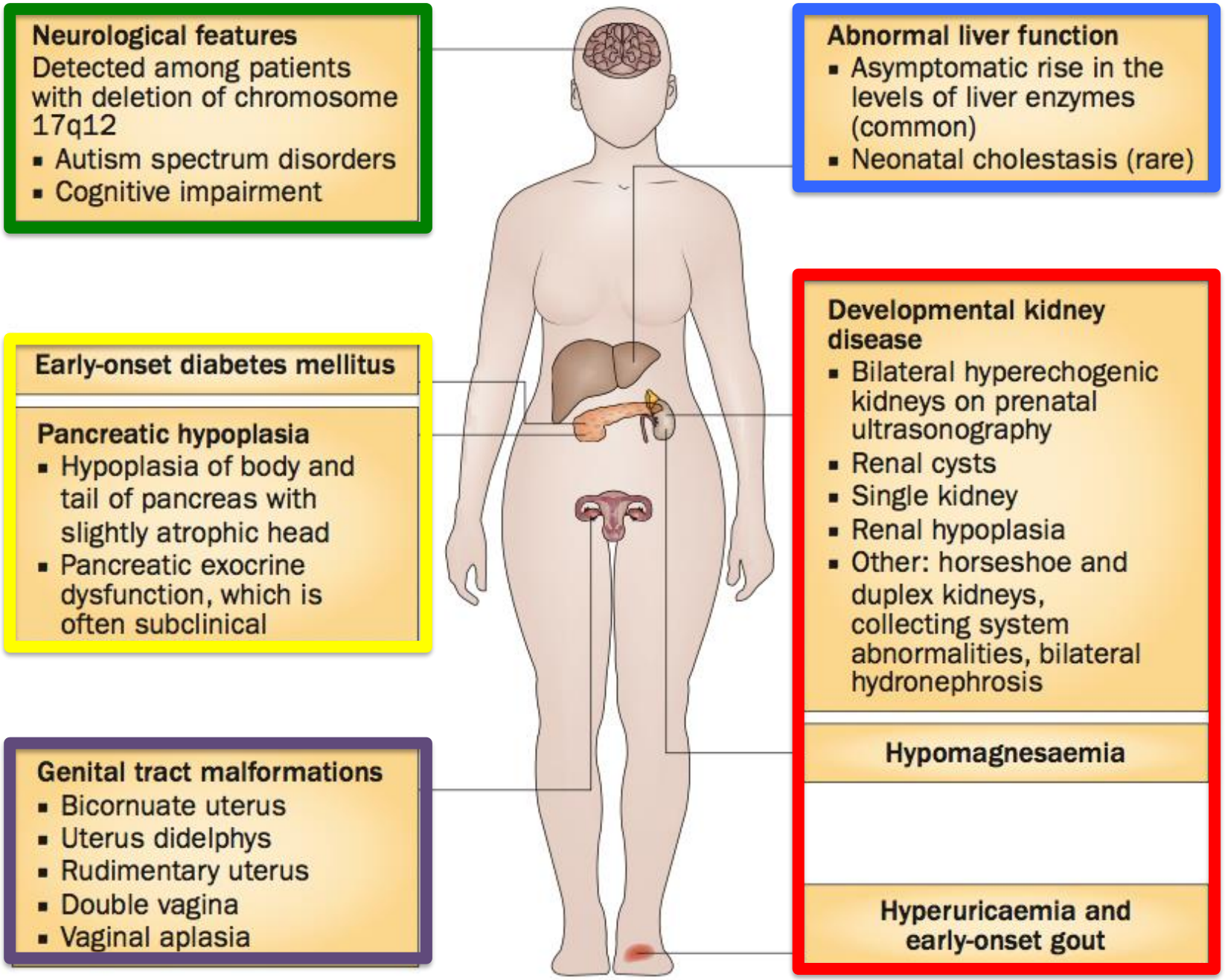
HNF1B

- Displasia renal, especialmente quística
- Quistes renales y diabetes
- Nefropatía túbulo intersticial AD

- 17q12
- Autosómico dominante
- Deleción completa del gen 50%



Nat. Rev. Nephrol. **11**, 102–112 (2015)



Nat. Rev. Nephrol. **11**, 102–112 (2015)

HNF1B nephropathy has a slow-progressive phenotype in childhood—with the exception of very early onset cases: results of the German Multicenter HNF1B Childhood Registry

Christine Okorn[1] · Anne Goertz[1] · Udo Vester[1] · Bodo B. Beck[2,3] · Carsten Bergmann[4] · Sandra Habbig[5] · Jens König[6] · Martin Konrad[6] · Dominik Müller[7] · Jun Oh[8] · Nadina Ortiz-Brüchle[9] · Ludwig Patzer[10] · Raphael Schild[8] · Tomas Seeman[11] · Hagen Staude[12] · Julia Thumfart[7] · Burkhard Tönshoff[13] · Ulrike Walden[14] · Lutz Weber[5] · Marcin Zaniew[15] · Hildegard Zappel[16] · Peter F. Hoyer[1] · Stefanie Weber[17]

62 pacientes con Nefropatía HNF1B con diagnóstico molecular

a

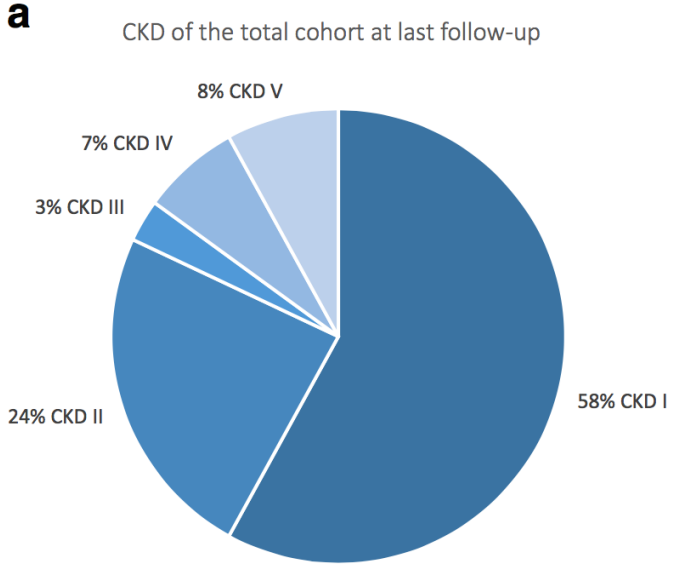


Table 3 Extrarenal manifestations at the end of observation (median age of the total cohort 8 years, mean 8.2 years)

Extrarenal manifestation	Patients	%	Age at diagnosis
Hypomagnesemia (< 0.65 mmol/l)	12/50	24	10.0 years (median)
Hyperuricemia	19/52	37	1.0 year (median)
Elevated liver enzymes	12/58	21	11.0 years (median)
Hyperglycemia	4/50	8	0, 4, 12, 14 years
Urogenital anomalies	1/62	2	Postnatal

Pediatric Nephrology (2019) 34:1065–1075

Detección de mutaciones del gen de HNF1B en niños con malformaciones congénitas renales y del tracto urinario

Detection of mutations of the HNF1B gene in children with congenital anomalies of the kidney and urinary tract

M. Nicole Bascur P.[a], M. Luisa Ceballos O.[b], Mauricio Farfán U.[b], Iván Gajardo H.[b] y Joaquín López C.[b]

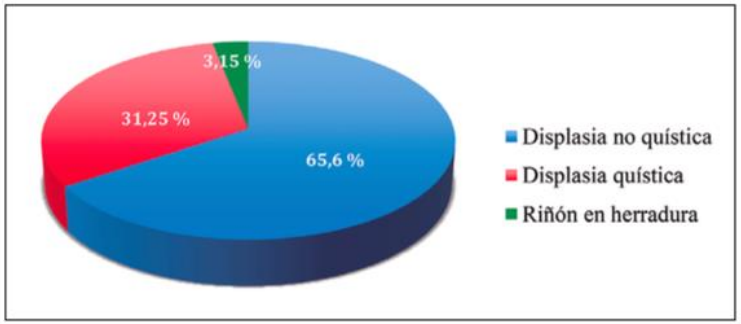


Figura 1. Caracterización de la muestra de acuerdo a tipo de Malformación Nefrourológica.

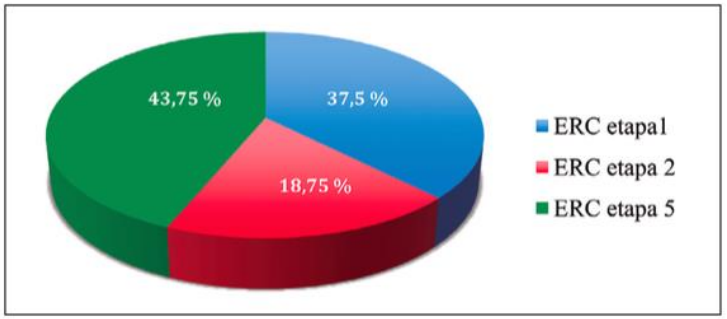


Figura 2. Caracterización de la muestra de acuerdo a la Etapa de Enfermedad Renal Crónica.

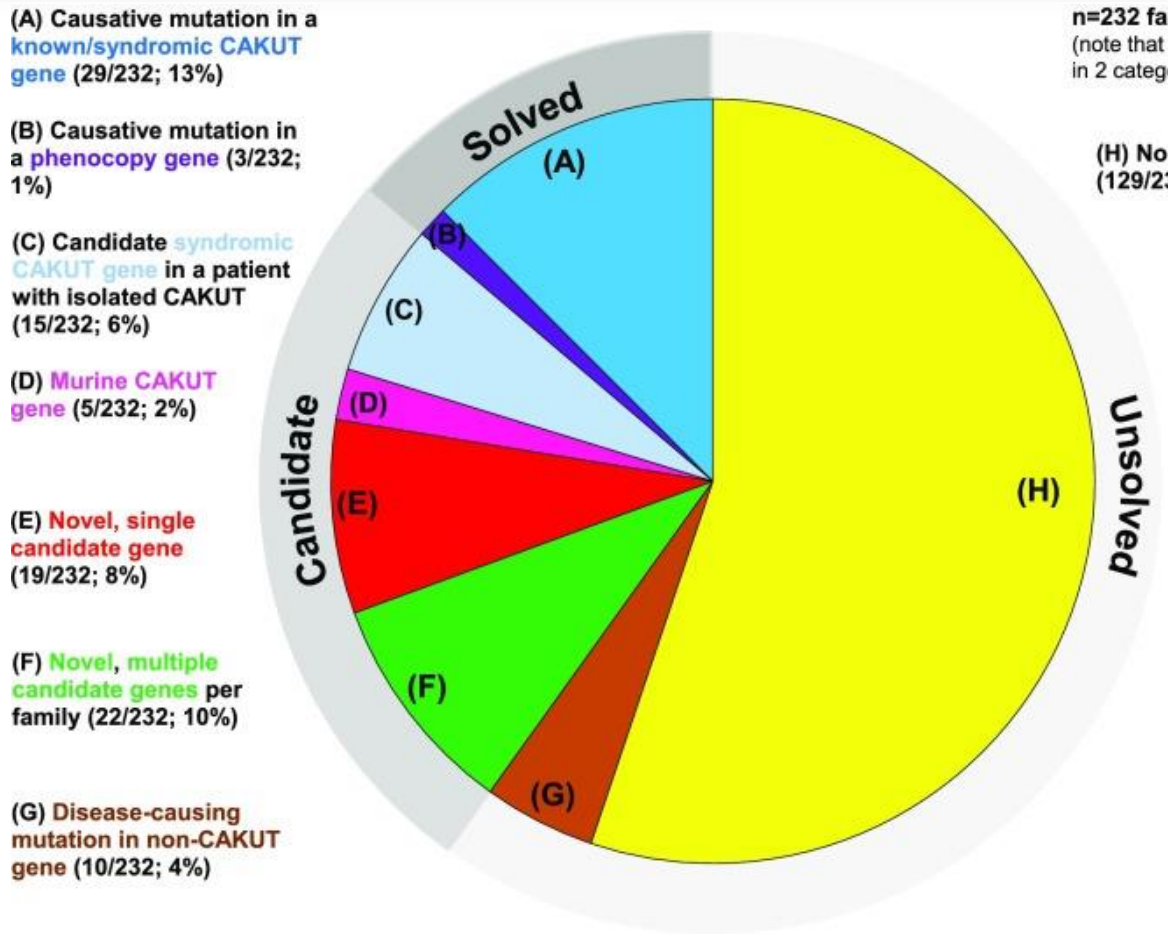
Tabla 1. Características generales de los casos índices

ID paciente	Edad (a)	Sexo	CAKUT	Etapa ERC	Exon	Mutación
10	17	F	Displasia quística izquierda	1	4	*C1027T*
24	8	M	Displasia no quística bilateral	5	4	*C1027T*

Rev Chil Pediatr. 2018;89(6):741-746

Whole-Exome Sequencing Identifies Causative Mutations in Families with Congenital Anomalies of the Kidney and Urinary Tract

Amelie T. van der Ven, Dervla M. Connaughton, [...], and Friedhelm Hildebrandt



232 fam CAKUT

J Am Soc Nephrol. 2018 Sep; 29(9): 2348–2361

Whole-Exome Sequencing in the molecular diagnosis of individuals with congenital anomalies of kidney and urinary tract and identification of a new causative gene

Mir Reza Bekheirnia, MD, FACMG[1,2,3,4], Nasim Bekheirnia, MBS, MS[1,2,4], Matthew N. Bainbridge, PhD[5], Shen Gu, PhD[1], Zeynep Hande Coban Akdemir, PhD[1], Tomek Gambin, PhD[1], Nicolette K. Janzen, MD[3,4], Shalini N. Jhangiani, MS[5], Donna M. Muzny, MS[5], Mini Michael, MD[4,6], Eileen D. Brewer, MD[4,6], Ewa Elenberg, MD[4,6], Arundhati S. Kale, MD[4,6], Alyssa A. Riley, MD[4,6], Sarah J. Swartz, MD[4,6], Daryl A. Scott, MD, PhD[1,4], Yaping Yang, PhD[1], Poyyapakkam R. Srivaths, MD[4,6], Scott E. Wenderfer, MD, PhD[4,6], Joann Bodurtha, MD, MPH[7], Carolyn D. Applegate, MS[7], Milen Velinov, MD, PhD[8], Angela Myers, MD[9], Lior Borovik, MS[9], William J. Craigen, MD, PhD[1,4], Neil A. Hanchard, MD, PhD[1,4], Jill A. Rosenfeld, MS[1], Richard Alan Lewis, MD[1,4,10], Edmond T. Gonzales, MD[3,4], Richard A. Gibbs, PhD[1,5], John W. Belmont, MD, PhD[1,4], David R. Roth, MD[3,4], Christine Eng, MD[1], Michael C. Braun, MD[4,6], James R. Lupski, MD, PhD[1,4,5,11], and Dolores J. Lamb, PhD[2,3,12]

62 familias CAKUT
5% fam SNVs: PAX2, HNF1B, EYA1
4 fam CNV patogénicas

Family ID	Gene	Sex	Ethnicity	Renal phenotype	Genome build	Chr: position	Nucleotide change	Amino-acid change	Other organ defects
1	*PAX2*	M,F	Spanish	RHD	Hg19	10: 102509528	c.70delG	p.G24fs	Optic nerve coloboma (previously undiagnosed)
2	*HNF1B*	M	Mixed Caucasian and African Caribbean	CRD	Hg19	17: 36070584	c.1132dupC	p.Q378fs	Gout, elevated LFTs (recent diagnosis) and increased echogenicity of pancreas (not noted prior to WES)
3	*EYA1*	F	AA	VUR, MCDK	Hg19	8: 72183988	c.867+5G>A	n/a	No

AA African American; **AD**, autosomal dominant, **BOR;** Branchio-oto-renal syndrome; **CADD,** Combined Annotation Dependent Depletion; **Chr,** chromoso
Exome Aggregation Consortium ; **LFT**, liver function tests; **LOF**, loss-of-function; **MCDK,** Multicystic dysplastic kidney; **N/R,** none reported, **RHD,** Renal

Genet Med. 2017 April ; 19(4): 412–420

Copy-number variants (CNVs) identified (from WES data of 62 families) which are relevant to the patient's phenotype

Family ID	Chromosomal region	CNV Type	Start (Mb)	End (Mb)	Size (Mb)	Number of genes	Syndrome	Phenotype	Parental Studies	Comments
Family 34	22q11	Trp	16.63	18.64	2.01	33	Cat eye syndrome	VUR, further details in text (multiple anomalies)	*De Novo*	Pathogenic
Family 39	16p13.11	Dup	15.12	16.29	1.17	19	16p13.11 dup	MCDK, facial dysmorphic features	Unknown	Pathogenic
Family 10	16p11.2	Dup	29.68	30.20	0.52	35	16p11.2 dup	Solitary kidney, psychiatric disorder, hypothyroidism	Unknown	Pathogenic
Family 31	16p11.2	Del	28.83	29.04	0.21	13	16p11.2 del	VUR, seizure, DD, LD, and optic edema	Unknown	Pathogenic
Family 33	3q29	Dup	197.51	197.59	0.08	2	-	VUR, cataract, and growth delay	Unknown	VUS
Family 25	2p24.3	Del	15.30	15.38	0.08	1	-	PUV, heterotaxy	Inherited	VUS
Family 21	4q35.1	Dup	185.99	189.11	3.12	30	-	PUV	Inherited	VUS

DD, developmental delay; **del,** deletion; **dup,** duplication; **LD,** learning disability; **MCDK,** multicystic dysplastic kidney; **PUV,** posterior urethral valve; **trp,** triplication; **VUR**, vesicoureteral reflux; **VUS,** variant of uncertain clinical significance

Genet Med. 2017 April ; 19(4): 412–420

¿Por qué hacer estudios genéticos en pacientes con CAKUT?

- Confirma diagnóstico clínico
- Acelera evaluación de manifestaciones extra renales
- Establece patrones de herencia
- Determinación de tratamientos
- Guía decisiones en el planeamiento familiar
- Identifica factores de riesgo de recurrencia en postTx
- Evaluación de miembros de la familia como donantes renales

Kidney International (2017) **92,** 796–808

- ¿ A quienes ?
- Sociedades científicas

- Cambios paradigmas, medicina individualizada, etiológica

Gracias