ORGANIZA:

SGAN
sociedad gallega de nefrología

VIII CONGRESO
de la
SOCIEDAD GALLEGA DE NEFROLOGÍA

A Coruña, 28 de octubre de 2022

FORMAS ATIPICAS DE LA ENFERMEDAD RENAL HEREDITARIA

Miguel A. García González

NefroCHUS
Laboratorio de Genética de Enfermedades Renales

Situaciones que nos encontramos

- **<u>Que el diagnóstico clínico sea inconcluso</u>**:
  - El diagnóstico genético puede ayudar a determinar la patología de base.
  - <u>Importante</u>: descripción fenotípica detallada del paciente o de familiares (si patología renal).
- **<u>Que el diagnóstico genético sea inconcluso:</u>**
  - Se identifican variantes de Significado Incierto (VUS): profundizar en su estudio.
  - Genes causantes no identificados: No desistir, retomarlo de cara a futuras generaciones, o incluso para el mismo paciente.
  - Abordaje diagnóstico incompleto. Hablar siempre con el genetista de otras posibilidades.
  - Técnicas poco sensibles o inapropiadas. En mejora constante, y cada vez más rápidamente.
  - - Mas allá..... <u>Investigación!</u>

Proyectos SGAN

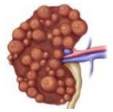
Creación de un flujo de trabajo, que se inicia en las **consultas monográficas** de los hospitales de referencia de Galicia, **establecimiento de un flujo de envío/recepción de muestras**, **recogida de datos** y **creación de un registro** centralizado en el Laboratorio de Santiago (NefroCHUS o FPGMX).

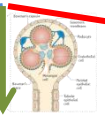
NefroCHUS
Laboratorio de Genética de Enfermedades Renales

Medicina Xenómica | FUNDACIÓN PÚBLICA GALEGA

Situaciones que nos encontramos

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*
Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*
Period 2012-2015





(2) *Cystic Disorders*

AE1.0_GalCyst *(ISCIII_PI15/01467)*
Year:*2015* **PI:** *Miguel A García González*
(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:
i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:
i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*
ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*
iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:
i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*
ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:
i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:*** Noa Carrera and Cándido Díaz (AES 21, ISCiii). **(???)**
ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

(3) *Glomerular Disorders*

AE2.0_GalGlom *(ISCIII_PI18/00378)*
Year:*2018* **PI:** *Miguel A García González*
(2019-2021) Co-PI: *Jesús Calviño (HULA)*

- Genotype/Phenotype Correlation:
i) 206 families, 1030 diagnosed patients.
ii) Col4A Nephropaties: Raquel Rodriguez et al (Under writting).
iii) New genes in Glomerulopathy: Raquel Rodriguez et al (Under writting).
iv) FSGS in clinical diagnosis. GLOSEN Project. PIs: Gema Fernández-Juárez and Miguel García (FRIAT project).

- New Diagnostic Tools:
i) **Glom*Analyser®*** *(Under Construction).*

- New Therapies:
i) ***Ongoing.***

- New Proyects/New PIs:
i) Gene Editing in Glomerulopahies. IP: Noa Carrera /Co-IP: Catarina Allegue
ii) SHUa and Complement Nephropathies. IP: Angel Alonso and Mercedes Cao (CHUAC).

(4) *Tubulo-interstitial Disease*

AE3.0_GalTubi (*ISCIII_PI???*)
Year:*???* **PI:** *Miguel A García González*
Co-PI: *Afonso Otero(CHUOU)*

- Genotype/Phenotype Correlation:
i) 126 families, 407 diagnosed patients.
ii) Gitelman/Bartter cohort: Laura González et al (Under writting).
iii) ADTKD families (Furlano et al, AJKD. 2018)

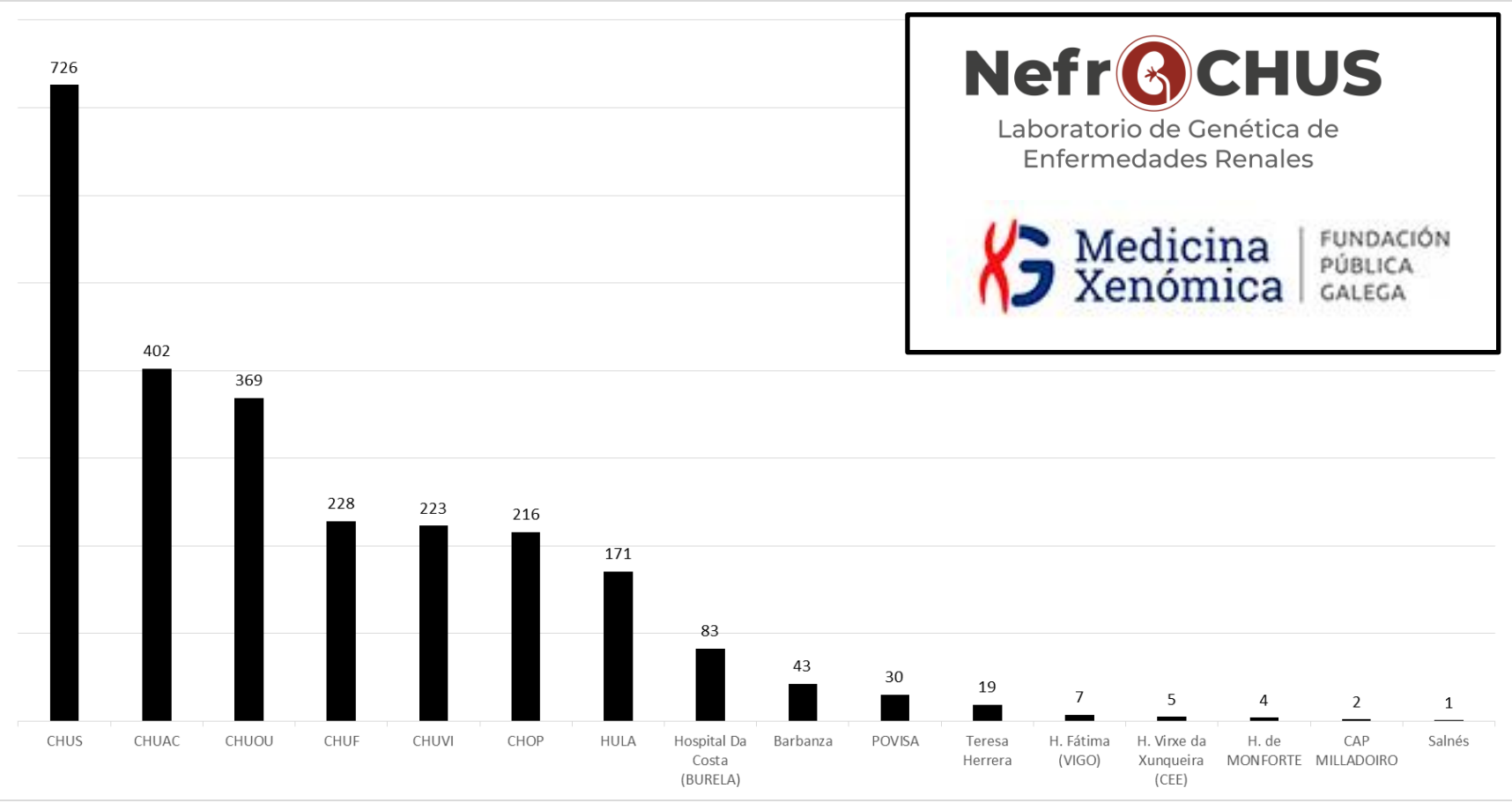
- New Diagnostic Tools:
i) **Tub*Analyser®*** *(Under Construction).*
ii) 3D-Bioprinting of pseudonephrons and pseudoarteries (Calviño et al, Submitted)

- New Therapies:
i) Future research

- New Proyects/New PIs:
i) Future research

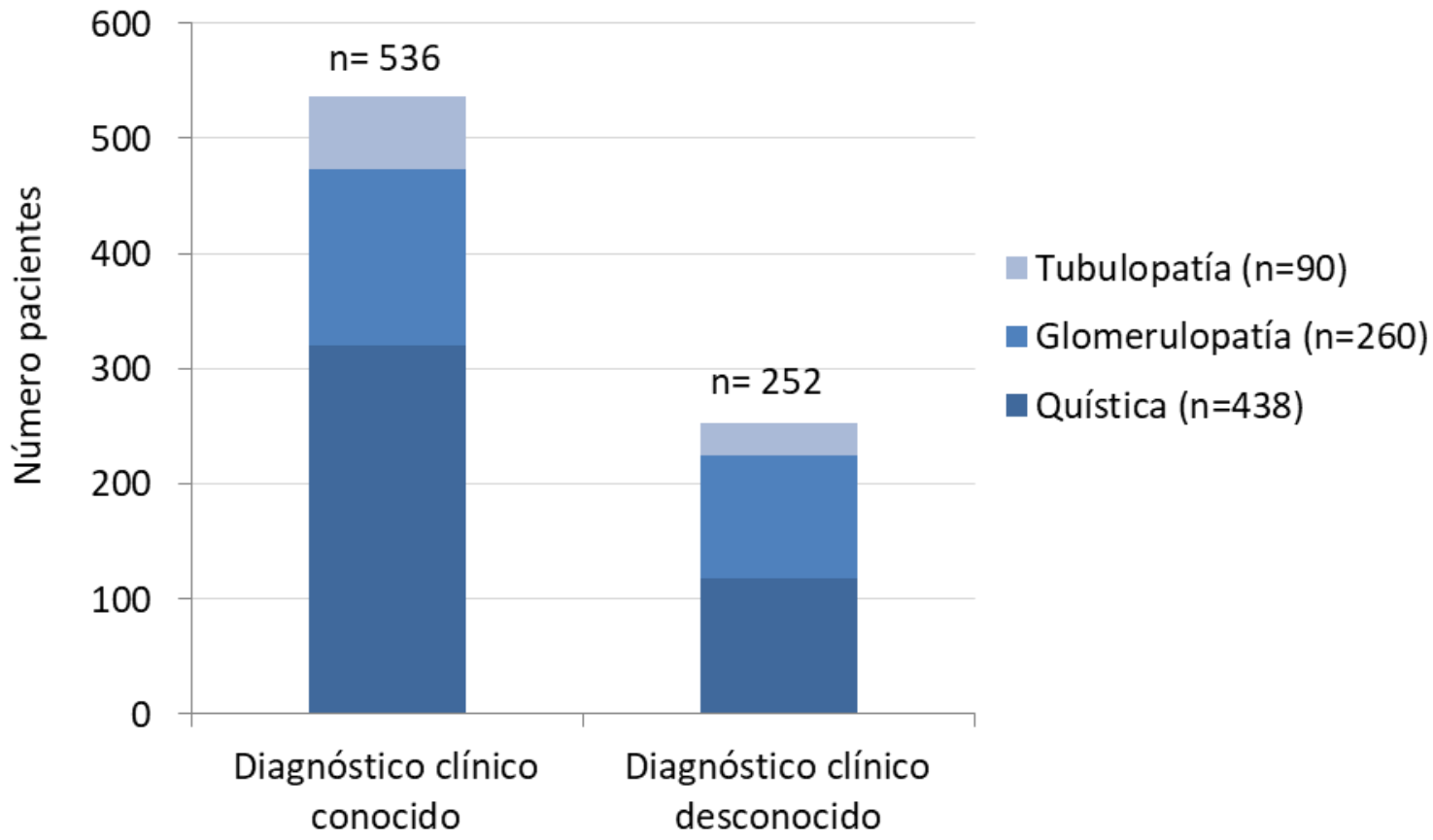
Pacientes por Hospital

2015-2022

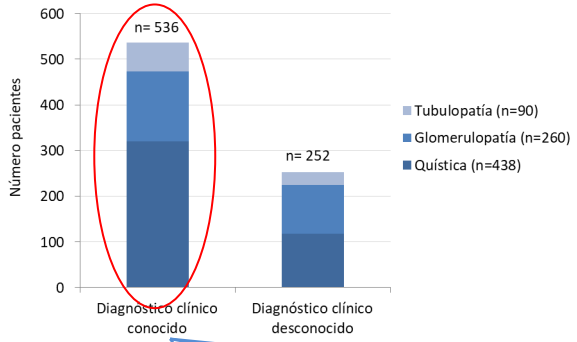


Galicia (n=2529)
Resto de España (n=1104)

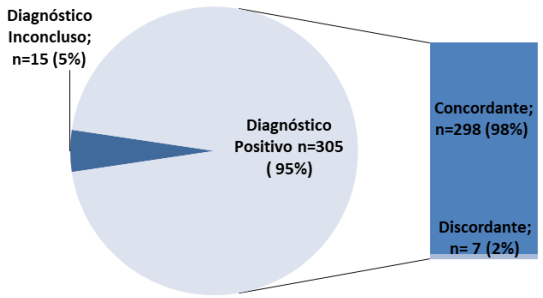
Situaciones que nos encontramos



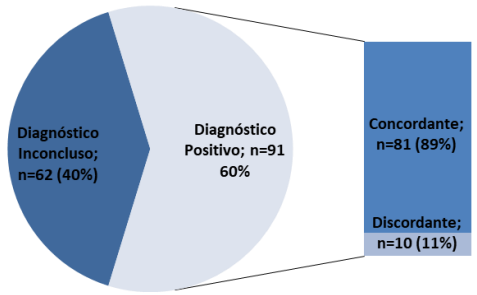
Situaciones que nos encontramos



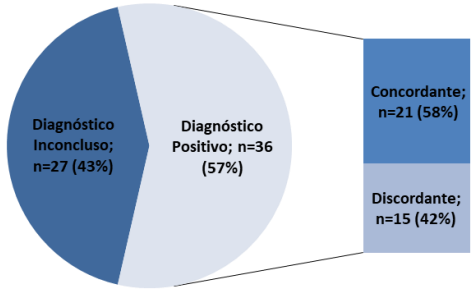
Enfermedad Quística



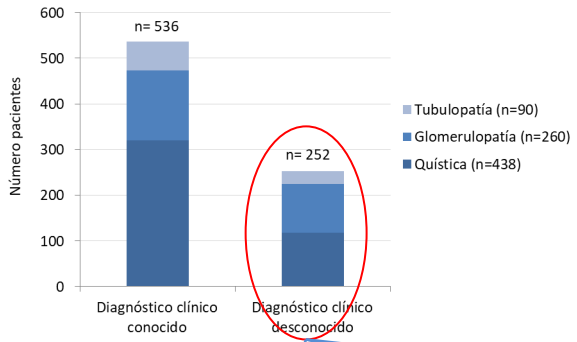
Enfermedad Glomerular



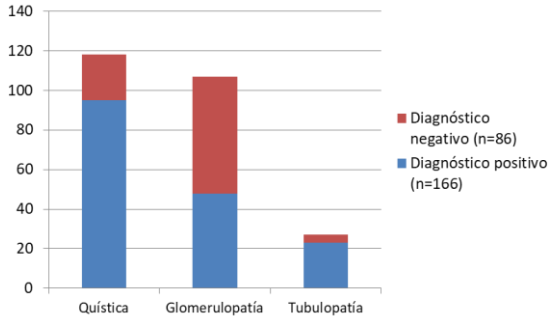
Enfermedad Tubular



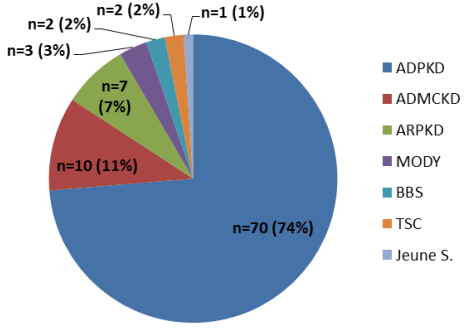
Situaciones que nos encontramos



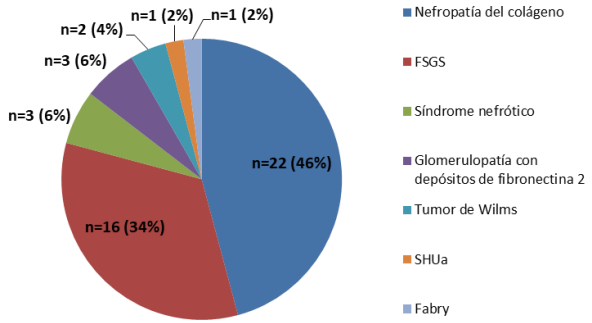
Concluimos en un alto porcentaje



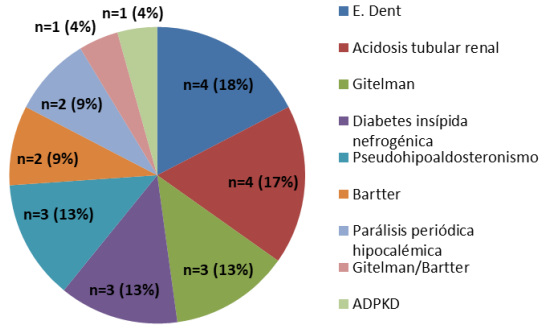
Enfermedad Quística



Enfermedad Glomerular



Enfermedad Tubular

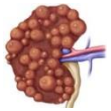


Abordaje de la Enfermedad Renal Hereditaria

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*

Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*

Period 2012-2015



(2) *Cystic Disorders*

AE1.0 GalCyst *(ISCIII PI15/01467)*

Year:*2015* **PI:** *Miguel A García González*

(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:

i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:

i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*

ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*

iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:

i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*

ii) ***MMT*** *(Adrián Cordido, Under Submission).*

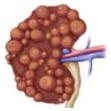
- New Proyects/New PIs:

i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:** Noa Carrera and Cándido Díaz (AES 21, ISCiii).* **(???)**

ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

Abordaje de la Enfermedad Renal Hereditaria

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*
Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*
Period 2012-2015



(2) *Cystic Disorders*

AE1.0 GalCyst *(ISCIII_PI15/01467)*
Year:*2015* **PI:** *Miguel A García González*
(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:
i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:
i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*
ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*
iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:
i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*
ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:
i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:*** Noa Carrera and Cándido Díaz (AES 21, ISCiii). **(???)**
ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

PKD is a frequent disease

ADPKD (1/600)
- **PKD1** – **GANAb (2017)**
- **PKD2** – **DNAJB11 (2018)**

ARPKD (1/10000)
- **PKHD1** – **DZIP1L (2017)**

Atypical PKD
- **Bardet Biedl (BBS1-12)**
- **Nephronophthisis (NPHP1-5)**
- **tuberous sclerosis (TSC1,2)**
- **Medullary Cystic (MCKD1,2)**
- **Oro-facial digital syndrome (OFD1)**
- **…. From 56 genes (2016) to 99 (2022)**
- **Atypical forms of ADPKD and ARPKD (mutation doses), Mosaicism and GENETIC INTERACTIONS!!!!!**

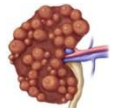
COL4A3/COL4A4 (2020) **IFT140 (2022)**

Abordaje de la Enfermedad Renal Hereditaria

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*

Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*

Period 2012-2015



(2) *Cystic Disorders*

AE1.0_GalCyst *(ISCIII_PI15/01467)*

Year:*2015* **PI:** *Miguel A García González*

(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:

i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:

i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*

ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*

iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:

i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*

ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:

i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:** Noa Carrera and Cándido Díaz (AES 21, ISCiii).* **(???)**

ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

Strategy to diagnose all hereditary kidney disease

Coverage Panels *vs* Coverage Exomes

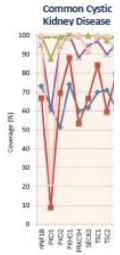
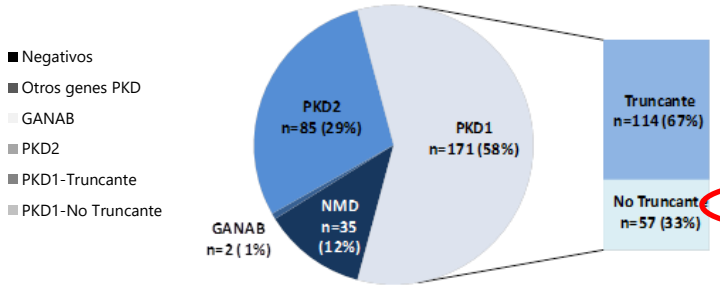


Figure 3. Percentage of coverage obtained with the panels (common cystic kidney disease (n=133); common, rare and ultra-rare cystic kidney disease (n=41), glomerular disease (n=71) and tubulo/interstitial disease (n=52) *versus* percentage of coverage obtained with NGS current technologies, such as Ampliseq (n=2), SureSelect (n=115) and Focused Exomes (n=2).



Cohorte del Proyecto AEG1.0_PQR

Tasas de mutagenicidad:

PKD1: 58.36%

PKD2: 29.01%

GANAB: 0.68%

NMD: 11.95%

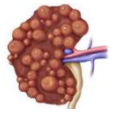
Situaciones que nos encontramos

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*

Project: *ISCIII_PI11/00690* . **Year:**2011 **PI:** *Miguel A García González*

Period 2012-2015

NEPHRO GENETOR®



Profundizamos en las NMDs (inconclusas/no-filiadas)?

(2) *Cystic Disorders*

AE1.0 GalCyst *(ISCIII PI15/01467)*

Year:2015 **PI:** *Miguel A García González*

(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:

i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:

i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*

ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*

iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:

i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*

ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:

i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:** Noa Carrera and Cándido Díaz (AES 21, ISCiii).* **(???)**

ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

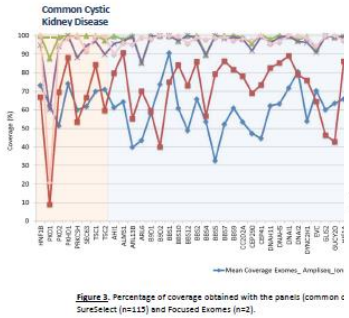
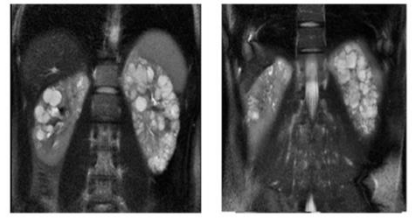


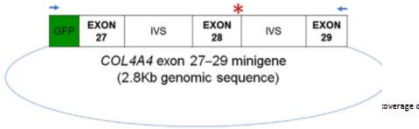
Figure 3. Percentage of coverage obtained with the panels (common c SureSelect (n=115) and Focused Exomes (n=2).

Collagen IV Gene Mutations in Adults With Bilateral Renal Cysts and CKD

Check for updates

Ashima Gulati[1], Angel M. Sevillano[2], Manuel Praga[2,3], Eduardo Gutierrez[2], Ignacio Alba[4], Neera K. Dahl[1], Whitney Besse[1], Jungmin Choi[5] and Stefan Somlo[1,5]





overage obtained with NGS current technologies, such as Ampliseq (n=2).

Variante asociado a quistes

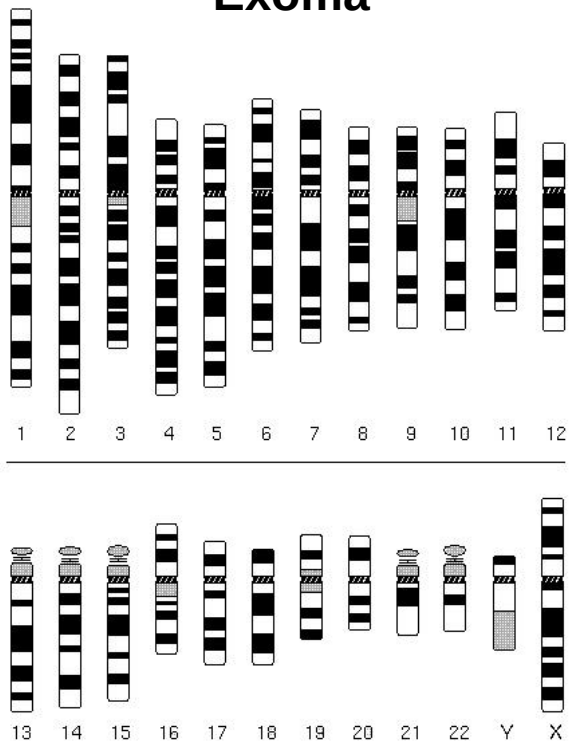
Situaciones que nos encontramos

Profundizamos en las NMDs (inconclusas/no-filiadas)?

INVESTIGACION (CONTACTANOS!!!)

Exoma

- \

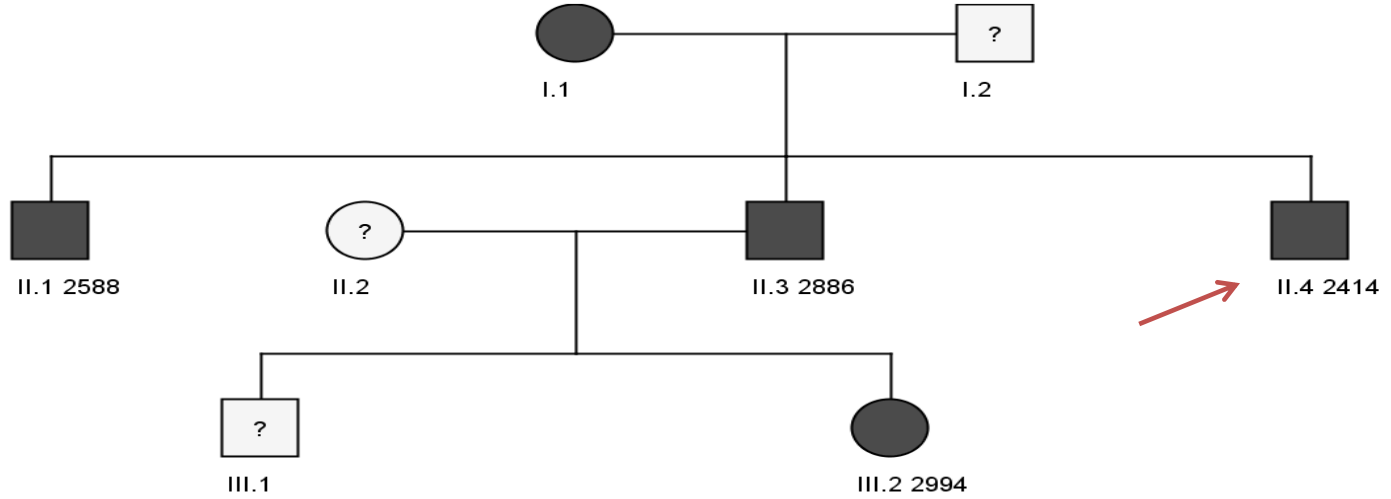


:s identificados

- **Análisis de genes renales (los 499 genes)**
- **Re- analisis: Nuevos genes (XXX genes)**
- **Búsqueda de Nuevos Genes**

CASO 1:

Poliquistosis Hepatorenal con Microhematuria y Proteinuria



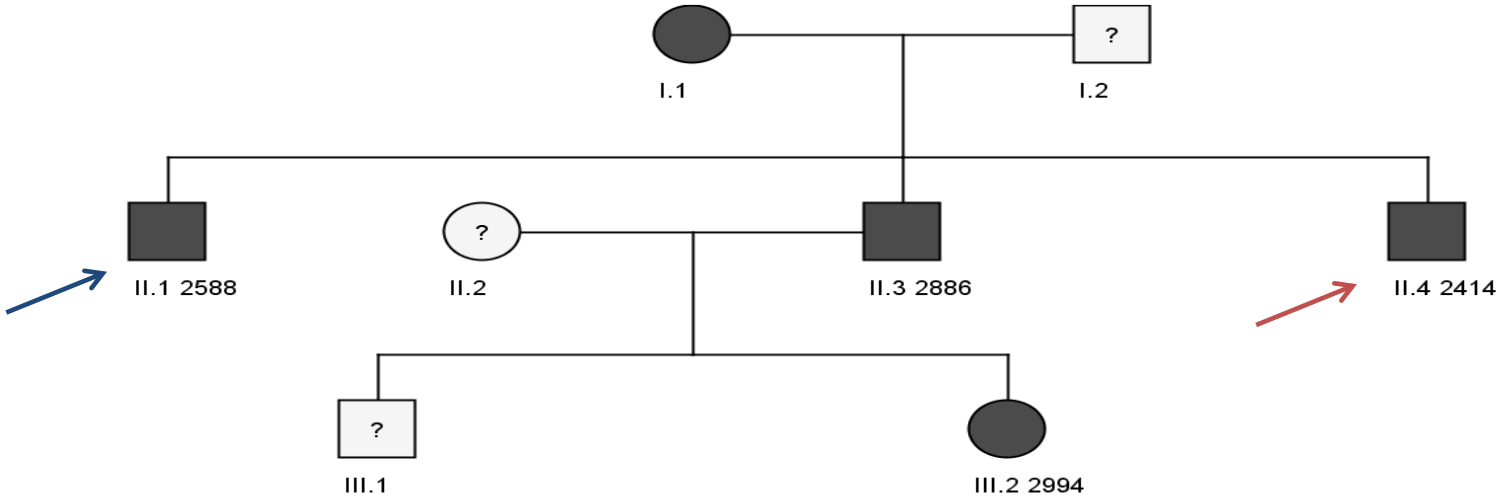
Dra. Fernanda Arrojo
CHU-Ferrol

Familia	Miembro	Edad diagnóstico	Quistes renales	Quistes hepáticos	Microhematuria	Proteinuria	Función renal	Mutación
PKD_CHUF338	2414 (V)	27 años	1 simple	+	+	Nefrótica	Normal	

Negativo para todas las enfermedades quísticas comunes, raras y ultrarraras

CASO 1:

Poliquistosis Hepatorenal con Microhematuria y Proteinuria



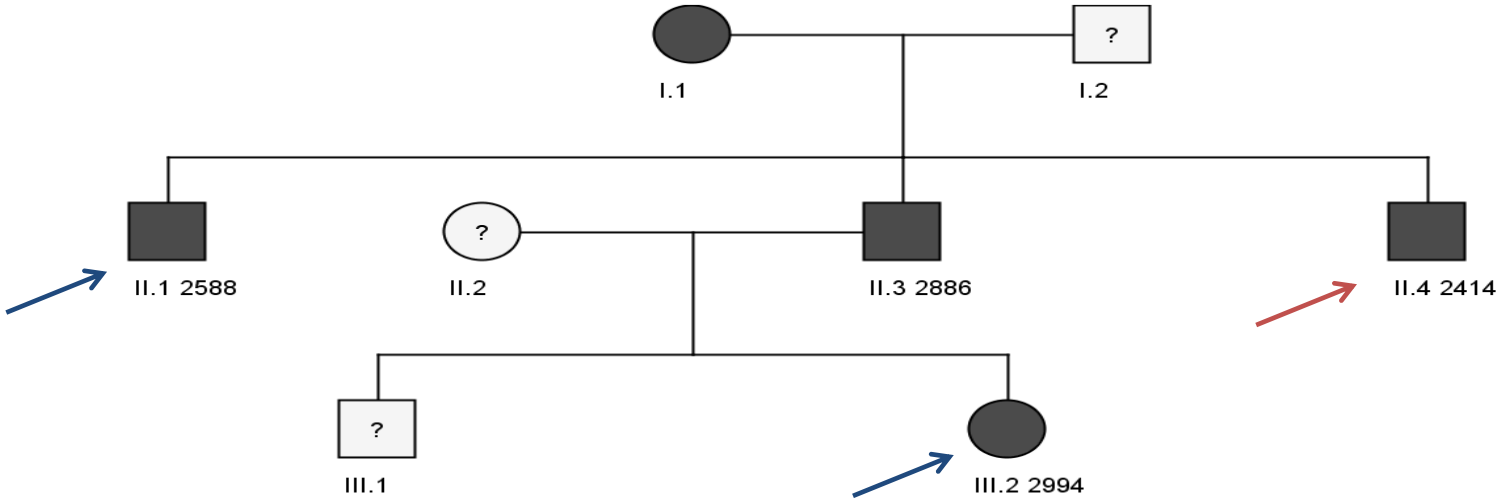
Dr. Manuel Fida
CHU-Santiago

Familia	Miembro	Edad diagnóstico	Quistes renales	Quistes hepáticos	Microhematuria	Proteinuria	Función renal	Mutación
PKD_CHUF338	2588 (V)	33 años	1 simple	1	+	Microalb.	Normal	
	2414 (V)	27 años	1 simple	+	+	Nefrótica	Normal	

Negativo para todas las enfermedades glomerulares

CASO 1:

Poliquistosis Hepatorenal con Microhematuria y Proteinuria



X

Dra. Adriana Torrado
CHU-Ferrol

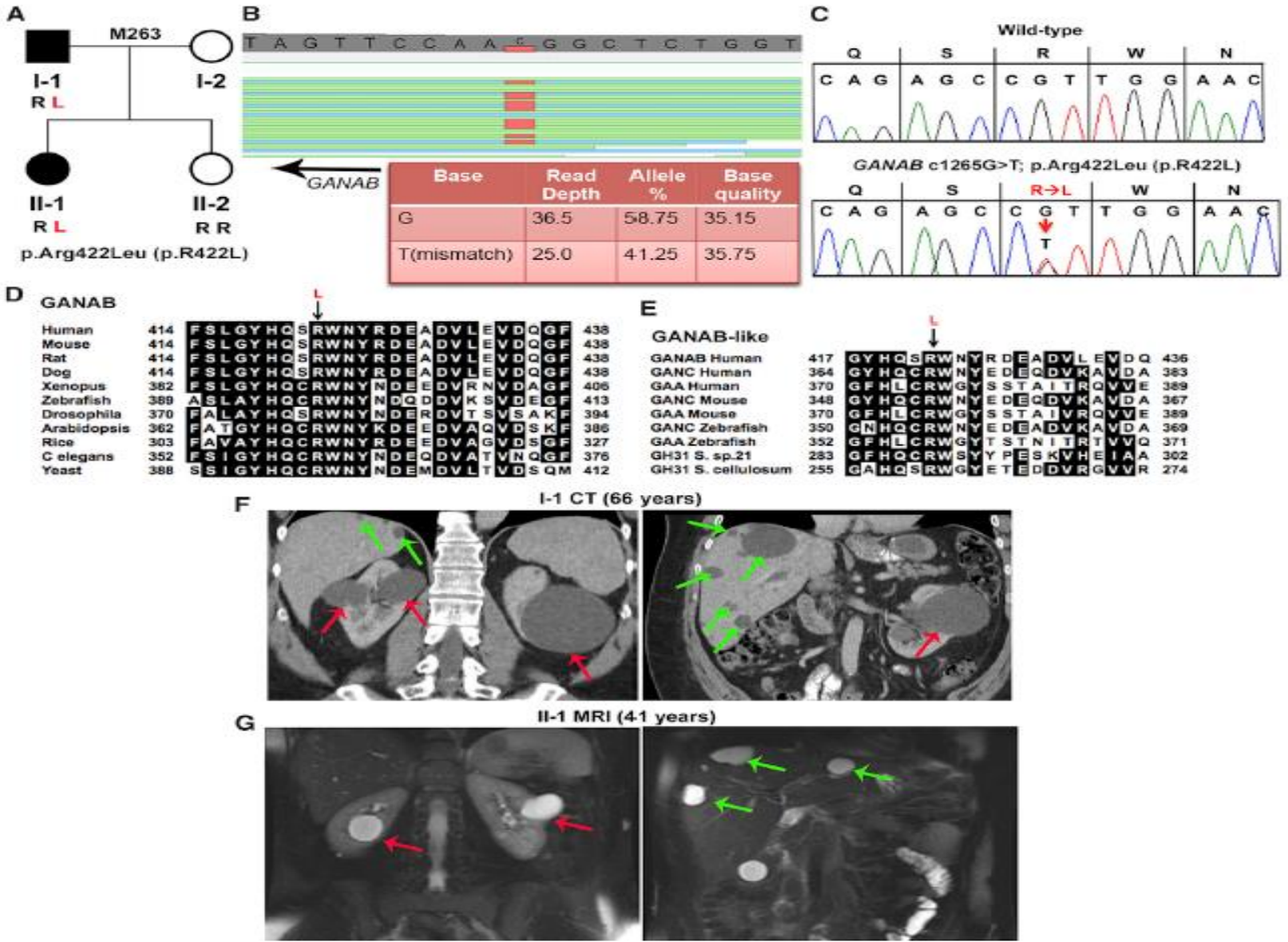
Am J Hum Genet. 2016 Jun 2;98(6):1193-1207. doi: 10.1016/j.ajhg.2016.05.004.

Mutations in GANAB, Encoding the Glucosidase IIα Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease.

Porath B[1], Gainullin VG[1], Cornec-Le Gall E[2], Dillinger EK[3], Heyer CM[1], Hopp K[4], Edwards ME[1], Madsen CD[1], Mauritz SR[1], Banks CJ[1], Baheti S[5], Reddy B[6], Herrero JI[7], Bañales JM[8], Hogan MC[1], Tasic V[9], Watnick TJ[10], Chapman AB[6], Vigneau C[11], Lavainne F[12], Audrézet MP[13], Ferec C[13], Le Meur Y[14], Torres VE[1]; Genkyst Study Group, HALT Progression of Polycystic Kidney Disease Group; Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, Harris PC[15].

Primer caso Gallego (Español?) con Poliquistosis Tipo-III asociado a Microalbuminuria y Proteinuria

ADPKD-atípica: GANAB

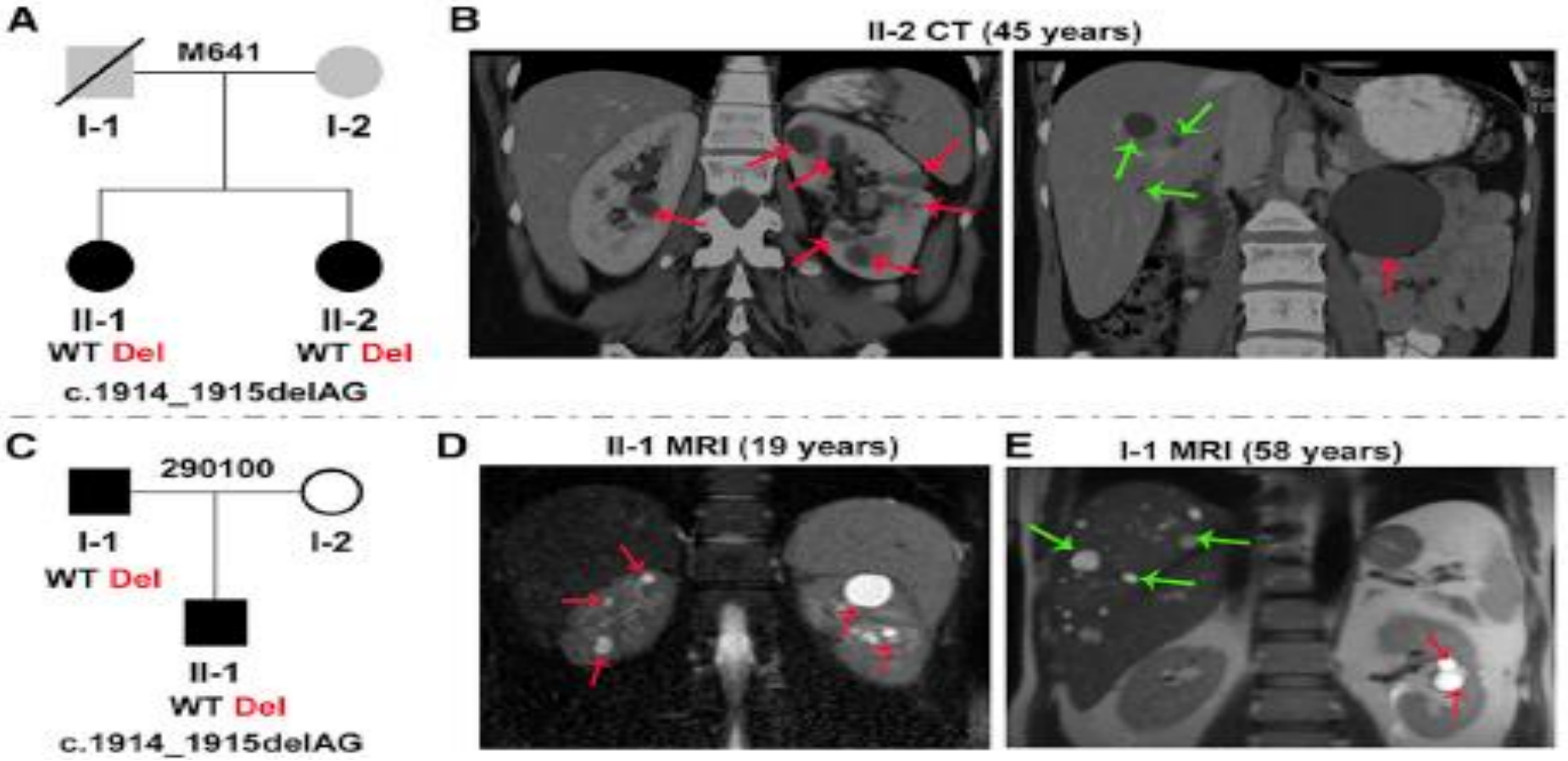


ADPKD-atípica: GANAB

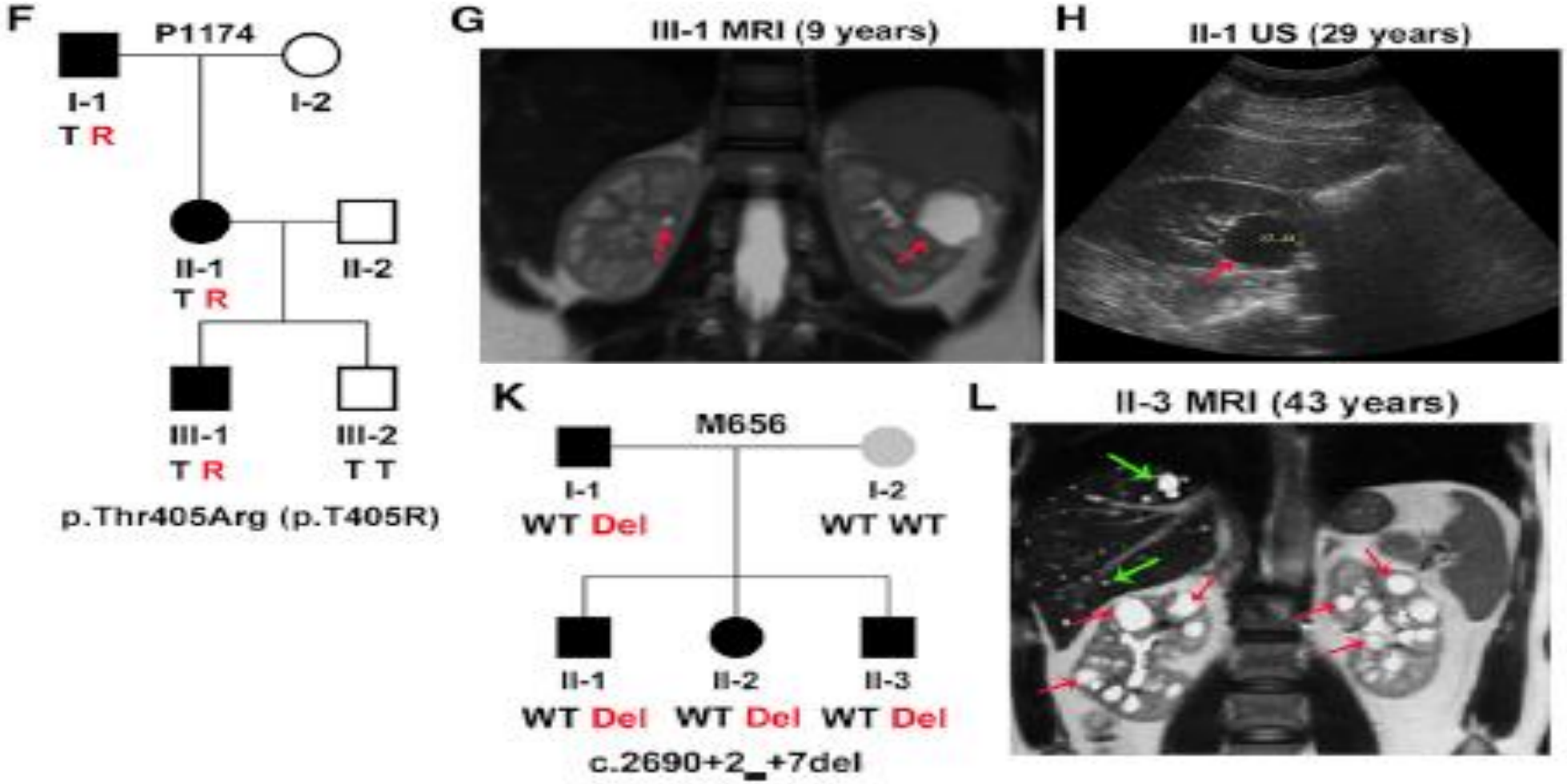
Table 1. Clinical Presentation of Kidney and Liver Disease in the 20 Affected Individuals from Nine Families with *GANAB* Mutations

						Radiologic Presentation							
						Kidneys					Liver		
Family	*GANAB* Mutation	Subject	Sex	eGFR[a] (Age in Years)	HBP (Age in Years[b])	Type	Age[c]	Cysts	Volume[d]	Figure	Cysts	Volume[e]	Figure
M263[f]	c.1265G>T (p.Arg422Leu)	I-1	M	78 (66)	N (67)	CT	66	~10 bilateral cysts (largest 11 cm)	302[g]	1F	>50 scattered cysts (largest 6 cm)	1,226	1F
		II-1	F	91 (42)	N (43)	MRI	41	~10 bilateral cysts (largest 3 cm)	211	1G	>20 scattered cysts (largest 3 cm)	835	1G
M641	c.1914_1915delAG (p.Asp640Glnfs*77)	II-1	F	86 (51)	Y (40)	CT	55	~15 bilateral cysts (largest 10 cm)	822[g]	S3A	no liver cysts detected	1,505[h]	S3A
		II-2	F	104 (46)	N (50)	CT	45	~10 bilateral cysts (largest 6 cm)	318[g]	2B	~20 scattered cysts (largest 2 cm)	764	2B
290100	c.1914_1915delAG (p.Asp640Glnfs*77)	I-1	M	78 (65)	N (65)	MRI	58	~8 bilateral cysts (largest 2 cm)	227	2E	>30 scattered cysts (largest 3 cm)	1,255	2E
		II-1	M	87 (25)	Y (13)	MRI	24	~12 bilateral cysts (largest 2.5 cm)	259	2D	none	832	2D
P1174	c.1214C>G (p.Thr405Arg)	I-1	M	NA[i]	N (61)	US	55	3 cysts in the left kidney	NE	S3B	1 cyst (1.5 cm)	NE	–
		II-1	F	NA[i]	N (35)	US	29	2 cysts in the right kidney	NE	2H	NA	NA	–
		III-1	M	122 (9)	N (9)	MRI	9	~5 bilateral cysts (largest 2 cm)	116	2G	none	492	–
M656	c.2690+2_+7del	I-1	M	NA[i]	Y (55)	CT[j]	67	multiple small cysts	NE	S3C	none	NE	S3C
		II-1	M	84 (39)	N (39)	US	44	multiple cysts reported	NA	–	multiple cysts reported	NA	–
		II-2	F	77 (50)	N (50)	US	52	~5–10 bilateral cysts (largest 2 cm)	NE	S3D	>20 scattered cysts (largest 5 cm)	NE	S3D
		II-3	M	95 (49)	Y (35)	MRI	43	>30 bilateral cysts (largest 3 cm)	SE	2L	>20 scattered cysts (largest 1 cm)	NE	2L
PK20016	c.39−1G>C	II-1	M	90 (53)	Y (45)	CT[j]	52	~20 bilateral cysts (largest 10 cm)	665[g]	3B	~20 scattered cysts (largest 2 cm)	1,449[h]	3B
PK20017	c.2176C>T (p.Arg726*)	II-1	F	77 (78)	Y (53)	US	78	~40 bilateral cysts (largest 3 cm)	NE	3D	~20 scattered cysts (largest 1.5 cm)	NA	3D
P1073	c.2515C>T (p.Arg839Trp)	I-2	F	NA	NA	US	(78)	unknown	NA	–	multiple cysts reported	NA	–
		II-1	F	86 (50)	N	CT[j]	43	~8 bilateral cysts (largest 1 cm)	196	3F	severe PLD, transplant at 43 years	4,641[h]	3F
		II-2	M	NA	NA	US	(44)	unknown	NA	–	multiple cysts reported	NA	–

ADPKD-atípica: GANAB



ADPKD-atípica: GANAB



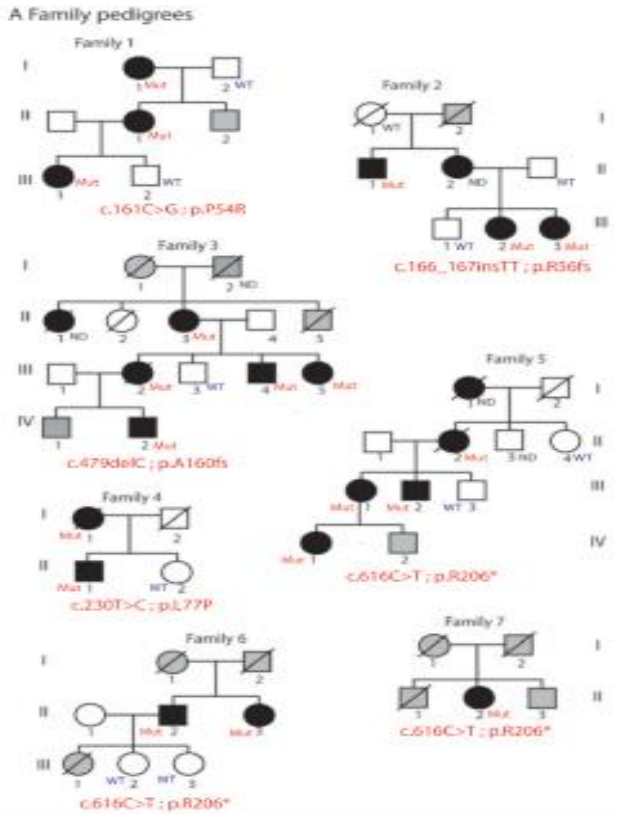
ADPKD-atípica: DNAJB11

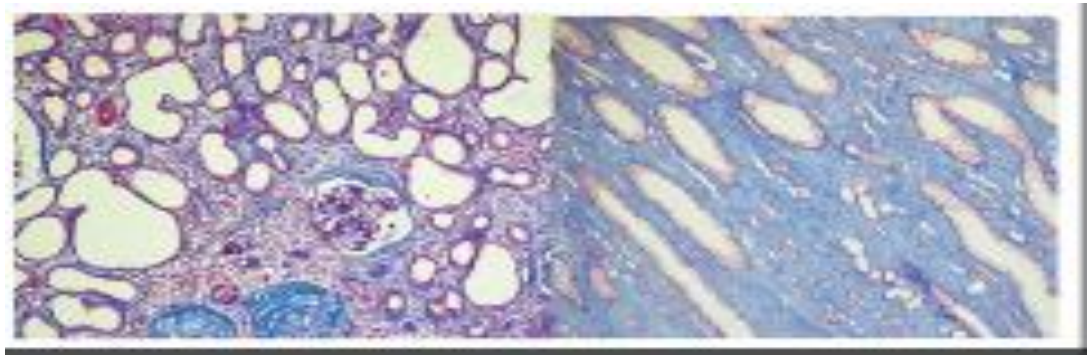
ARTICLE

Monoallelic Mutations to *DNAJB11* Cause Atypical Autosomal-Dominant Polycystic Kidney Disease

Emilie Cornec-Le Gall,[1,4,5] Rory J. Olson,[2] Whitney Besse,[6] Christina M. Heyer,[1] Vladimir G. Gainullin,[1] Jessica M. Smith,[1] Marie-Pierre Audrézet,[5] Katharina Hopp,[7] Binu Porath,[1] Beili Shi,[8] Saurabh Baheti,[3] Sarah R. Senum,[1] Jennifer Arroyo,[1] Charles D. Madsen,[1] Claude Férec,[5] Dominique Joly,[10] François Jouret,[11] Oussamah Fikri-Benbrahim,[12] Christophe Charasse,[13] Jean-Marie Coulibaly,[13] Alan S. Yu,[14] Korosh Khalili,[9] York Pei,[8] Stefan Somlo,[6] Yannick Le Meur,[4] Vicente E. Torres,[1] Genkyst Study Group, the HALT Progression of Polycystic Kidney Disease Group, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, and Peter C. Harris[1,2,*]

ADPKD-atípica: DNAJB11



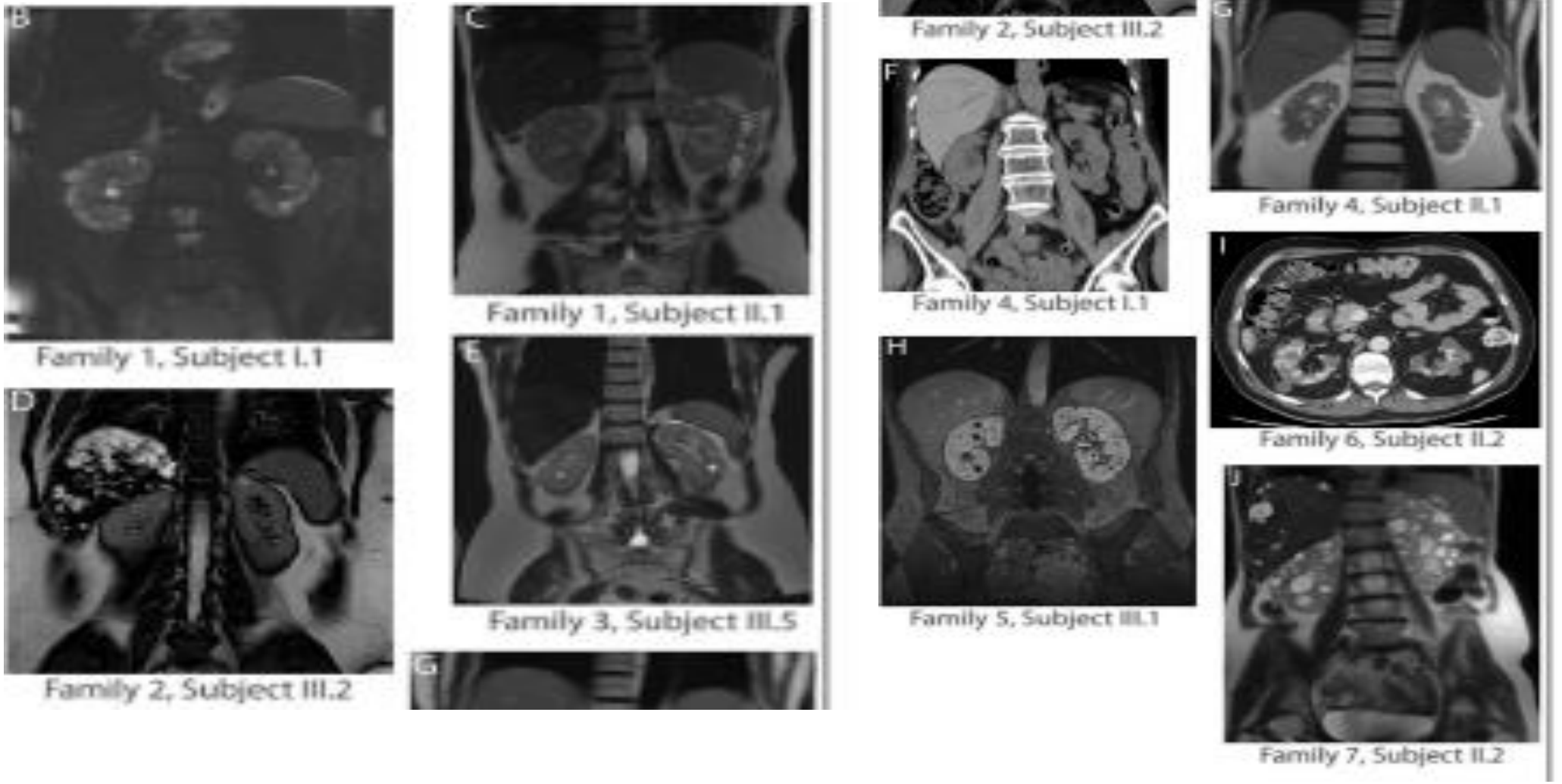


ADPKD-atípica: DNAJB11

Table 1. Clinical Presentation and Pathogenic Variants in the 23 Affected Individuals from Seven DNAJB11-Affected Families

Family	Pathogenic Variant	Subject	Sex	eGFR[a] (age) or ESRD (age)	Context of Diagnosis (age)	HBP (age)[b]	Morphology of the Kidneys					Liver Cysts (number)	Other Significant Conditions (age)
							Type	Age	Description of the Cysts	Kidney Length, (TKVml)[c]	Figure		
1[d]	c.161C>G (p.Pro54Arg)	I.1	F	28 (79)	renal insufficiency (78)	yes (60)	MRI	80	multiple bilateral small cysts (mostly < 1 cm, largest 2 cm)	R:9.2, L:10 (323)	1B	yes (3)	epilepsy (10)
		II.1	F	96 (45)	incidental (43)	no (45)	MRI	44	multiple bilateral small cysts (largest 1.3 cm)	R:9.5, L:10 (335)	1C	yes (10)	metanephric adenoma, partial nephrectomy (43)
		III.1	F	93 (19)	familial study (19)	no (19)	MRI	19	no renal cysts	R:9.7, L:10.0 (277)	NA	no	none
2[d]	c.166_167insTT (p.Arg56fs)	II.1	M	54 (66)	familial study (na)	yes (56)	MRI	53	multiple bilateral small cysts (largest 0.8 cm)	NA	NA	no	parathyroid adenoma, hypertrophic cardiomyopathy
		II.2[e]	F	84 (76)	familial study (61)	yes (~50)	CT	70	small cortical cysts in the left kidney	R: 9.5, L: 9.6	S1A	yes (> 50)	Parkinson disease (60)
		III.2	F	101 (45)	incidental (31)	no (45)	MRI	38	multiple bilateral small cysts	R:11.5, L:12	1D	yes (> 50)	breast cancer (36)
		III.3	F	77 (56)	familial study (42)	yes (~50)	US	42	three parapelvic cysts on left kidney (largest 1 cm), no cysts detected on left kidney	R:9.7, L:10.6	NA	yes (> 20)	none
3	c.479delC (p.Ala160fs)	II.1[e]	F	ESRD (75)	renal insufficiency (~65)	NA	NA	NA	NA	NA	NA	NA	none
		II.3	F	ESRD (89)	NA	NA	CT[d]	91	atrophic kidneys with multiple cysts	R:6; L:6	S1B	No	none
		III.2	F	39 (59)	incidental (57)	yes (51)	US	57	multiple bilateral small cysts (largest 1.2 cm)	R:12, L:10	S1C	yes (na)	glioblastoma (59)
		III.4	M	85 (66)	familial study (66)	no (66)	CT	62	multiple bilateral small cysts (largest 1.1 cm)	R:11, L:11 (483)	S1D	no	kidney stones (52)
		III.5	F	82 (57)	familial study (57)	no (57)	MRI	57	multiple bilateral small cysts	R:11, L:11 (300)	1E	no	none
		IV.2	M	97 (36)	familial study (35)	no (35)	MRI	36	seven bilateral small cysts (largest 0.3 cm)	R:10, L:9 (299)	S1E	yes (9)	none

ADPKD-atípica: DNAJB11



ADPKD-atípica: DZIP1L

ARTICLES

nature genetics

Mutations in *DZIP1L*, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease

Hao Lu[1,20], Maria C Rondón Galeano[2,20], Elisabeth Ott[3,20], Geraldine Kaeslin[2], P Jaya Kausalya[1], Carina Kramer[3], Nadina Ortiz-Brüchle[4], Nadescha Hilger[4], Vicki Metzis[2,19], Milan Hiersche[5], Shang Yew Tay[1], Robert Tunningley[6], Shubha Vij[1,19], Andrew D Courtney[2], Belinda Whittle[6], Elke Wühl[7], Udo Vester[8], Björn Hartleben[9], Steffen Neuber[5], Valeska Frank[5], Melissa H Little[2,19], Daniel Epting[3], Peter Papathanasiou[6,19], Andrew C Perkins[2,10], Graham D Wright[11], Walter Hunziker[1,12,13], Heon Yung Gee[14,15], Edgar A Otto[16], Klaus Zerres[4], Friedhelm Hildebrandt[14], Sudipto Roy[1,17,18], Carol Wicking[2,21] & Carsten Bergmann[3–5,21]

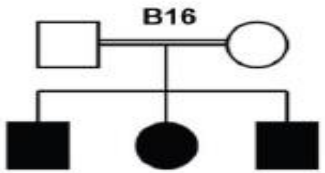
ADPKD-atípica: DZIP1L

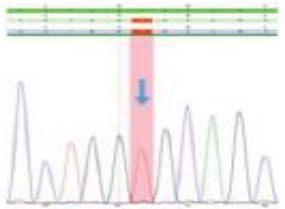
Table 1 *DZIP1L* **mutations in patients with ARPKD**

Family Individual	Sex	Ancestry	Mutation	Protein change	Exon (state)	Continuously conserved to	Polyphen-2/ MutTast/SIFT	ExAC	Parental consanguinity	Phenotype
B16-1	Male	Turkish	c.269C>T	p.Ala90Val	2 (hom)	*Xenopus tropicalis*	0.99/DC/dam	0/5/116158	Yes	ARPKD, enlarged polycystic kidneys with increased echogenicity (kidney volumes >97th p), diminished CMD, pepper-salt pattern. Arterial hypertension since early toddler age. ESRD at age 18; RTX at age 26.
B16-2	Female	Turkish	c.269C>T	p.Ala90Val	2 (hom)	*Xenopus tropicalis*	0.99/DC/dam	0/5/116158	Yes	ARPKD, kidney morphology like that of elder brother, with polycystic kidneys with increased echogenicity and volumes constantly >97th p (at age 11, left kidney, 175 ml and right kidney, 190 ml; at age 20, left kidney, 225 ml and right kidney, 217 ml). Arterial hypertension since early toddler age. ESRD at age 26; RTX at age 27.
B16-3	Male	Turkish	c.269C>T	p.Ala90Val	2 (hom)	*Xenopus tropicalis*	0.99/DC/dam	0/5/116158	Yes	Characteristic ARPKD phenotype with hyperechogenic kidneys with lack of CMD. Kidney volumes at age 3, left, 75th p and right, 97th p; at age 7, left, 97 ml (90th p) and right, 112 ml (97th p); at age 14, left, 167 ml and right, 240 ml (both >97th p). Hepatosplenomegaly. Arterial hypertension since early toddler age. Normal kidney function at age 15 (serum creatinine 0.9 mg/dl; creatinine clearance, 112 ml/min/1.73 m^2).
A3533-1	Female	Arab	c.273G>C	p.Gln91His	2 (hom)	*Danio rerio*	1.00/DC/dam	0/0/116158	Yes	ARPKD, enlarged polycystic kidneys with increased echogenicity. Arterial hypertension first diagnosed at age 8. ESRD and RTX at age 12.
A3533-2	Female	Arab	c.273G>C	p.Gln91His	2 (hom)	*Danio rerio*	1.00/DC/dam	0/0/116158	Yes	ARPKD, enlarged polycystic kidneys with increased echogenicity. Arterial hypertension first diagnosed at age 3. Kidney function at age 9: serum creatinine, 0.8 mg/dl; creatinine clearance, 94 ml/min/1.73 m^2; slightly increased cystatin C, 1.4 mg/l; cystatin-GFR, 67 ml/min/1.73 m^2.
B155	Male	Palestinian	c.463C>T	p.Gln155*	2 (hom)	*Danio rerio*	NA/DC/NA	0/0/116158	Yes	First diagnosed with arterial hypertension and massively symmetrically enlarged kidneys with hyperechogenicity with poor CMD at 8 months of age. ESRD at age 18; RTX at age 20.
B8031	Female	Egyptian	c.1061_ 1062del	p.Glu354Alafs*39	7 (hom)	*Danio rerio*	NA/NA/NA	0/0/116158	Yes	Characteristic ARPKD phenotype with bilaterally enlarged kidneys with increased echogenicity, twinkling phenomenon/calcification spots, and diminished CMD. Normal renal function at age 13. Kidney volumes 90th–97th p (age 8, 146 ml; age 10, 163 ml; age 13, 195 ml).

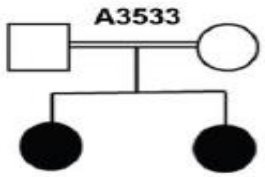
DZIP1L cDNA mutations are numbered according to human cDNA reference sequence NM_173543.2. +1 corresponds to the A of the ATG start codon in exon 2. ARPKD, autosomal recessive polycystic kidney disease; CMD, corticomedullary differentiation; het, heterozygous; hom, homozygous; DC, disease causing; ExAC, Exome Aggregation Consortium; MutTast, Mutation Taster; SIFT, sorting intolerant from tolerant; dam, damaging; ESRD, end-stage renal disease; NA, not applicable; RTX, renal transplantation; TOP, termination of pregnancy; p, percentile. 'Continuously conserved' denotes evolutionary conservation of affected amino acids.

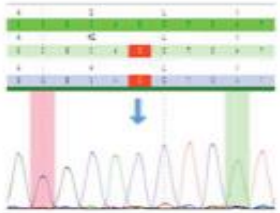
ADPKD-atípica: DZIP1L



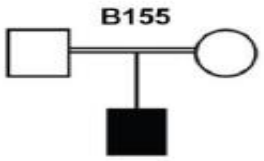


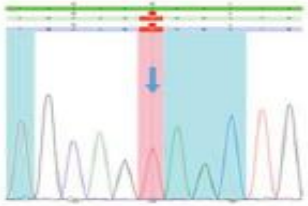
c.269C>T (p.Ala90Val) (P)
c.269C>T (p.Ala90Val) (M)



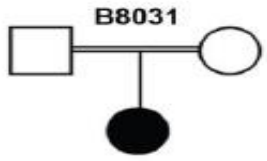


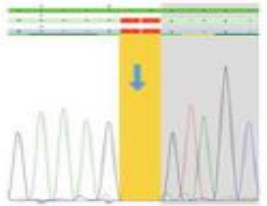
c.273G>C (p.Gln91His) (P)
c.273G>C (p.Gln91His) (M)



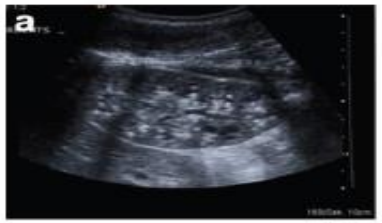


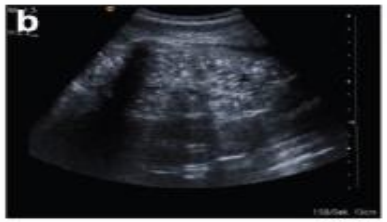
c.463C>T (p.Gln155*) (P)
c.463C>T (p.Gln155*) (M)

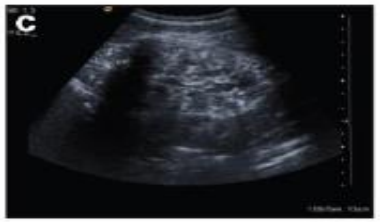


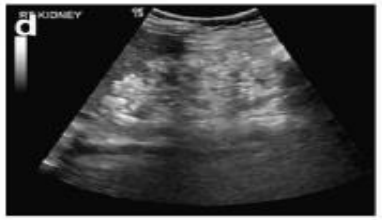


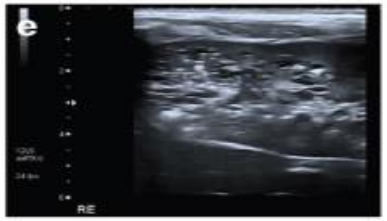
c.1061_1062del (p.Glu354Alafs*39) (P)
c.1061_1062del (p.Glu354Alafs*39) (M)

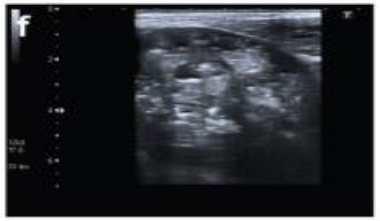


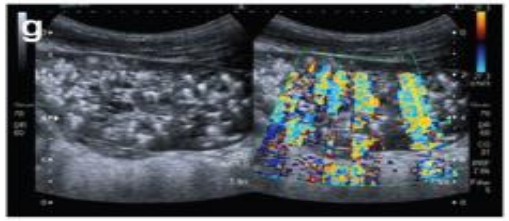












Mosaicismo germinal

NefroCHUS
Laboratorio de Genética de las Enfermedades Renales

CLINICAL RESEARCH www.jasn.org

Polycystic Kidney Disease without an Apparent Family History

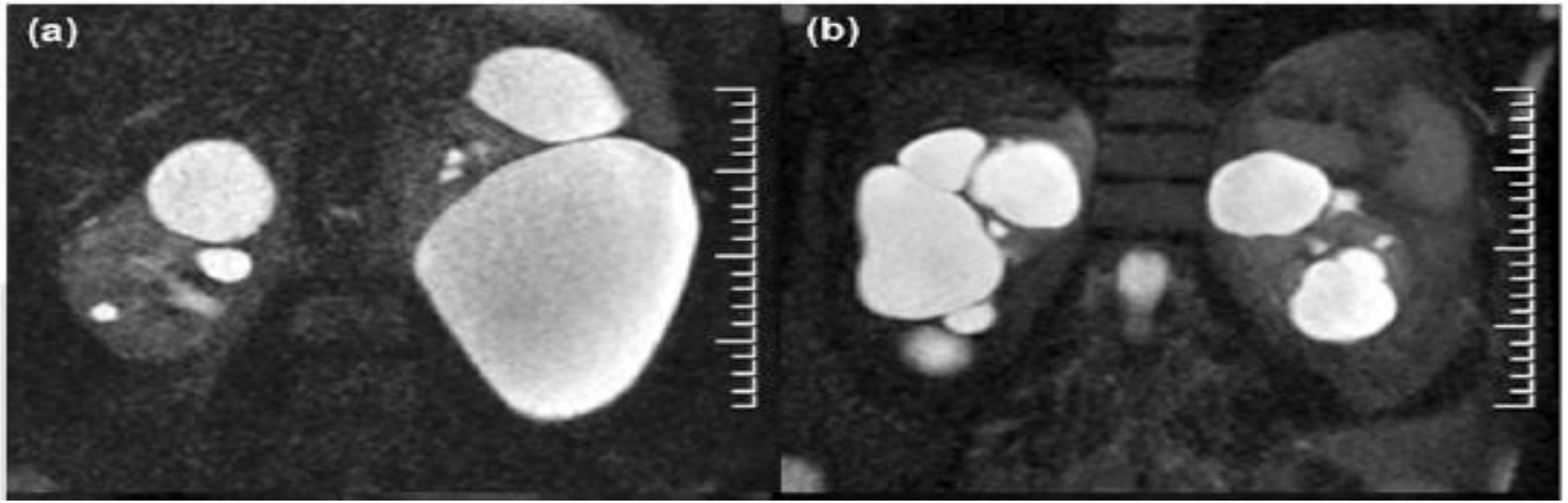
Ioan-Andrei Iliuta,* Vinusha Kalatharan,* Kairong Wang,* Emilie Cornec-Le Gall,† John Conklin,‡ Marina Pourafkari,‡ Ryan Ting,* Chen Chen,* Alessia C. Borgo,* Ning He,* Xuewen Song,* Christina M. Heyer,† Sarah R. Senum,† Young-Hwan Hwang,§ Andrew D. Paterson,‖ Peter C. Harris,† Korosh Khalili,‡ and York Pei*

*Division of Nephrology and ‡Department of Medical Imaging, University Health Network and University of Toronto, Toronto, Ontario, Canada; †Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota; §Truewords Dialysis Clinic, Incheon, South Korea; and ‖Program in Genetics and Genome Biology, Hospital for Sick Children, Toronto, Ontario, Canada

Mosaicismo germinal

NefroCHUS
Laboratorio de Genética de las Enfermedades Renales

Pacientes Sin Mutación Detectada Con Enfermedad De Novo Presentaron PKD Focal



Mosaicismo germinal

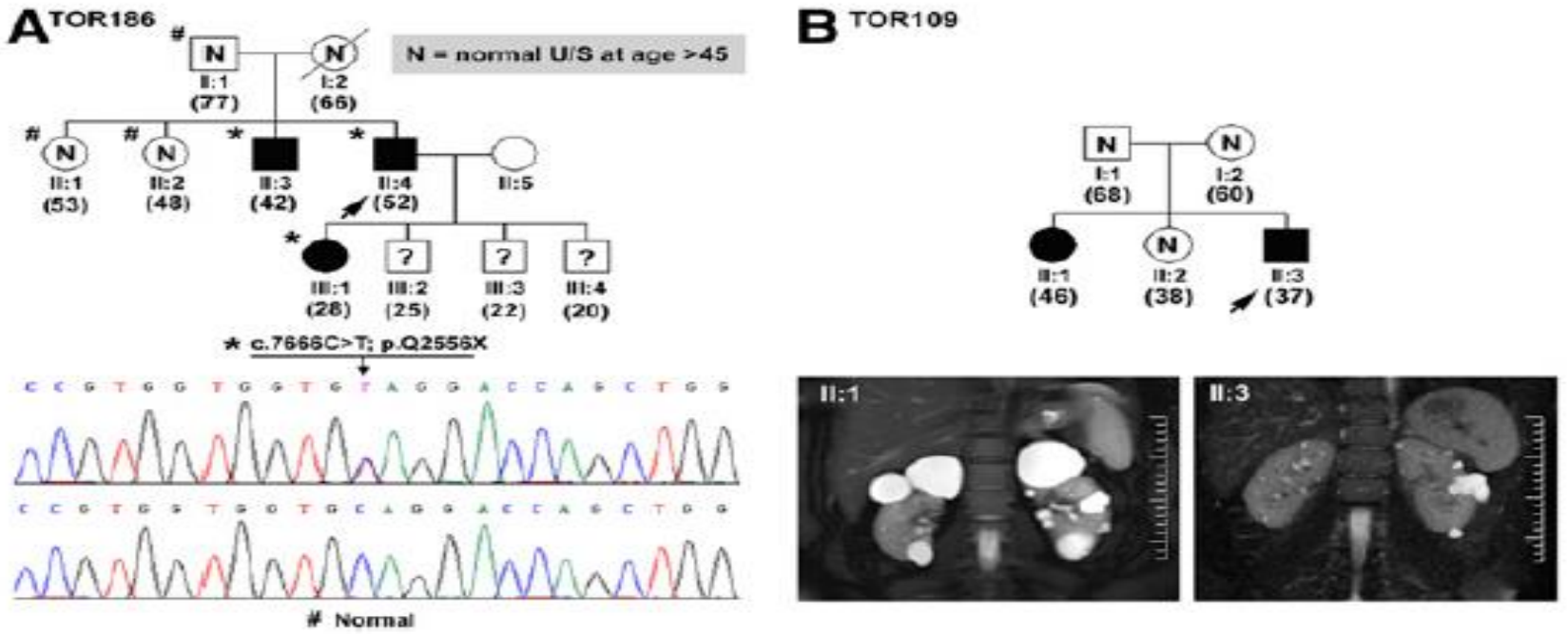


Figure 5. Examples of germline mosaicism. (A) TOR186 is a pedigree with proven germline mosaicism. Two members (II:3 and II:4) inherited the same pathogenic *PKD1* mutation (c.7666C>T; p.Q2556X) from their apparently unaffected parents. (B) TOR109 is a pedigree with suspected germline mosaicism with no detectable *PKD1* or *PKD2* mutation. U/S, ultrasound scan.

Mosaicismo germinal

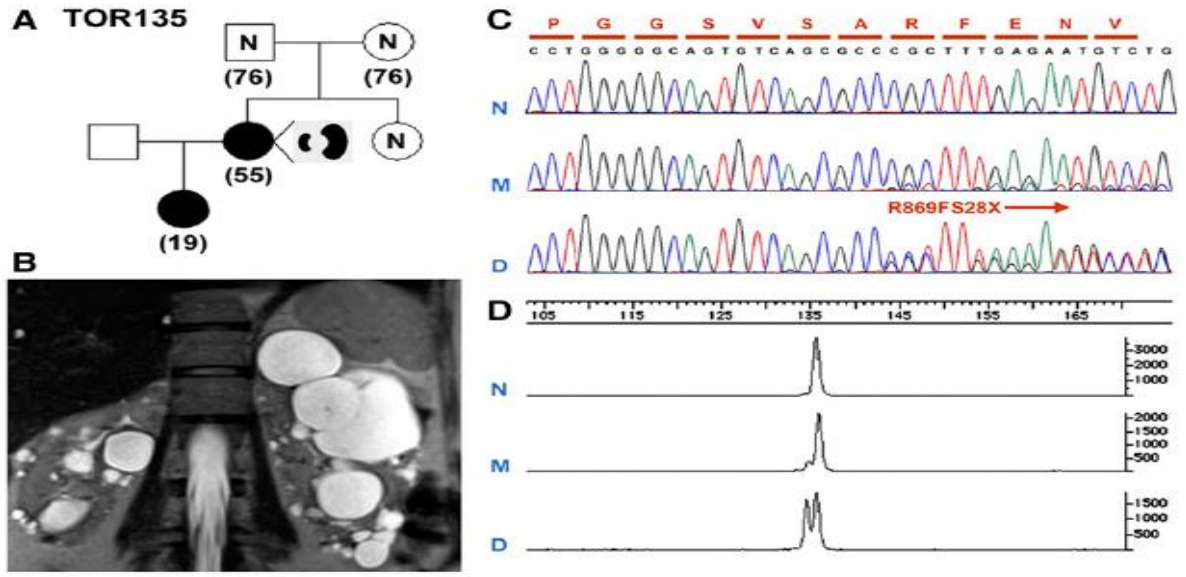


Figure 6. An example of PKD1 somatic mosaicism. (A) A pedigree (TOR135) with somatic mosaicism and germline disease transmission. (B) MRI shows asymmetric PKD in the affected mother with somatic mosaicism. (C) Sanger sequencing showing a 1-bp *PKD1* frameshift deletion (c.2605delC; p.R869FS28X) unequivocally in the daughter (D) but not in the mother (M). (D) Quantitative analysis by capillary electrophoresis of the PCR product encompassing the *PKD1* mutation site shows that the ratio of mutant to normal alleles is approximately 1:1 in the daughter (D) but only approximately 1:10 the mother (M).

6 de los 32 pacientes con enfermedad de novo (18.8%) tenían PKD asimétrica.

Interacción Génica entre genes PQR

NefroCHUS
Laboratorio de Genética de las Enfermedades Renales

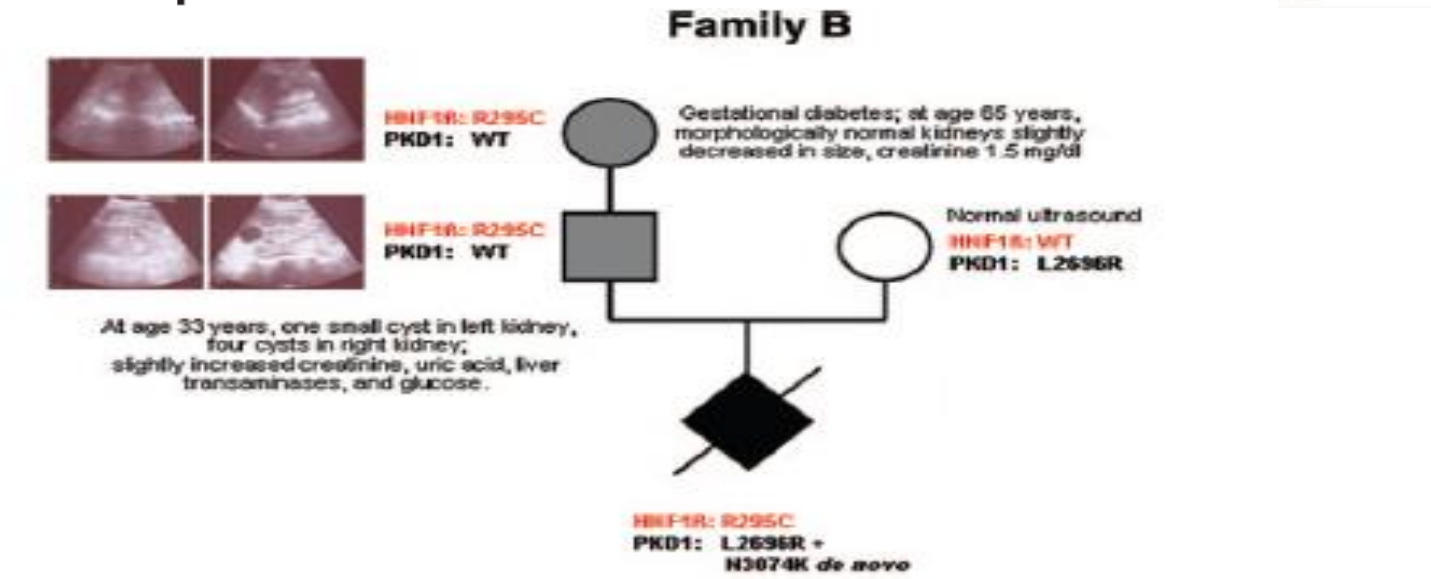
1. We have evidences of genetic interaction between PKD genes …

Genetic interaction stuc
dominant and recessive
disease in a common p

Miguel A. Garcia-Go
David L. Huso[2], Terr
and Gregory G. Geri

Mutations in Multiple PKD Genes May Explain Early and Severe Polycystic Kidney Disease

Carsten Bergmann,*† Jennifer von Bothmer,† Nadina Ortiz Brüchle,† Andreas Venghaus,† Valeska Frank,* Henry Fehrenbach,‡ Tobias Hampel,‡ Lars Pape,§ Annegret Buske,‖ Jon Jonsson,¶** Nanette Sarioglu,†† Antónia Santos,‡‡ Jose Carlos Ferreira,‡‡ Jan U. Becker,§§ Reinhold Cremer,‖‖ Julia Hoefele,¶¶ Marcus R. Benz,¶¶ Lutz T. Weber,¶¶ Reinhard Buettner,*** and Klaus Zerres†



$Pkhd1^{del3\text{-}4/del3\text{-}4}$ _ $Pkhd1^{del3\text{-}4/del3\text{-}4}$
y $Pkd1^{+/-}$

…and for this reason, the genetic test will be an invaluable tool to anticipate the prognosis.

CASO 2:
Interacción Génica entre genes PQR

Kidney Int. 2012 February ; 81(4): 412–417. doi:10.1038/ki.2011.370.

Attenuated Renal Disease Severity Associated with a Missense *PKD1* Mutation

York Pei[1], **Zheng Lan**[2], **Kairong Wang**[1], **Miguel Garcia-Gonzalez**[2,3], **Ning He**[1], **Elizabeth Dicks**[4], **Patrick Parfrey**[4], **Gregory Germino**[2,5], and **Terry Watnick**[2]

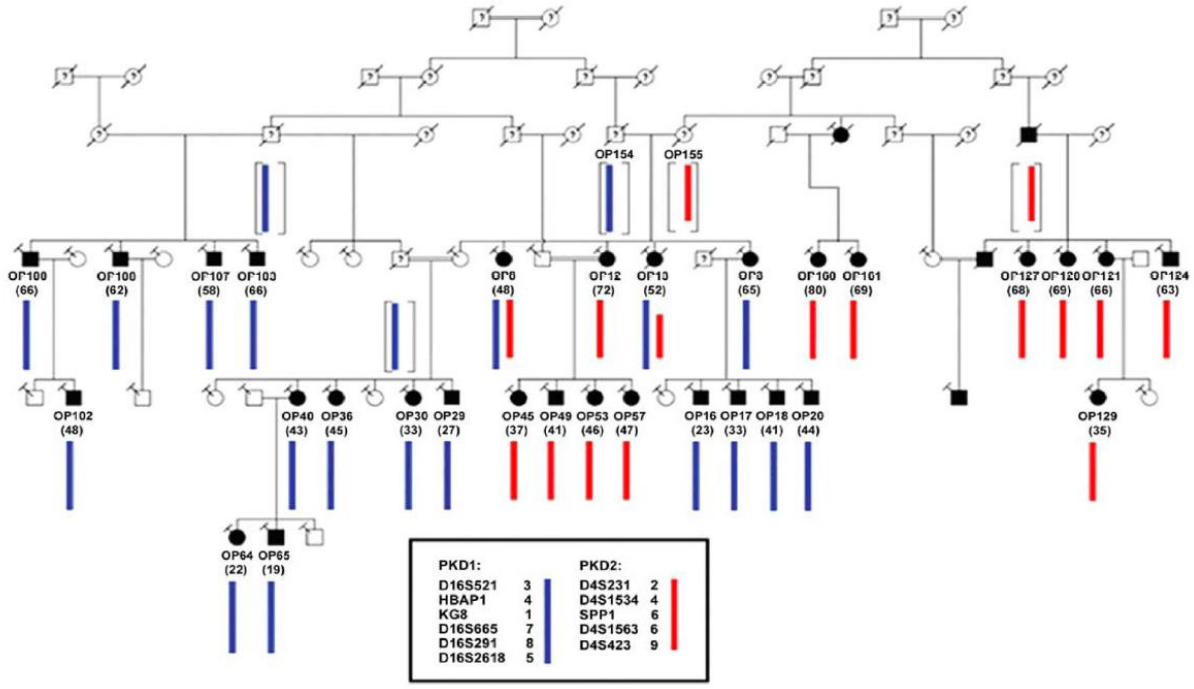


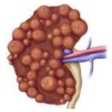
Figure 1. Disease segregation pattern in NFL10

Situaciones que nos encontramos

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*

Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*

Period 2012-2015



(2) *Cystic Disorders*

AE1.0_GalCyst *(ISCIII_PI15/01467)*

Year:*2015* **PI:** *Miguel A García González*

(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:

i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:

i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*

ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*

iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:

i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*

ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:

i) ***AE1.1_Cyst: Beyond known genetics in cystic disease.* PIs:** Noa Carrera and Cándido Díaz (AES 21, ISCiii). **(???)**

ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

(3) *Glomerular Disorders*

AE2.0_GalGlom *(ISCIII_PI18/00378)*

Year:*2018* **PI:** *Miguel A García González*

(2019-2021) Co-PI: *Jesús Calviño (HULA)*

- Genotype/Phenotype Correlation:

i) 206 families, 1030 diagnosed patients.

ii) Col4A Nephropaties: Raquel Rodriguez et al (Under writting).

iii) New genes in Glomerulopathy: Raquel Rodriguez et al (Under writting).

iv) FSGS in clinical diagnosis. GLOSEN Project. PIs: Gema Fernández-Juárez and Miguel García (FRIAT project).

- New Diagnostic Tools:

i) **Glom*Analyser®*** *(Under Construction).*

- New Therapies:

i) ***Ongoing.***

- New Proyects/New PIs:

i) Gene Editing in Glomerulopahies. IP: Noa Carrera /Co-IP: Catarina Allegue

ii) SHUa and Complement Nephropathies. IP: Angel Alonso and Mercedes Cao (CHUAC).

Diagnóstico Genético en Enfermedad Glomerular

FSGS con mutaciones en los genes del colágeno (COL4A)

NefroCHUS
Laboratorio de Genética de las Enfermedades Renales

NEPHRO GENETOR

Casos esporádicos

Familia	Miembro	Microhematuria	Proteinuria	Debut	ERT	Alt. auditivas	Biopsia	Mutación
-	2327 (M)	+	Nefrótica	<36 a.	+	-	FSGS	COL4A4 c.2690G>A:p.G897E
-	2371 (V)	+	Nefrótica	<24 a.	-	N/D	FSGS	COL4A5 c.4877C>T:p.S1626L
-	2475 (V)	+	Nefrótica	1 a.	-	N/D	FSGS	COL4A3 c.2827G>A:p.G943R
-	2563 (M)	+	Nefrótica	2 a.	-	N/D	FSGS	COL4A5 c.2793dupA:p.P931fs

Casos subclínicos (Noa Carrera)

Diagnóstico Genético en Enfermedad Glomerular
FSGS con mutaciones en los genes del colágeno (COL4A)

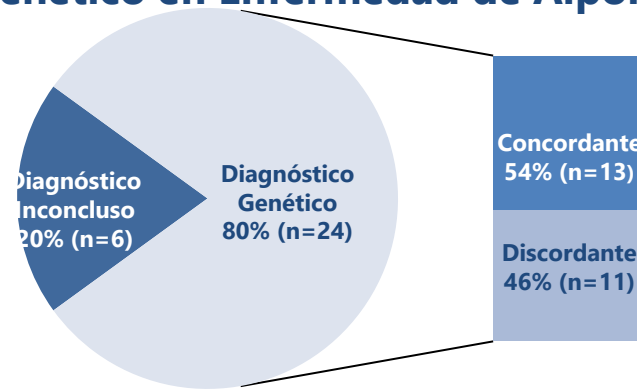
Cohorte de familias n=138

		Nº de pacientes
Género	Hombres	68
	Mujeres	70
Diagnóstico clínico	FSGS	41
	Alport	30
	SNCR	5
	Cambios mínimos/ SNCR	1
Sin diagnóstico clínico		61

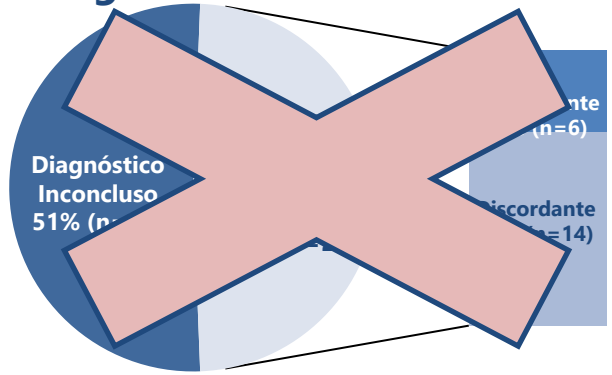
Gen	Cromosoma	Exones	Tamaño (pb)	% Cobertura (≥30X)
ACTN4	19	21	3156	98.3
APOE	19	3	1014	96.4
APOL1	22	6	1365	99
CD2AP	6	18	2280	100
COL4A3	2	52	6053	98.2
COL4A4	2	47	6013	100
COL4A5	X	51	6078	98.7
COL4A6	X	46	6044	99.5
COQ2	4	7	1406	98
COQ6	14	12	1647	99.3
CTNS	17	11	1423	99.4
FN1	2	46	7988	99.9
GLA	X	7	1430	100
INF2	14	21	4170	97.7
ITGB4	17	39	6249	96.4
LAMB2	3	32	6037	100
LMX1B	9	8	1381	98.6
MYH9	22	40	6683	99.6
MYO1E	15	28	3887	100
NPHS1	19	29	4306	100
NPHS2	1	8	1312	100
PLCE1	10	31	7481	98.8
PTPRO	12	26	4171	96.7
SCARB2	4	12	1677	98.1
TRPC6	11	13	3056	95.5
WT1	11	10	1109	100

Diagnóstico Genético en Enfermedad Glomerular
FSGS con mutaciones en los genes del colágeno (COL4A)

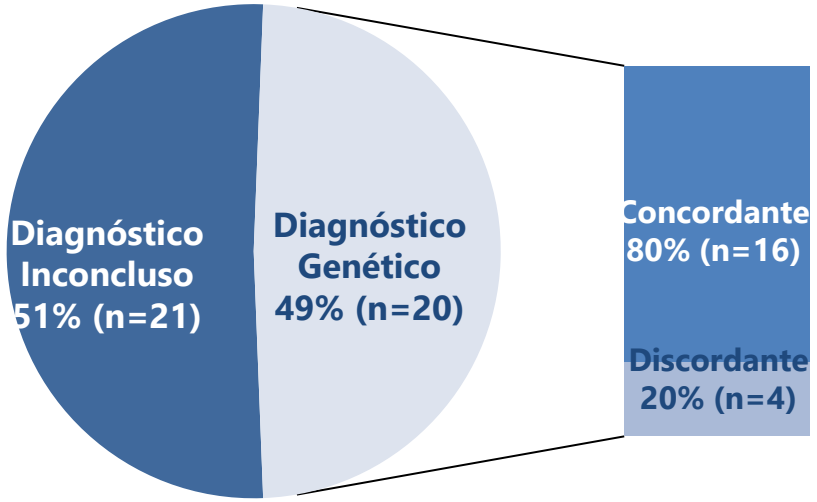
Diagnóstico clínico *versus* diagnóstico genético en Enfermedad de Alport



Diagnóstico clínico *versus* diagnóstico genético en FSGS



Diagnóstico clínico *versus* diagnóstico genético en FSGS-COL4A



Nat Rev Nephrol. 2016 Aug;12(8):472-83. doi: 10.1038/nrneph.2016.87. Epub 2016 Jul 4.

The expanding phenotypic spectra of kidney diseases: insights from genetic studies.

Stokman MF[1], Renkema KY[1], Giles RH[2], Schaefer F[3], Knoers NV[1], van Eerde AM[1].

Nephrol Dial Transplant. 2016 Jun;31(6):961-70. doi: 10.1093/ndt/gfv325. Epub 2015 Sep 7.

Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis.

Gast C[1], Pengelly RJ[2], Lyon M[3], Bunyan DJ[3], Seaby EG[2], Graham N[2], Venkat-Raman G[4], Ennis S[2].

Diagnóstico Genético en Enfermedad Glomerular

FSGS con mutaciones en los genes del colágeno (COL4A)

Casos esporádicos

Familia	Miembro	Microhematuria	Proteinuria	Debut	ERT	Alt. auditivas	Biopsia	Mutación
-	2327 (M)	+	Nefrótica	<36 a.	+	-	FSGS	COL4A4 c.2690G>A:p.G897E
-	2371 (V)	+	Nefrótica	<24 a.	-	N/D	FSGS	COL4A5 c.4877C>T:p.S1626L
-	2475 (V)	+	Nefrótica	1 a.	-	N/D	FSGS	COL4A3 c.2827G>A:p.G943R
-	2563 (M)	+	Nefrótica	2 a.	-	N/D	FSGS	COL4A5 c.2793dupA:p.P931fs

Casos subclínicos (Noa Carrera)

Fenotipado Guias KDIGO 2022 (GloSEN)

Nuevos genes?

CASO 5
Nuevo Síndrome Nefrótico

Fenotipo:

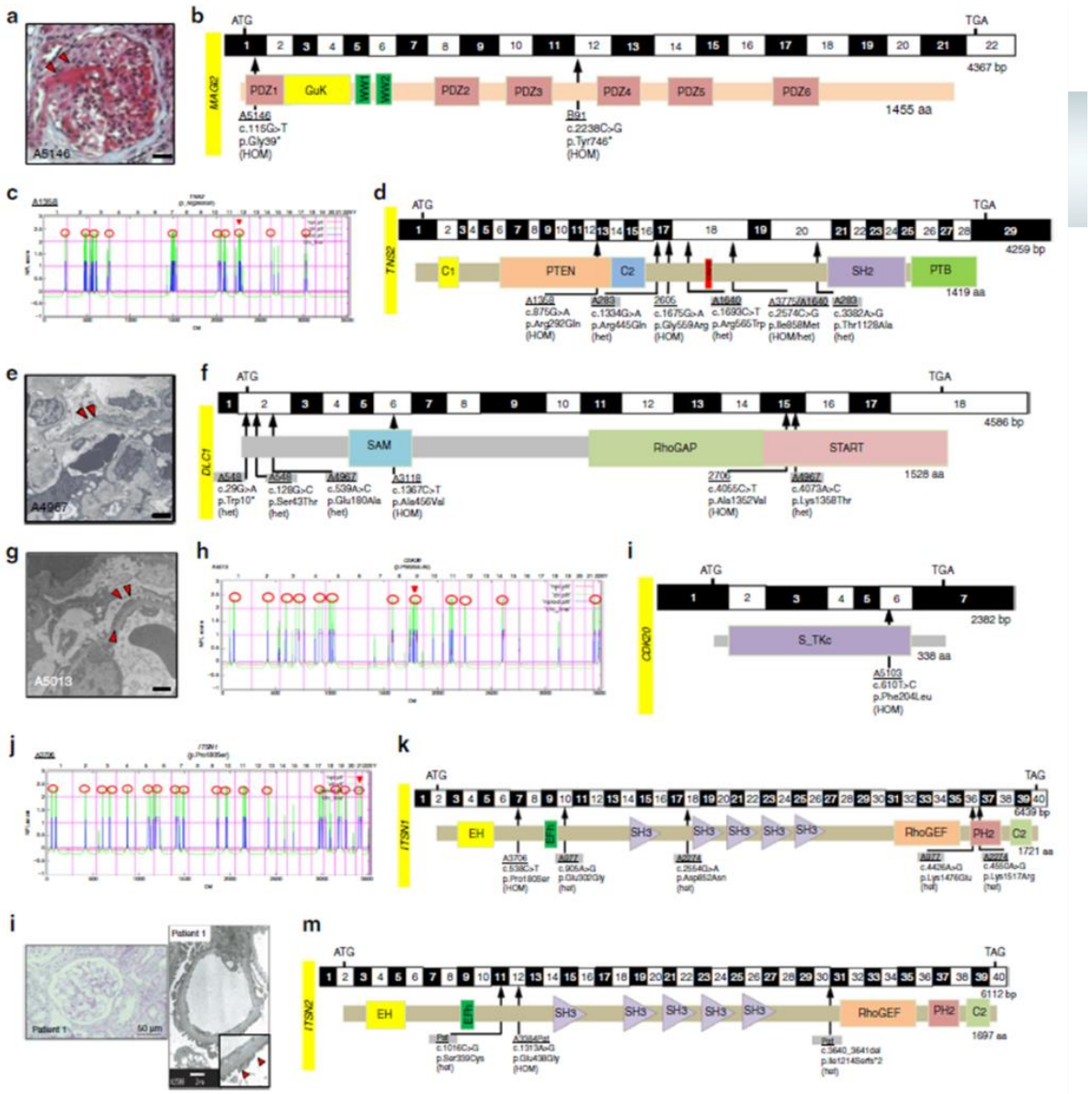
- Síndrome Nefrótico parcialmente sensible a esteroides
- Talla baja
- Hipertensión
- Sin antecedentes

Dr. Fidalgo
CHU-Santiago

E. Genético:

- Negativo Panel de Glomerulares
- Negativo Exoma subpanelizado a E. Renal (499 genes)

CASO 5
Nuevo Síndrome Nefrótico



MAGI2

TNS2

DLC1

CDK20

ITSN1

ITSN2

Dr. Fidalgo
CHU-Santiago

CASO 5
Nuevo Síndrome Nefrótico

Family -Individual	Ethnic origin	Parental consan-guinity	Nucleotide alteration (s)	Alteration(s) in coding sequence[a]	Exon (segrega-tion)	Amino acid sequence conservation	GnomAD Allele count (zygosity)	Age at Onset	Kidney disease	Age at ESKD	Treatment and renal transplantation	Histology (at age)	Extrarenal manifestations
MAGI2													
A5146 -21	Arab (Iraq)	Yes	c.115G>T	p.Gly39*	1 (HOM, M, P)	NA	NP	4 yr	SSNS	ND	partial response to Pred/CsA	FSGS (4 yr)	Hydrocephalus
B91 (1302/11)	Europe	No	c.2238C>G	p.Tyr746*	12 (HOM, maternal isodisomy)	NA	NP	8 wks	CNS	ND	ND	FSGS (20 mo)	Microcephaly, severe global developmental delay, cryptorchidism, hypothyroidism, gastroesophageal reflux (IUGR and postnatal short stature - probably attributable to matUPD7)
TNS2													
A1358 -21	Turkey	Yes	c.875G>A	p.Arg292Gln	11 (HOM, ND)	*C. intestinalis*	NP	7 yr	NS	ND	no treatment attempt	MCNS (7 yr)	Asthma
A283 -21	Europe	No	c.1334G>A c.3382A>G	p.Arg445Gln p.Thr1128Ala	17 (het, M) 20 (het, P)	*D. rerio* *G. gallus*	68 / 277,108 (het) 1522/ 240,618 (het)	7 yr	SDNS	ND	partial response to CsA; complete remission to MMF (no relapse during 2 years)	MCNS (7 yr)	ND
2605	Nigeria	No	c.1675G>A	p. Gly559Arg	17 (HOM, ND)	*D. rerio*	34 / 160,586 (het)	ND	SSNS	ND	partial response to Pred	FSGS (ND)	Hypertension
A3775 -21	India	No	c.2574C>G	p.Ile858Met	18 (HOM, ND)	*C. elegans*	186 / 232,392 (het)	2 yr	SSNS	ND	complete, remission with steroids	DMS (2 yr)	ND
A1640 -21	India	No	c.1693C>T c.2574C>G	p.Arg565Trp p.Ile858Met	18 (het, P) 18 (het, M)	*D. rerio* *C. elegans*	22/ 119,318 (het) 186 / 232,392 (het)	3 yr	SDNS	ND	complete remission to CsA, MMF, CTX and RTX	MCNS (3 yr)	Short stature
DLC1													
A548 -21	Europe	No	c.29G>A c.128G>C	p.Trp10* p.Ser43Thr	2 (het, ND) 2 (het, ND)	NA *G. gallus*	NP 2/ 246,110 (het)	56 yr	SRNS	62 yr	Dialysis at 62 yrs and 1st transplant at 64 yrs of age!	FSGS (56 yr)	ND
A4967 -21	Arab	No	c.539A>C c.4073A>C	p.Glu180Ala p.Lys1358Thr	2 (het, M) 15 (het, P)	*G. gallus* *C. intestinalis*	NP NP	7 yr	SRNS	7 yr	no response to Methyl-Pred/Pred	FSGS (7 yr)	HT, seizures (mild brain atrophy with dilated ventricles), Nephritis

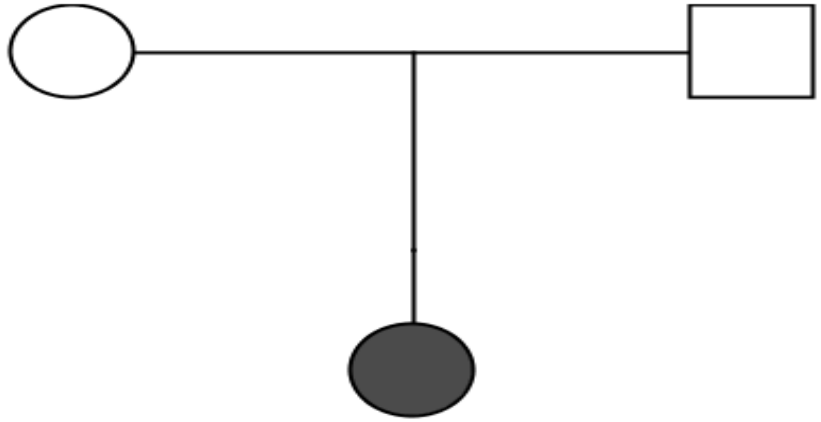
Dr. Fidalgo
CHU-Santiago

CASO 5
Nuevo Síndrome Nefrótico

Fenotipo:

- Síndrome Nefrótico parcialmente sensible a esteroides
- Talla baja
- Hipertensión
- Sin antecedentes ?

Adoptada



TNS2: p.(Asn1262Ile) Homocigosis

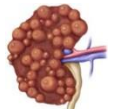
Dr. Fidalgo
CHU-Santiago

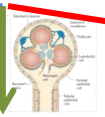
E. Genético:

- Negativo Panel de Glomerulares
- Negativo Exoma subpanelizado a E. Renal (499 genes)
- Reanálisis del Exoma ... Bingo

Situaciones que nos encontramos

(1) *Development of New Technologies for the Diagnosis, prognosis and possible therapies for Hereditary Renal Disorders*
Project: *ISCIII_PI11/00690* . **Year:***2011* **PI:** *Miguel A García González*
Period 2012-2015





(2) *Cystic Disorders*

AE1.0_GalCyst *(ISCIII_PI15/01467)*
Year:*2015* **PI:** *Miguel A García González*
(2016-2018) Co-PI: *Cándido Díaz (CHUS)*

- Genotype/Phenotype Correlation:
i) Lara Besada et al (Under Submission). 719 ADPKD-families, 3127 diagnosed patients.

- New Diagnostic Tools:
i) **KitGAG** (Olaya Lamas, Patent *WO/2017/042416, Licenced to Nasas Biotech).*
ii) ***CystAnalyser®*** *(Reg: SC-208/19 and Adrián Cordido et al, Plos Comp. Biol. 2020).*
iii) ***NefroCHUS: Unidad de Diagnóstico de NefroGenética*** (Certification: C15003866/ U78-Genética, Xunta de Galicia) and Besada et al (U. Sub).

- New Therapies:
i) ***Anti-TWEAK*** *(Cordido et al, JASN 2021 and Reg:PAT2014/08).*
ii) ***MMT*** *(Adrián Cordido, Under Submission).*

- New Proyects/New PIs:
i) ***AE1.1_Cyst: Beyond known genetics in cystic disease. PIs:*** Noa Carrera and Cándido Díaz (AES 21, ISCiii). **(???)**
ii) Pre-Implantation Genetic Testing in PKD. ***PIs:*** *Miguel A. García and Luz Cuiña (CHOP).*

(3) *Glomerular Disorders*

AE2.0_GalGlom *(ISCIII_PI18/00378)*
Year:*2018* **PI:** *Miguel A García González*
(2019-2021) Co-PI: *Jesús Calviño (HULA)*

- Genotype/Phenotype Correlation:
i) 206 families, 1030 diagnosed patients.
ii) Col4A Nephropaties: Raquel Rodriguez et al (Under writting).
iii) New genes in Glomerulopathy: Raquel Rodriguez et al (Under writting).
iv) FSGS in clinical diagnosis. GLOSEN Project. PIs: Gema Fernández-Juárez and Miguel García (FRIAT project).

- New Diagnostic Tools:
i) **Glom*Analyser®*** *(Under Construction).*

- New Therapies:
i) ***Ongoing.***

- New Proyects/New PIs:
i) Gene Editing in Glomerulopahies. IP: Noa Carrera /Co-IP: Catarina Allegue
ii) SHUa and Complement Nephropathies. IP: Angel Alonso and Mercedes Cao (CHUAC).

(4) *Tubulo-interstitial Disease*

AE3.0_GalTubi (*ISCIII_PI???*)
Year:*???* **PI:** *Miguel A García González*
Co-PI: *Afonso Otero(CHUOU)*

- Genotype/Phenotype Correlation:
i) 126 families, 407 diagnosed patients.
ii) Gitelman/Bartter cohort: Laura González et al (Under writting).
iii) ADTKD families (Furlano et al, AJKD. 2018)

- New Diagnostic Tools:
i) **Tub*Analyser®*** *(Under Construction).*
ii) 3D-Bioprinting of pseudonephrons and pseudoarteries (Calviño et al, Submitted)

- New Therapies:
i) Future research

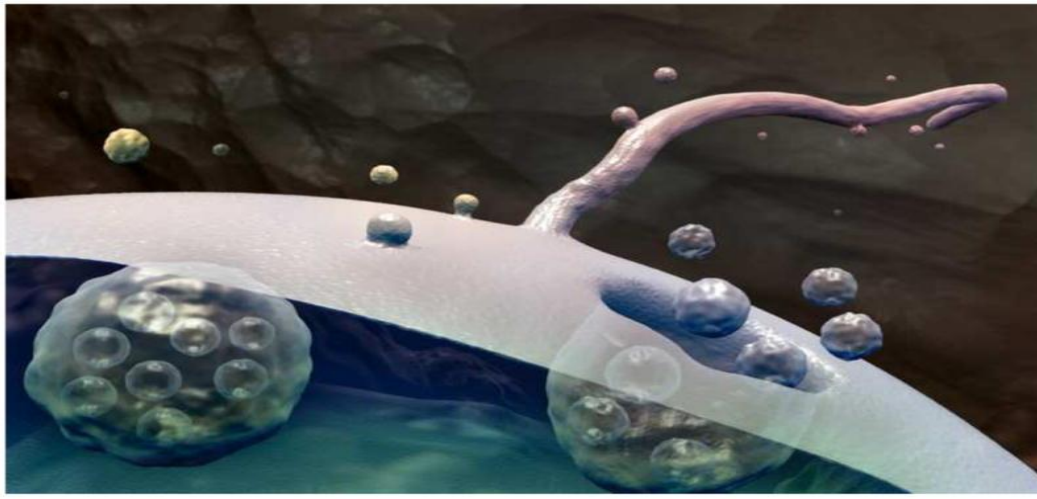
- New Proyects/New PIs:
i) Future research

Nefropatía Tubulointesticial de base Genética

Las Nefropatías intersticiales de origen genético se engloban en dos grupos en función del patrón de herencia:

- **Autosómico Recesivo:** Nefronoptisis o NefropatíaTubulointersticial Autosómica Recesiva NTAR/ARTKD.
- **Autosómico Dominante**: NefropatíaTubulointersticial Autosómica Autosómica Dominante NTAD/ADTKD

Característica común ?
SON CILIOPATIAS (entre otras cosas!)



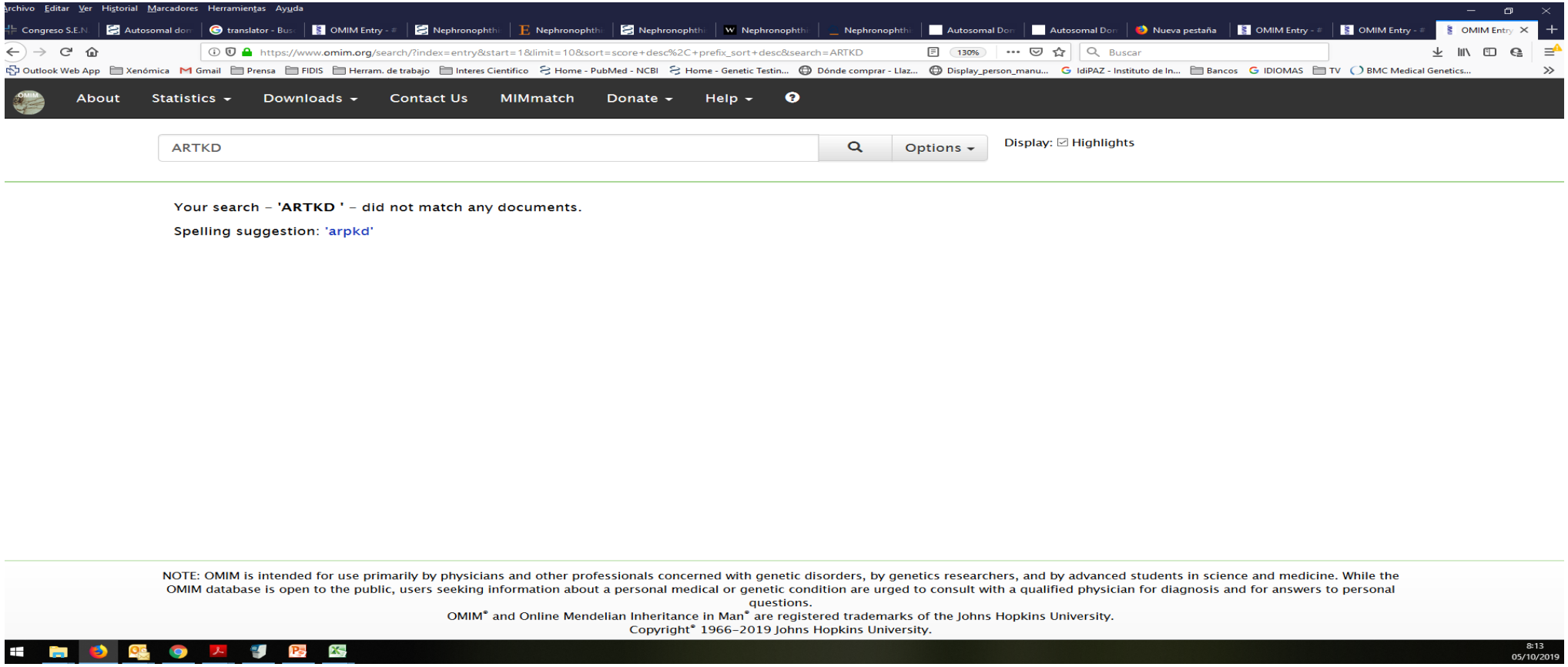
Nefropatía Tubulointesticial de base Genética

Las Nefropatías intersticiales de origen genético se engloban en dos grupos en función del patrón de herencia:

- **Autosómico Recesivo:** Nefronoptisis o NefropatíaTubulointersticial Autosómica Recesiva NTAR/ARTKD.
- **Autosómico Dominante**: NefropatíaTubulointersticial Autosómica Autosómica Dominante NTAD/ADTKD

Nefropatía Tubulointesticial Autosómica Recesiva
NTAR/ARTKD = Nefronoptisis

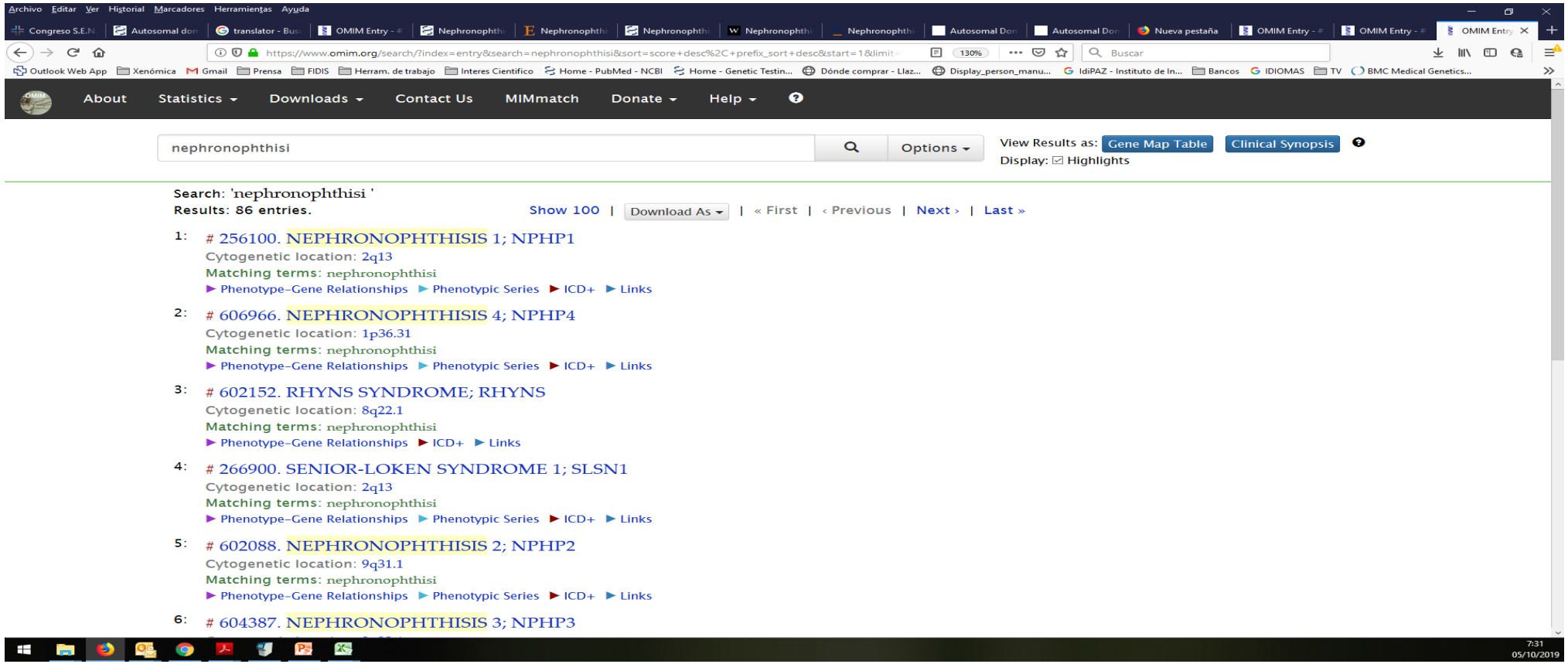
Entidad ???



0 registros de identidades genéticas relacionadas a ARTKD

Nefropatía Tubulointesticial Autosómica Recesiva
NTAR/ARTKD = Nefronoptisis

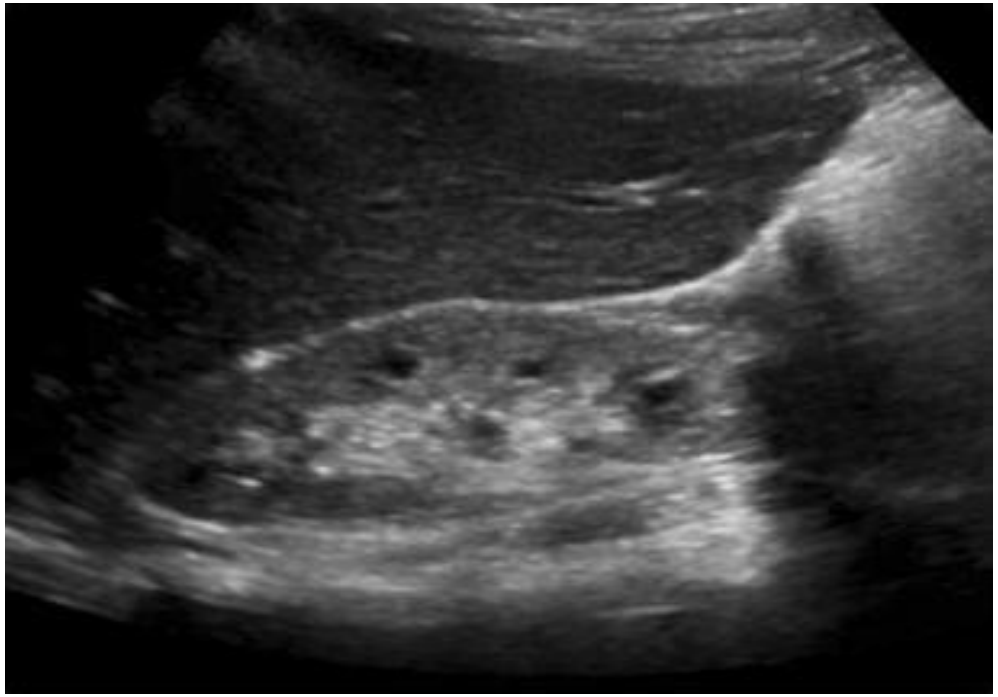
Entidad ???



86 registros de identidades genéticas relacionadas a Nefronoptisis

Nefropatía Tubulointesticial Autosómica Recesiva
NTAR/ARTKD = Nefronoptisis

Características fenotípicas



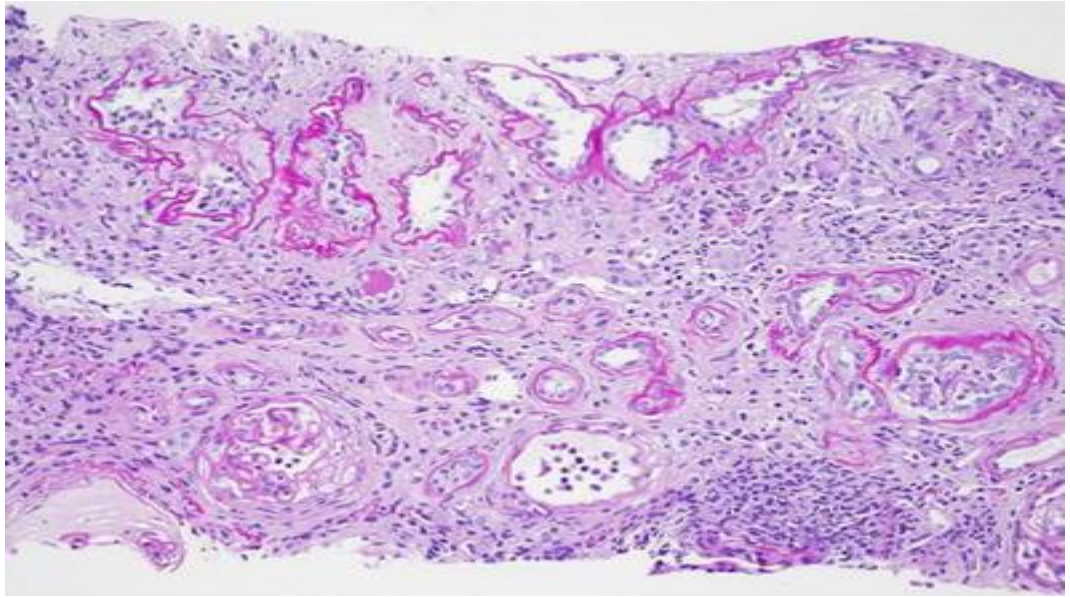
ECOGRAFIA

Riñones pequeños bilaterales, elevada ecogenicidad (en hígado baja), diferenciación corticomedular disminuida y quístes corticomedulares

Adaptado de Wolf, M.T.F. & Hildebrandt, F. Pediatr Nephrol (2011)

Nefropatía Tubulointesticial Autosómica Recesiva
NTAR/ARTKD = Nefronoptisis

Características fenotípicas



ANATOMÍA PATOLÓGICA

Tríada de quistes tubulares, disrupción de la membrana basal tubular y fibrosis intersticial con infiltración de células intersticiales. (PAS, 20 ×)

Adaptado de Wolf, M.T.F. & Hildebrandt, F. Pediatr Nephrol (2011)

Nefropatía Tubulointesticial Autosómica Recesiva
NTAR/ARTKD = Nefronoptisis

Frecuencia génica

Gene (protein)	Chromosome	Phenotype (median age at ESRD)	Extrarenal symptoms	Mutation frequency	Interaction partners
NPHP1 (nephrocystin-1)	2q13	NPHP (13years)	RP (10%), OMA (2%), JS (rarely)	23.4% homozygous deletion 2.1% point mutation	Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B
NPHP2/INVS (inversin)	9q31	Infantile NPHP (<5years)	RP (10%), LF, *situs inversus* , VSD	0.014	Nephrocystin-1, calmodulin, catenins, β-tubulin, APC2
NPHP3 (nephrocystin-3)	3q22	Infantile and adolescent NPHP	LF, RP (10%), *situs inversus* , MKS	0.7% If truncating mutation infantile form	Nephrocystin-1
NPHP4 (nephrocystin-4)	1p36	NPHP (21years)	RP (10%), OMA, LF	0.026	Nephrocystin-1, BCAR1, PTK2B
NPHP5/IQCB1 (nephrocystin-5)	3q21	NPHP (13years)	Early-onset RP	0.036	Calmodulin, RPGR, nephrocystin-6
NPHP6/CEP290 (nephrocystin-6/CEP290)	12q21	NPHP	JS, MKS	0.01	ATF4, nephrocystin-5, CC2D2A
NPHP7/GLIS2 (nephrocystin-7/GLIS2)	16p	NPHP	_	0.001	_
NPHP8/RPGRIP1L (nephrocystin-8/RPGRIP1L)	16q	NPHP	JS, MKS	0.005	Nephrocystin-1
NPHP9/NEK8 (nephrocystin-9/NEK8)	17q11	Infantile NPHP	_	0.001	_
TMEM67/MKS3/NPHP11 (Meckelin/nephrocystin-11)	8q22.1	MKS, JS, NPHP + LF	JS, MKS		
NPHP1L/XPNPEP3 (nephrocystin-1 L/XPNPEP3)					

MAYORITARIAMENTE NPHP1

Adaptado de Wolf, M.T.F. & Hildebrandt, F. Pediatr Nephrol (2011)

Nefropatía Tubulointesticial de base Genética

Las Nefropatías intersticiales de origen genético se engloban en dos grupos en función del patrón de herencia:

- **Autosómico Recesivo:** Nefronoptisis o NefropatíaTubulointersticial Autosómica Recesiva NTAR/ARTKD.
- **Autosómico Dominante**: NefropatíaTubulointersticial Autosómica Autosómica Dominante NTAD/ADTKD

Nefropatía Tubulointesticial de base Genética

Las Nefropatías intersticiales de origen genético se engloban en dos grupos en función del patrón de herencia:

- **Autosómico Recesivo:** Nefronoptisis o NefropatíaTubulointersticial Autosómica Recesiva NTAR/ARTKD.
- **Autosómico Dominante**: NefropatíaTubulointersticial Autosómica Autosómica Dominante NTAD/ADTKD

Nefropatía Tubulointesticial Autosómica Dominante
NTAD/ADTKD

meeting report

http://www.kidney-international.org

Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—A KDIGO consensus report

Kai-Uwe Eckardt[1], Seth L. Alper[2], Corinne Antignac[3,4], Anthony J. Bleyer[5], Dominique Chauveau[6], Karin Dahan[7], Constantinos Deltas[8], Andrew Hosking[9], Stanislav Kmoch[10], Luca Rampoldi[11], Michael Wiesener[1], Matthias T. Wolf[12] and Olivier Devuyst[13]

Nueva clasificación de la tubulopatía Intesticial

Nefropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

Qué entidades fenotípicas/enfermedades engloba?

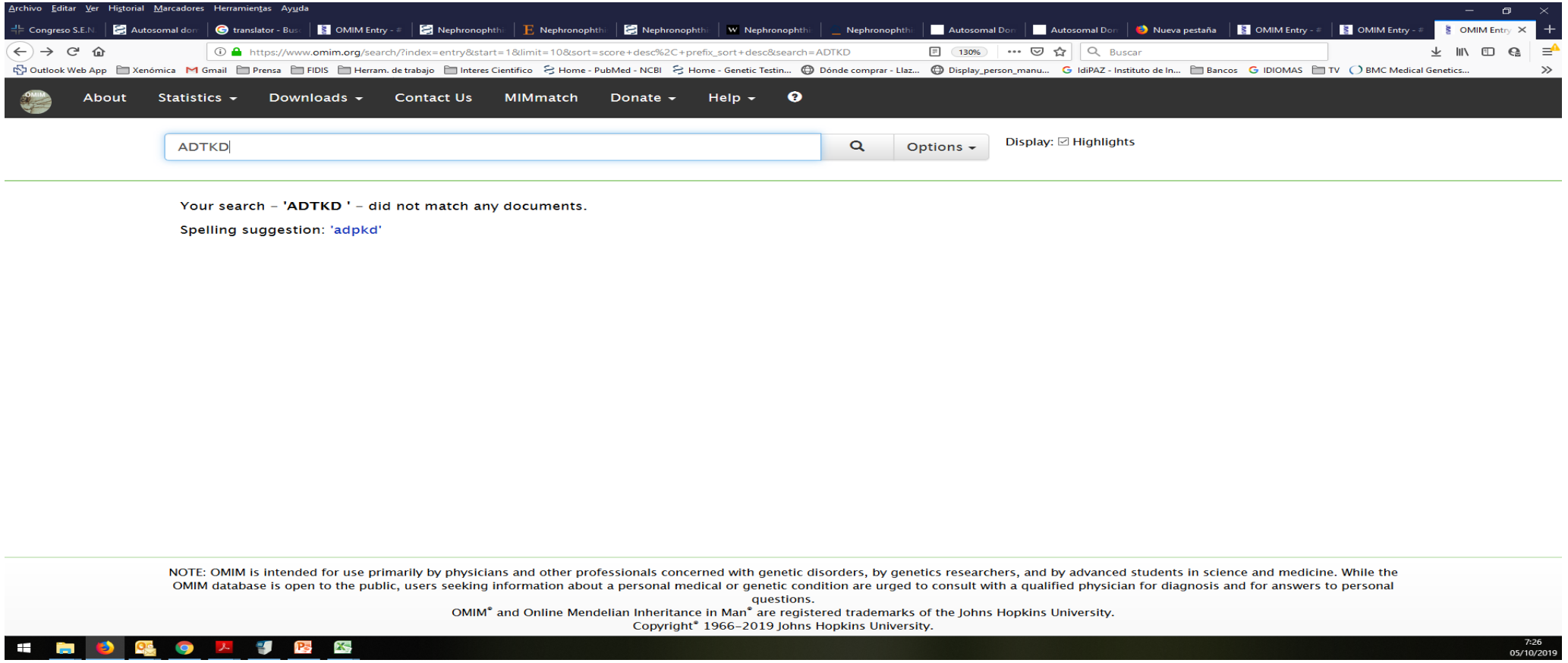
Table 1 | New gene-based classification and terminology of different types of ADTKD

Causal Gene	Proposed terminology	Previously used terminology
UMOD	ADTKD–*UMOD*	UKD (Uromodulin Kidney Disease)[a] UAKD (Uromodulin-Associated Kidney Disease) FJHN (Familial Juvenile Hyperuricemic Nephropathy) MCKD2 (Medullary Cystic Kidney Disease type 2)

Abbreviations: ADTKD, Autosomal Dominant Tubulointerstitial Kidney Disease; HNF1B, hepatocyte nuclear factor 1β; MUC1, mucin-1; NOS, not otherwise specified; REN, renin; UMOD, uromodulin.
[a]These terms may be easier to use in communicating with patients.

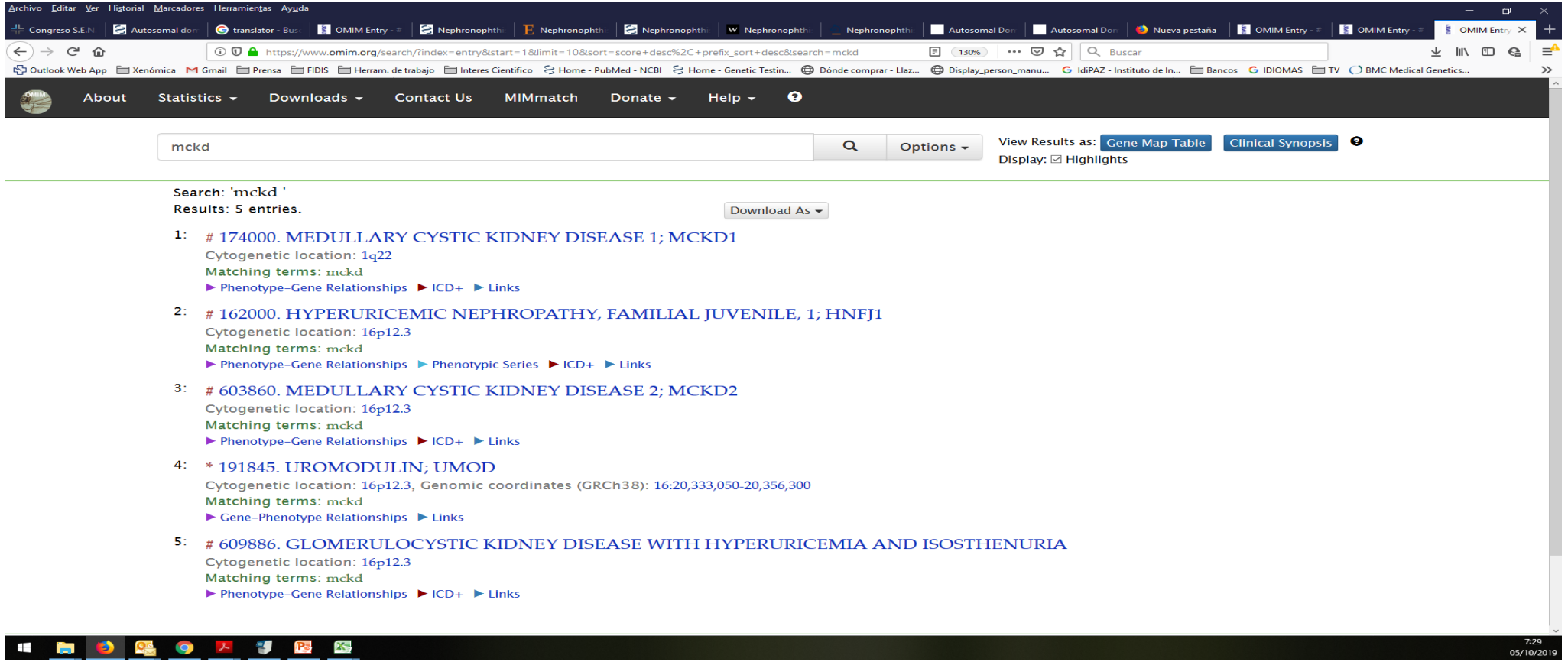
Nueva clasificación basada en los genes y terminología de los tipos de ADTKD
… de momento 5 entidades

efropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD



... búsqueda esta mañana (OMIM)

efropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD



... 5 entradas esta mañana (OMIM)

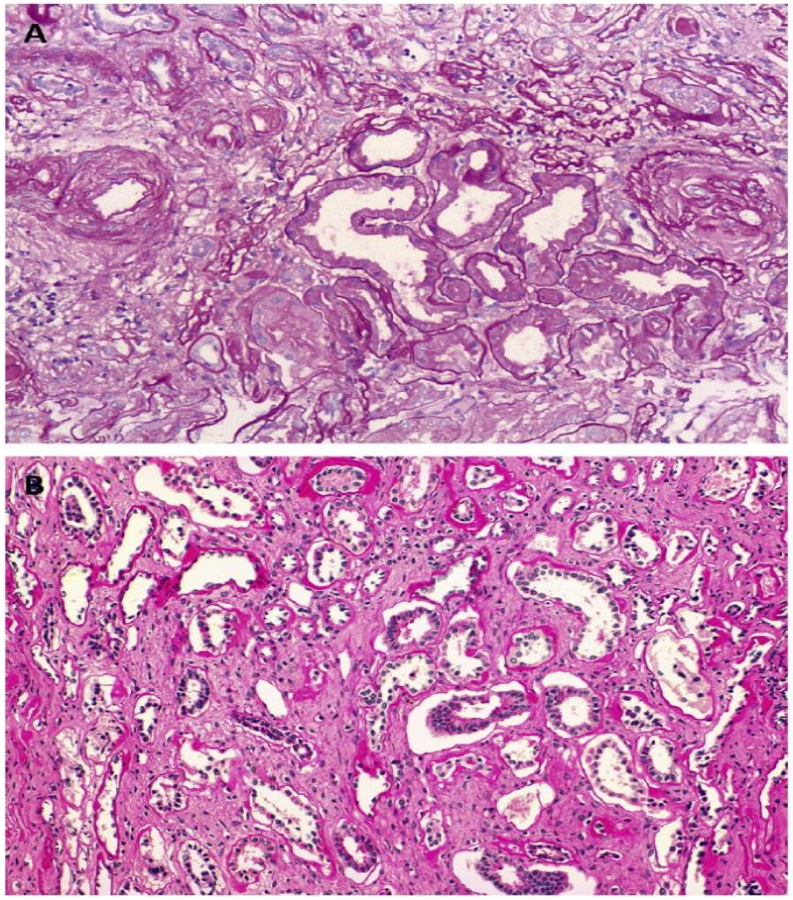
Características clínicas de la ADTKD

- Herencia autosómica dominante
- Pérdida progresiva de la función renal.
- Sedimento urinario suave
- Albuminuria / proteinuria ausente a leve
- Sin hipertensión severa durante las primeras etapas
- No hay exposición a medicamentos que puedan causar nefritis tubulointersticial
- Riñones normales o pequeños en ecografía
- Nocturia o enuresis en niños (debido a la pérdida de concentración renal capacidad)

Nefropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

NefroCHUS
Laboratorio de Genética de las Enfermedades Renales

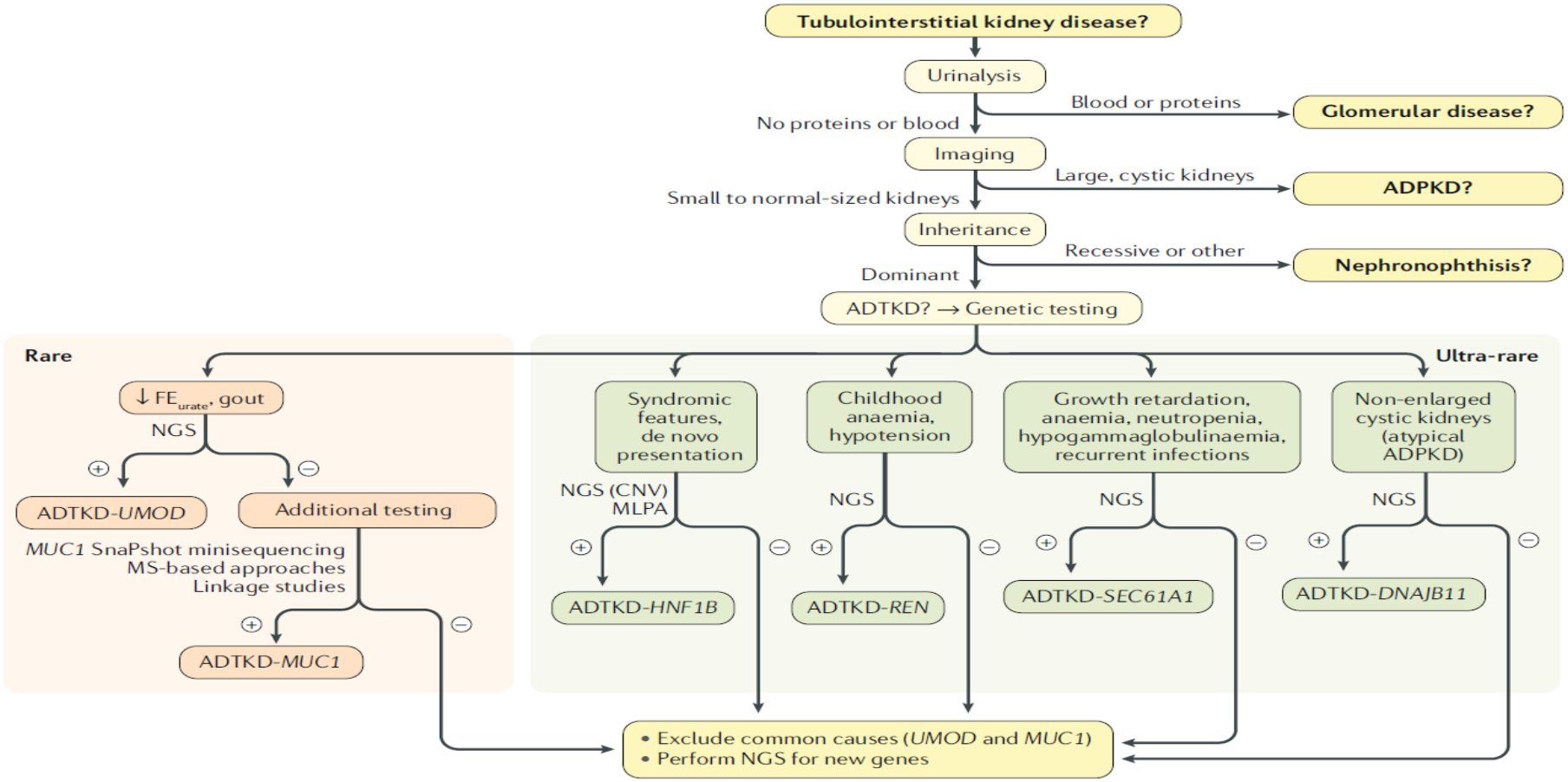
Anatomía Patológica de la ADTKD



- Fibrosis intersticial
- Atrofia tubular
- Engrosamiento y laminación de membranas basales tubulares
- Posiblemente dilatación tubular (microquistes)
- Inmunofluorescencia negativa para complemento e inmunoglobulinas.

efropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

Cómo dianosticar la ADTKD



CONCLUSION: Lo más sencillo y apropiado, realización de estudio genético.

Beneficios del diagnótico genético en la ADTKD

- Adultos con ERC sospechosos de tener ADTKD que desean confirmar la diagnóstico
- Miembros de familias afectadas con función renal normal que desean donar un riñón
- Individuos adultos sanos en riesgo que estén interesados en establecer un diagnóstico genético
- Adultos interesados en someterse a DGP para evitar la herencia de su hijo de un alelo mutante que le cause la enfermedad
- Niños sospechosos de tener una mutación REN

PREGUNTA: Aún pensáis en hacerle biopsia renal?

Nefropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

Qué diagnóstico genético se debe realizar para la ADTKD

Gene (protein product)	OMIM #	Chromosome	Exons	Genetic testing method
UMOD (Uromodulin)	191845	16p12.3	11	Direct sequencing of coding regions (mutations in exons 3 and 4 account for 93% of reported mutations)

CONSEJO: Ahora compensa hacer otras cosas … excepto para MUC-1!

Qué nos queda por conocer (INVESTIGACION)?

- Mejor comprensión del papel fisiológico de los genes involucrados y los mecanismos de enfermedad renal y progresión
- Grandes registros de familias afectadas.
- Caracterización fenotípica adicional: función tubular y capacidad de concentración
- Mejor comprensión de las manifestaciones clínicas en la infancia.
- Mejor comprensión del papel de los genes involucrados en multifactoriales
- Establecimiento de correlaciones genotipo / fenotipo
- Identificación nuevos genes causales y genes modificadores de la enfermedad
- Identificación de biomarcadores para la progresión de la enfermedad
- Modelos de enfermedad celulares y animales para identificar y probar estrategias terapéuticas

EN DEFINITIVA: Queda casi todo por conocer e investigar!

efropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

Qué nos queda por conocer (INVESTIGACION)?

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Red Renal de Nefrología (REDinREN)

Original Investigation — AJKD

Autosomal Dominant Tubulointerstitial Kidney Disease: Clinical Presentation of Patients With ADTKD-*UMOD* and ADTKD-*MUC1*

Nadia Ayasreh, Gemma Bullich, Rosa Miquel, Mónica Furlano, Patricia Ruiz, Laura Lorente, Oliver Valero, Miguel Angel García-González, Nisrine Arhda, Intza Garin, Víctor Martínez, Vanessa Pérez-Gómez, Xavier Fulladosa, David Arroyo, Alberto Martínez-Vea, Mario Espinosa, Jose Ballarín, Elisabet Ars, and Roser Torra**

YA HEMOS EMPEZADO!!!

Nefropatía Tubulointesticial Autosómica Dominant
NTAD/ADTKD

Características clínicas de la cohorte Española

Findings	*UMOD* Patients	*MUC1* Patients	Total
Normal kidney size without cysts	5 (31%)	17 (32%)	22
Normal kidney size with cysts	2 (13%)	14 (26%)	16
Small hyperechogenic kidneys	8 (50%)	16 (30%)	24
Hyperechogenic kidneys with cortical cysts	—	6 (11%)	6
Other findings	1 (6%)	—	1

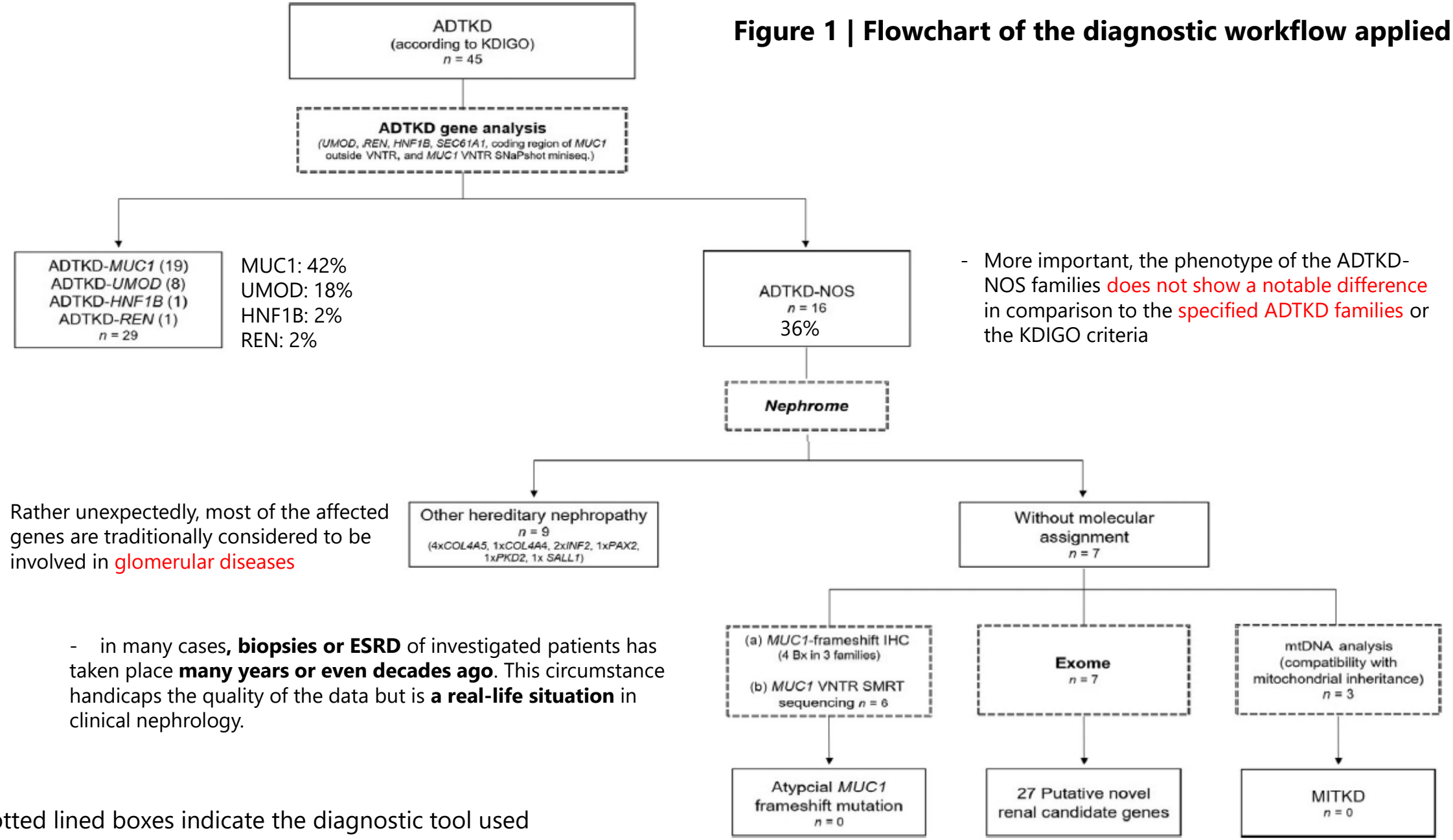
Resonancia Magnética renal

Diverse molecular causes of unsolved autosomal dominant tubulointerstitial kidney diseases

OPEN

Florian J. Wopperer[1,2], Karl X. Knaup[1], Kira J. Stanzick[3], Karen Schneider[1], Tilman Jobst-Schwan[1,2], Arif B. Ekici[4], Steffen Uebe[4], Andrea Wenzel[5], Stefan Schliep[6], Carsten Schürfeld[7], Randolf Seitz[8], Wanja Bernhardt[9], Markus Gödel[10], Antje Wiesener[4], Bernt Popp[4,11], Klaus J. Stark[3], Hermann-Josef Gröne[12,13], Björn Friedrich[14], Martin Weiß[15], Nikolina Basic-Jukic[16], Mario Schiffer[1], Bernd Schröppel[17], Bruno Huettel[18], Bodo B. Beck[5], Genomics England Research Consortium, John A. Sayer[19], Christine Ziegler[20], Maike Büttner-Herold[21], Kerstin Amann[21], Iris M. Heid[3], André Reis[4], Francesca Pasutto[4,22] and Michael S. Wiesener[1,22]

Figure 1 | Flowchart of the diagnostic workflow applied



MUC1: 42%
UMOD: 18%
HNF1B: 2%
REN: 2%

- More important, the phenotype of the ADTKD-NOS families does not show a notable difference in comparison to the specified ADTKD families or the KDIGO criteria

Rather unexpectedly, most of the affected genes are traditionally considered to be involved in glomerular diseases

- in many cases**, biopsies or ESRD** of investigated patients has taken place **many years or even decades ago**. This circumstance handicaps the quality of the data but is **a real-life situation** in clinical nephrology.

- Dotted lined boxes indicate the diagnostic tool used

Table 2| ADTKD families with their respective mutation

Family ID	Index patient ID	Gene	cDNA	Amino acid
A-5	ADTKD-0003	*MUC1*	c.428dupC	MUC1-fs
A-11	ADTKD-0013	*MUC1*	c.428dupC	MUC1-fs
A-12	ADTKD-0015	*MUC1*	c.428dupC	MUC1-fs
A-14	ADTKD-0017	*MUC1*	c.428dupC	MUC1-fs
A-15	ADTKD-0018	*MUC1*	c.428dupC	MUC1-fs
A-21	ADTKD-0024	*MUC1*	c.428dupC	MUC1-fs
A-23	ADTKD-0026	*MUC1*	c.428dupC	MUC1-fs
A-24	ADTKD-0027	*MUC1*	c.428dupC	MUC1-fs
A-29	ADTKD-0032	*MUC1*	c.428dupC	MUC1-fs
A-30	ADTKD-0041	*MUC1*	c.428dupC	MUC1-fs
A-33	ADTKD-0048	*MUC1*	c.428dupC	MUC1-fs
A-35	ADTKD-0055	*MUC1*	c.428dupC	MUC1-fs
A-36	ADTKD-0056	*MUC1*	c.428dupC	MUC1-fs
A-37	ADTKD-0057	*MUC1*	c.428dupC	MUC1-fs
A-38	ADTKD-0058	*MUC1*	c.428dupC	MUC1-fs
A-43	ADTKD-0070	*MUC1*	c.428dupC	MUC1-fs
A-47	ADTKD-0077	*MUC1*	c.428dupC	MUC1-fs
A-50	ADTKD-0082	*MUC1*	c.428dupC	MUC1-fs
A-59	ADTKD-0106	*MUC1*	c.428dupC	MUC1-fs
A-6	ADTKD-0006	*UMOD*	c.397_405del	p.(Tyr133_Cys135del)
A-13	ADTKD-0016	*UMOD*	c.586G>A[43]	p.(Asp196Asn)
A-16	ADTKD-0019	*UMOD*	c.707C>G[44]	p.(Pro236Arg)
A-27	ADTKD-0030	*UMOD*	c.768C>G	p.(Cys256Trp)
A-32	ADTKD-0047	*UMOD*	c.509G>A[45]	p.(Cys170Tyr)
A-41	ADTKD-0066	*UMOD*	c.1463G>A[46]	p.(Gly488Asp)
A-44	ADTKD-0072	*UMOD*	c.899G>T	p.(Cys300Phe)
A-61	ADTKD-0132	*UMOD*	c.(464G>A; 907G>C)	p.(Cys155Tyr; Asp303His)
A-18	ADTKD-0021	*HNF1B*	c.780G>C[47]	p.(Glu260Asp)
A-10	ADTKD-0012	*REN*	c.45_47del[14]	p.(Leu16del)

Family ID	Index patient ID	Variant	ACMG class	CADD score	Reason for exclusion	Diagnostic mutation
A-1	ADTKD-0001	**None**	–	–	–	–
A-2	ADTKD-0102	***COL4A5*** (NM_000495.4): exon 47: c.435G>T, p.(Gly1451Val), hemizygous	5	28.3	–	***COL4A5***
A-7	ADTKD-0062	***PAX2***: GRCh37/hg19: NC_000010.10: g.(?_102495466)_(102510648_?)dup	4	N/A	–	***PAX2***
A-8	ADTKD-0010	**None**	–	–	–	–
A-17	ADTKD-0020	***INF2*** (NM_22489.3): exon 6: c.764G>A, p.(Asp255Asn), heterozygous	3	27.1	–	***INF2***
A-26	ADTKD-0029	***INF2*** (NM_22489.3): exon 2: c.212A>C, p.(Gln71Pro), heterozygous	4	21.4	–	***INF2***
A-31	ADTKD-0045	**None***	–	–	–	–
A-42	ADTKD-0067	***FN1*** (NM_002026.2): intron 22: c.3518-3T>C, heterozygous	3	9.1	No splice effect	–
A-48	ADTKD-0079	***COL4A5*** (NM_000495.4) exon 25: c.1871G>A, p.(Gly624Asp)	5	24.6	–	***COL4A5***
A-49	ADTKD-0080	***COL4A4*** (NM_000092.4): intron 45: c.4333+2T>C, heterozygous	4	26.9	–	***COL4A4***
		PKD1 (NM_000296.3): exon 15: c.4057G>A, p.(Gly1353Ser), heterozygous	3	25	Gene curation	–
A-51	ADTKD-0085	***COL4A5*** (NM_000495.4) exon 25: c.1871G>A, p.(Gly624Asp), hemizygous	5	24.6	–	***COL4A5***
A-52	ADTKD-0090	***COL4A5*** (NM_000495.4) exon 51: c.5030G>A, p.(Arg1677Gln), hemizygous	5	33	–	***COL4A5***
A-53	ADTKD-0091	***SLC7A9*** (NM_014270.4): exon 5: c.544G>A, p.(Ala182Thr), heterozygous	4	15.73	Segregation	–
A-54	ADTKD-0092	***SALL1*** (NM_001127892): genomic, heterozygous deletion around exon 2 and 3'UTR: HGVS: NC_000016.9: g.(?_51168112)_(51171538_?)del	4	N/A	–	***SALL1***
		PKD2 (NM_000297): genomic, heterozygous deletion of exon 13: HGVS: NC_000004.11: g.88989050-88989213del, r. 2458_2621del, p.Leu842ProfsTer20	4	N/A	–	***PKD2***
A-56	ADTKD-0094	***COL4A3*** (NM_000091.49): exon 23: c.1483C>T, p.(His495Tyr), heterozygous	3	15.02	Segregation	–
		BLK (NM_001715.2): exon 11: c.1075C>T, p.(Arg359Cys), heterozygous	3	29.4	Segregation	–
A-57	ADTKD-0095	GRCh37/hg19: heterozygous deletion NC_000020.10:g.(?_62669975)_(62694737_?) Deleted genes: ***C20orf204, SOX18, TCEA2***	3	N/A	Segregation	–
		EHHADH (NM_001966.3): exon 7: c.1411G>C, p.(Val471Leu), heterozygous	3	25.3	Segregation	–

Take Home Message

- Nos encontramos en un momento ciertamente emocionante, porque la NGS está teniendo un tremendo impacto en la investigación, la medicina y la atención clínica.

- El Diagnóstico genético ya no **es un tabú**: Más **barato**, más **rápido** y más **eficiente. Debemos convencer a nuestros hospitales!!!!**

- Empezamos a cerrar el cerco para la investigación e **identificación de nuevos genes y** mecanismos genéticos de enfermedad asociados a **nuevas enfermedades complejas, raras y ultra-raras en NEFROLOGIA**.

- La genética empieza a proporcionar resultados con un **beneficio directo en nuestros pacientes y sus familias**: no solo en el uso de **posibles tratamientos**, también en el establecimiento de estrategias poblacionales de **erradicación de enfermedades** como el Diagnóstico Genético Preimplantaciónal **DGP (UNA REALIDAD).**

GRACIAS

NefroCHUS

maria.garcia.murias@sergas.es -
nefrochus@gmail.com

981 950 904 www.nefrochus.com