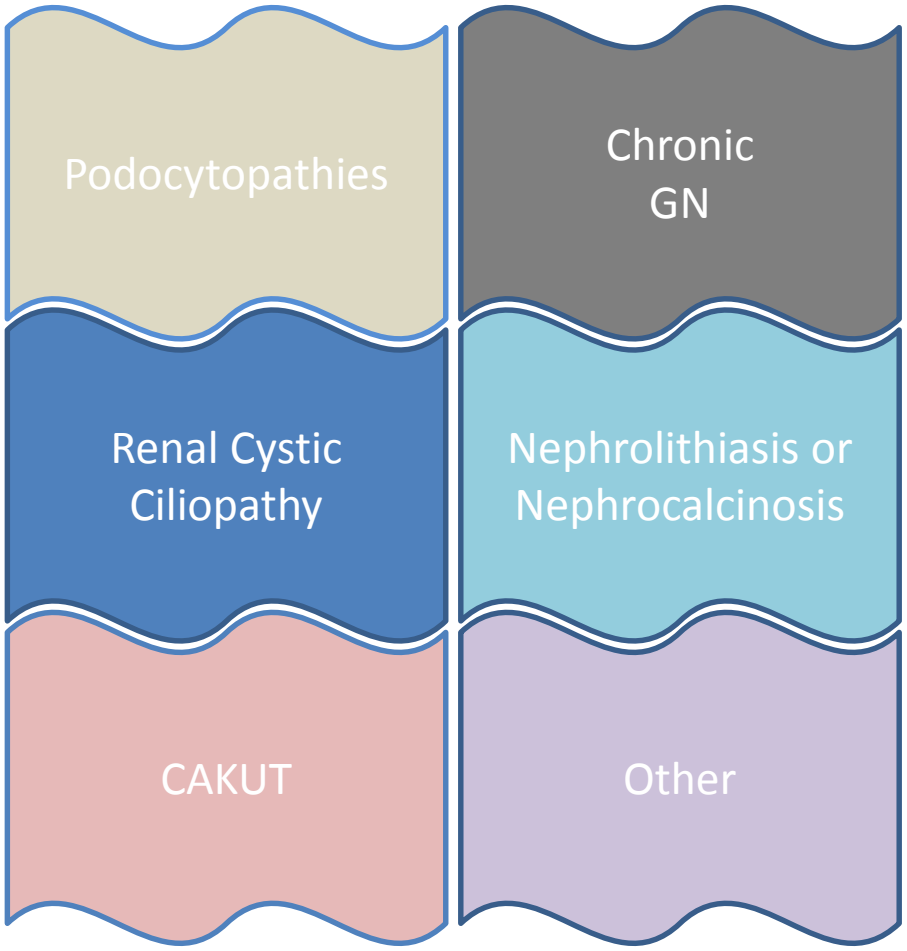
Gian Marco Ghiggeri

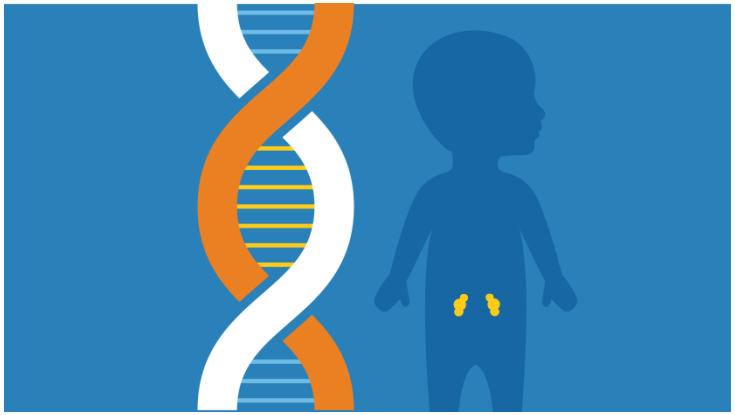
La nuova via della genetica delle malattie renali

PRENDIAMOCI A
CUORE IL RENE

Milano 2-3 dicembre 2016



NephroExome
225 Renal OMIM genes



Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA–EDTA registry

Nicholas Chesnaye · Marjolein Bonthuis · Franz Schaefer · Jaap W. Groothoff · Enrico Verrina · James G. Heaf · Augustina Jankauskiene · Viktorija Lukosiene · Elena A. Molchanova · Conceicao Mota · Amira Peco-Antić · Ilse-Maria Ratsch · Anna Bjerre · Dimitar L. Roussinov · Alexander Sukalo · Rezan Topaloglu · Koen Van Hoeck · Ilona Zagozdzon · Kitty J. Jager · Karlijn J. Van Stralen · on behalf of theESPN/ERA–EDTA registry

Pediatr Nephrol. 2015 May;30(5):839-47.

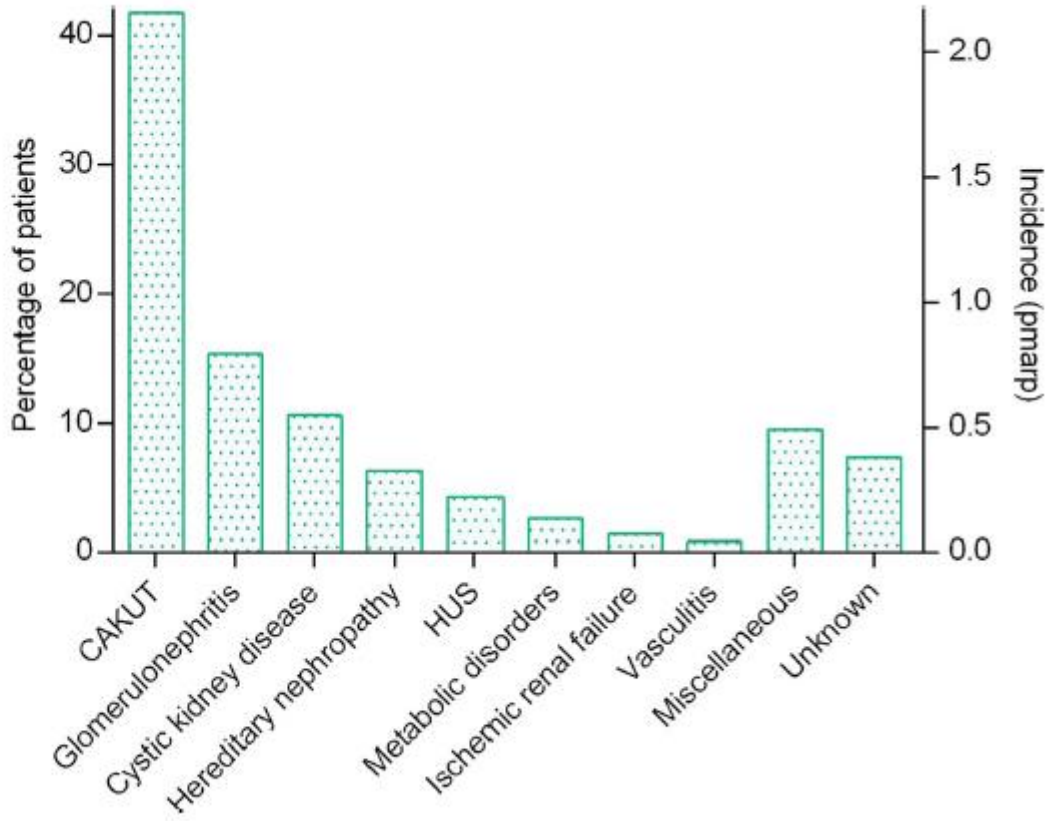


Fig. 2 Frequency distribution and incidence of primary renal disease for paediatric patients aged 0–14 years starting RRT between 2009 and 2011. *CAKUT* Congenital anomalies of the kidney and urinary tract, *HUS* haemolytic uraemic syndrome

EXHIBIT 1.1 (continued)
DIALYSIS PATIENT DEMOGRAPHICS

	N	%
All Dialysis Patients	7039	100.0
Primary Diagnosis		
FSGS	1016	14.4
A/hypo/dysplastic kidney	998	14.2
Obstructive uropathy	888	12.6
Reflux nephropathy	244	3.5
SLE nephritis	226	3.2
HUS	216	3.1
Chronic GN	214	3.0
Polycystic disease	201	2.9
Congenital nephrotic syndrome	182	2.6
Prune Belly	144	2.0
Medullary cystic disease	140	2.0
Idiopathic crescentic GN	130	1.8
Familial nephritis	130	1.8
MPGN - Type I	116	1.6
Pyelo/interstitial nephritis	101	1.4
Cystinosis	99	1.4
Renal infarct	90	1.3
Berger's (IgA) nephritis	86	1.2
Henoch-Schonlein nephritis	67	1.0
MPGN - Type II	64	0.9
Wilms tumor	55	0.8
Wegener's granulomatosis	49	0.7
Drash syndrome	39	0.6
Other systemic immunologic disease	37	0.5
OXALOSIS	32	0.5
Membranous nephropathy	29	0.4
Sickle cell nephropathy	21	0.3
Diabetic GN	10	0.1
Other	887	12.6
Unknown	528	7.5

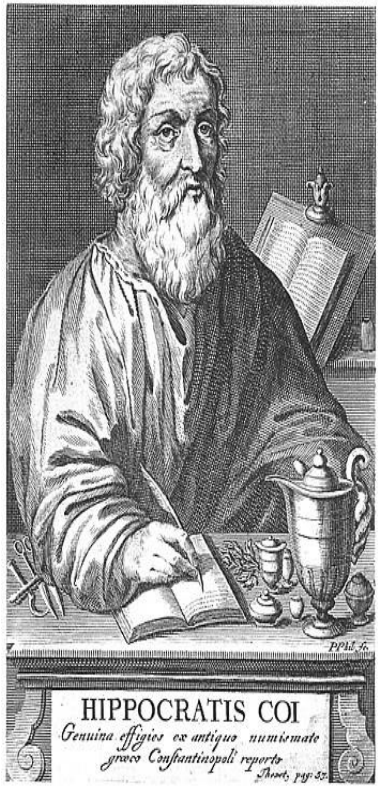
CKD

Table 1 | **Causes and genetic diagnosis of early-onset CKD**

Diagnostic group	Indication to run a gene panel	Proportion of cases of early-onset CKD	Number of known causative genes	Percentage of cases caused by known genes (multiplied by fraction of all CKD)	Refs
CAKUT	CAKUT evident by renal imaging	49.1% (obstructive uropathy 20.7%; renal aplasia, hypoplastic or dysplastic kidneys 17.3%; reflux nephropathy 8.4%; prune belly syndrome 2.7%)	36	~17% (8.5%)*	6,9,10, 39,84
SRNS	SRNS	10.4% (FSGS 8.7%; congenital nephrotic syndrome 1.1%; membranous nephropathy 0.5%; Denys–Drash syndrome 0.1%)	39	~30% (3%)	19,44,64
Chronic GN‡	Evidence of proteinuria and haematuria	8.1% (SLE nephritis 1.6%; familial nephritis (Alport syndrome) 1.6%; chronic GN 1.2%; MPGN type I 1.1%; MPGN type II 0.4%; IgAN 0.9%; idiopathic cresentic GN 0.7%; Henoch–Schönlein nephritis 0.6%)	10	~20% (4%)	4
Renal cystic ciliopathies	Increased echogenicity on renal ultrasound or presence of ≥2 renal cysts	5.3% (polycystic kidney disease 4.0%; medullary cystic kidney disease 1.3%)	95	~70% (3.7%)	11,20, 85,86
aHUS	Microangiopathic haemolytic anaemia, thrombocytopaenia, and AKI	2.0%	9	~60% (1.2%)	87–90
Nephrolithiasis or nephrocalcinosis	Known stone disease or nephrocalcinosis	1.6% (cystinosis 1.5%; oxalosis 0.1%)	30	21% (0.4%)	45,91
Other	Other indications of genetic disease	23.5% (renal infarct 2.2%; pyelonephritis or interstitial nephritis 1.4%; Wilms tumour 0.5%; other systemic immunologic diseases 0.4%; granulomatosis with polyangiitis 0.4%; sickle cell nephropathy 0.2%; diabetic glomerulopathy 0.2%; other nonimmunologic causes 18.2%)	Not known	Not known	Not available
Total	—	100%	~219	(~20%)	—

Data are from the 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies[12]. aHUS; atypical haemolytic uraemic syndrome; AKI, acute kidney injury; CAKUT, congenital anomalies of the kidneys and urinary tract; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus; SRNS, steroid-resistant nephrotic syndrome. *10% of CAKUT can be caused by deleterious copy number variants[47]. ‡The estimates for chronic nephritis monogenic aetiologies are based only on the relative prevalence of Alport syndrome and MPGN, which together account for 20% of the aetiologies of chronic GN and for which a monogenic cause has been established in almost 100% of cases (in one of the following genes: Alport: *COL4A3*, *COL4A4*, *COL4A5* and *COL4A6*; MPGN: *Factor H*, *Factor I*, *MCP/CD46*, *CFHR 5* and *C3*).

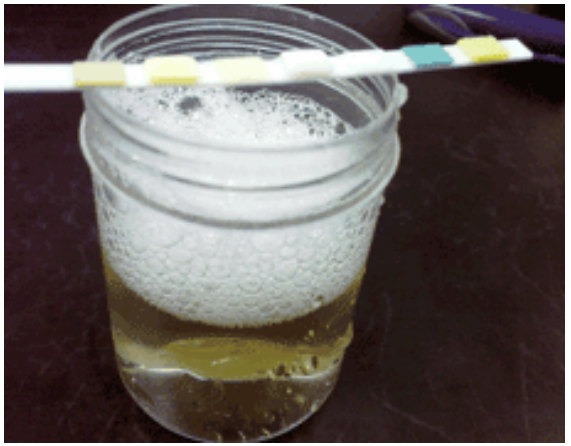
Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease
Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.205



Hippocrates of Kos (460-377 a.C)

"When bubbles settle on surface of the urine, they indicate disease of the kidneys and that the complaint will be protracted…"

aforisma VII 34



NGS workflow overview

Wet lab

- Library Preparation
- Template Preparation
- Sequencing

Primary analysis

- De-multiplexing
- Base Calling

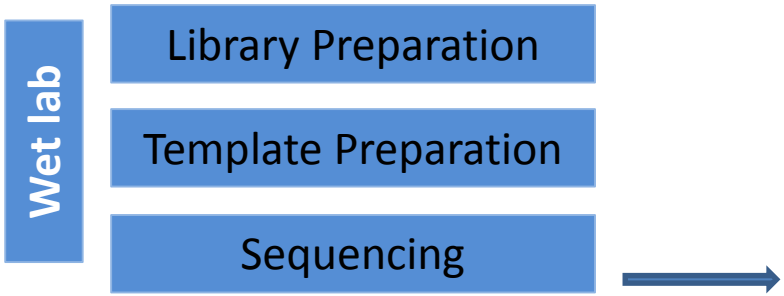
Secondary analysis

- Read mapping
- Variant Calling

Tertiary analysis

- Variant annotation
- Variant filtering

NGS workflow overview



Sequencing by sinthesys
Detection by:
Illumina- fluorescence
IonTorrent: pH
Roche/454 – PO4 and light

illumina®

ion torrent
by life technologies™

Roche
454
SEQUENCING

Towards:

- an extension of genetic tests
- an extension of translated messages from genetic tests
- a personalized medicine

-Diseases of Podocyte

-CAKUT

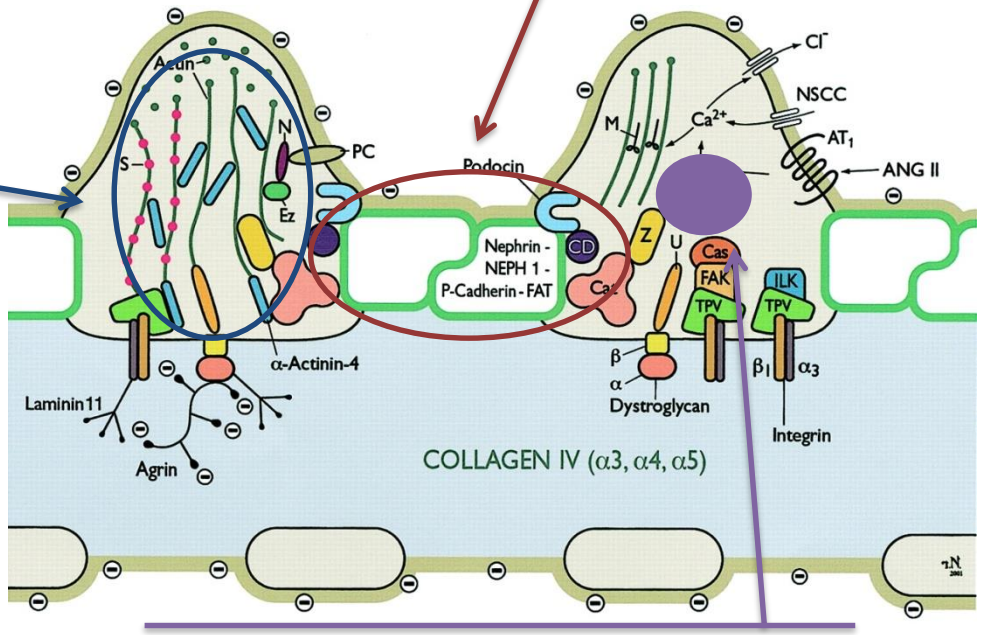
-PKD

ACTIN CYTOSKELETON AND SIGNALING

ACTN4	AD	Adult onset NS
MYH9	Risk allele	Adult onset NS
INF2	AD	Familial/sporadic NS; Charcot-Marie-Tooth
SYNPO	?	Adult onset NS
APOL1	Complex; AR	Adult onset NS
MYO1E	AR	Early or adult onset NS
ARHGAP24	AD	Adult onset NS
ARHGDIA	AR	CNS

SD ASSOCIATED AND ADAPTOR PROTEINS

NPHS1	AR	CNS/NS
NPHS2	AR	CNS, NS – childhood and adult onset
CD2AP	AD-AR ?	Early-onset NS, HIV nephropathy
PLCE1	AR	Early-onset NS
TRPC6	AD	Adult onset NS
PTPRO	AR	Childhood-onset NS



NUCLEAR PROTEINS

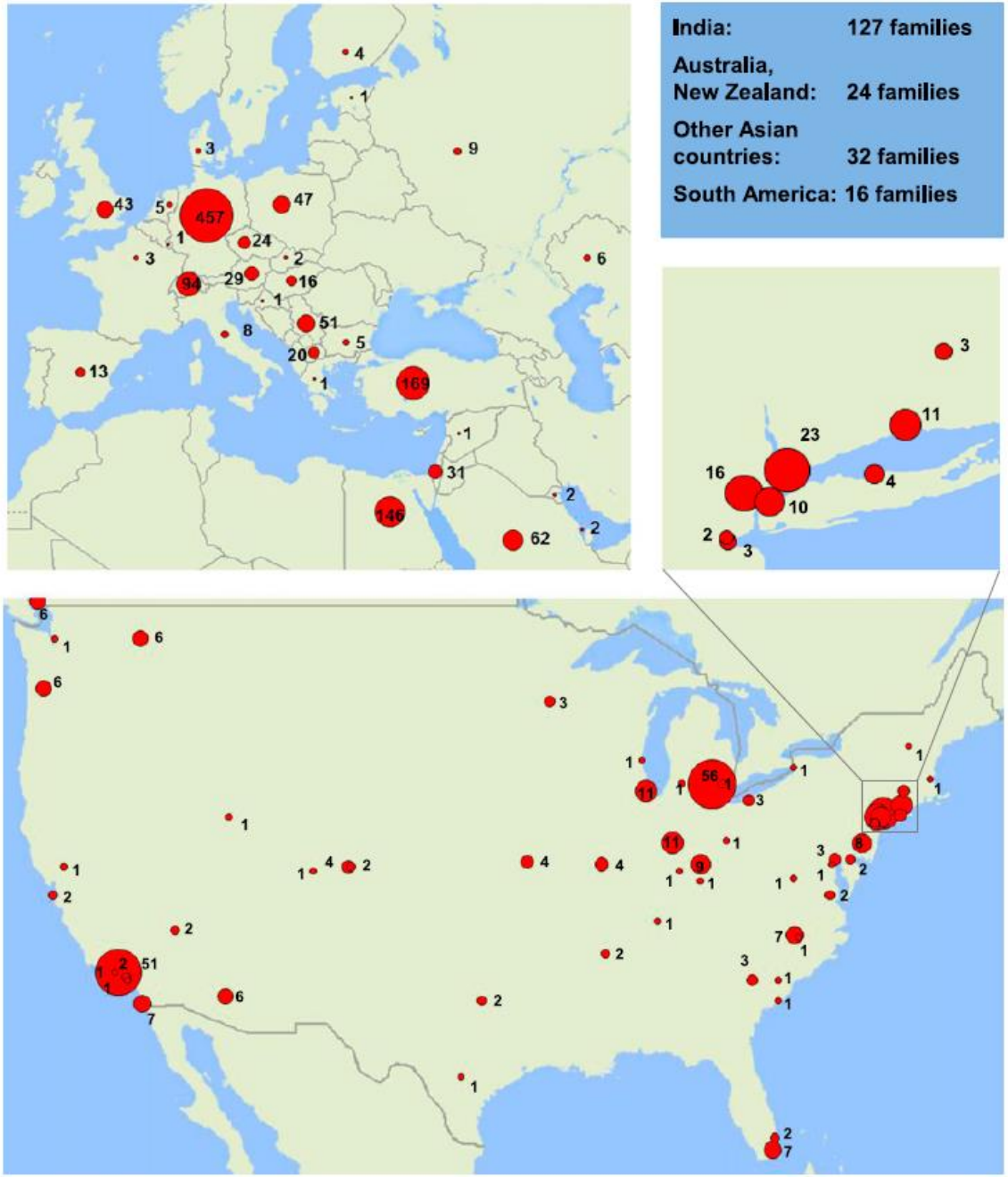
WT1	Sporadic; AD	Adult onset NS, Denys–Drash and Frasier Syndromes
LMX1B	AR	Nail–Patella Syndrome/NS only
SMARCAL1	AR	Schimke immuno-osseous dysplasia

State of art on podocyte gene analysis in nephrotic syndrome (NGS)

• **Florence study**	*Giglio et al.*	JASN 2015
• **Harvard study**	*Sadowski et al.*	JASN 2015
• **PODONET**	*Trautman et al.*	cJASN 2015 ongoing study
• **ItaNet**	*Gigante-Caridi et al.*	ongoing study

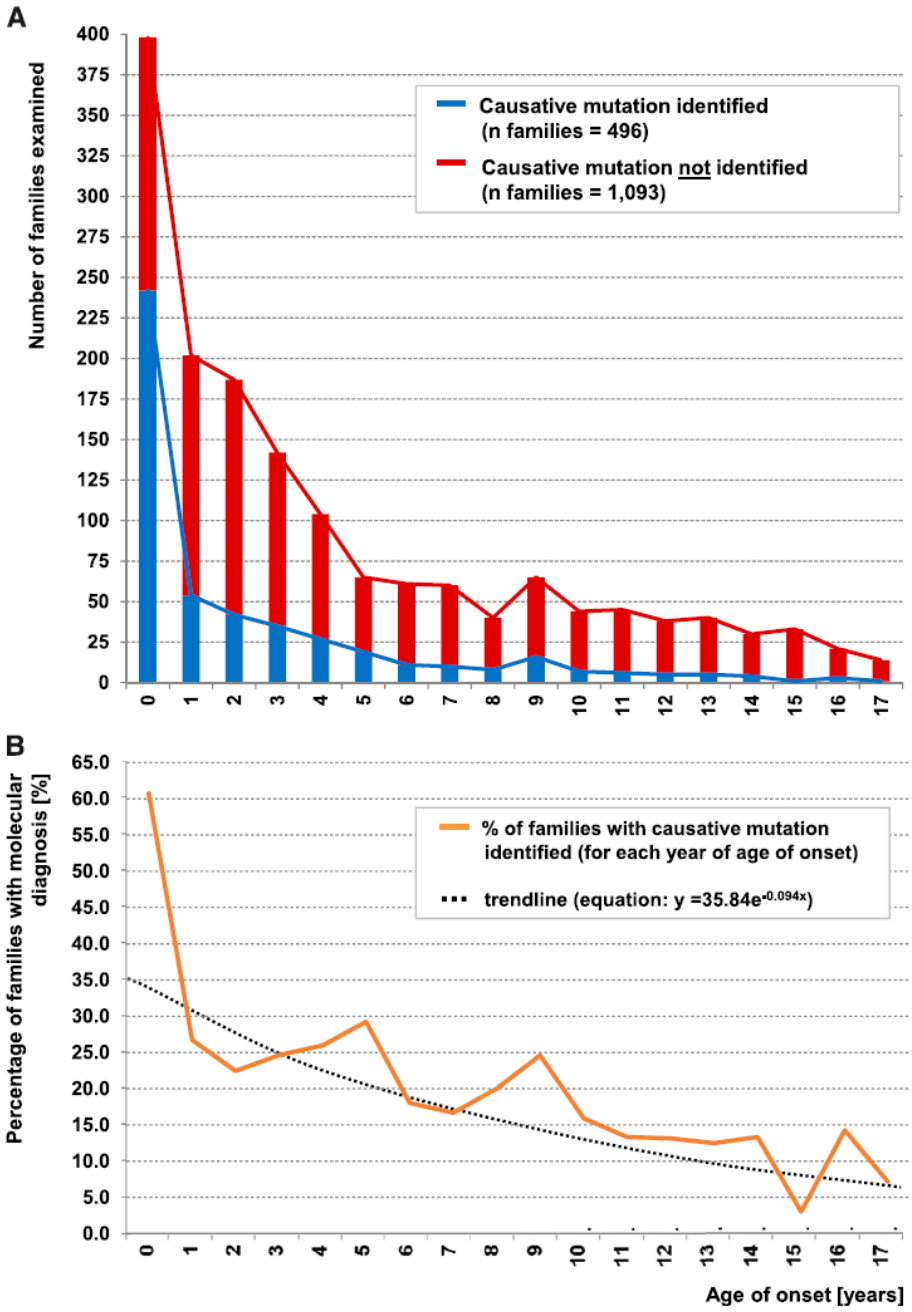
	N	age/yrs	Study Cohort	Technique
Florence	31	<15	**Steroid Resistant**	**NGS**
	38		**Steroid sensitive**	
Harvard	1.783 (+233 Fm)	<50	**Steroid Resistant**	**NGS, Sanger**
	185		**Steroid Sensitive**	
PODONET	514	<17	**Steroid Resistant**	**NGS, Sanger**
	243		**Drug Resistant (CNI)**	
	464		**Drug Dependent (CNI)**	
ItaNet	910	0.2-60		
	370	<30	**Multidrug Resistant**	**NGS, Sanger**
	170		**Multidrug Dependent**	

Harvard



J Am Soc Nephrol 26: 1279–1289, 2015. doi: 10.1681/ASN.2014050489

Harvard



J Am Soc Nephrol 26: 1279–1289, 2015. doi: 10.1681/ASN.2014050489

ItaNet (ongoing study….)

Genoa Center

430 DNA from Italy centers

Sanger seq. for (*NPHS2*, *WT1, INF2 or specific gene for syndrome)*

Complete clinical data available for 385 pts (30.6.2015)

NGS Nephrotic syndrome panel for 17 genes

IonTorrent platform

Bari-Foggia Center

380 DNA from Italy centers

Sanger seq. for (NPHS1, NPHS2, WT1, TRPC6 or specific gene for syndrome)

Complete clinical data available for 183 pts (30.6.2015)

NGS Nephrotic Syndrome panel for 34 genes

Myseq Illumina platform

MultiDrug Resistant

N° 231

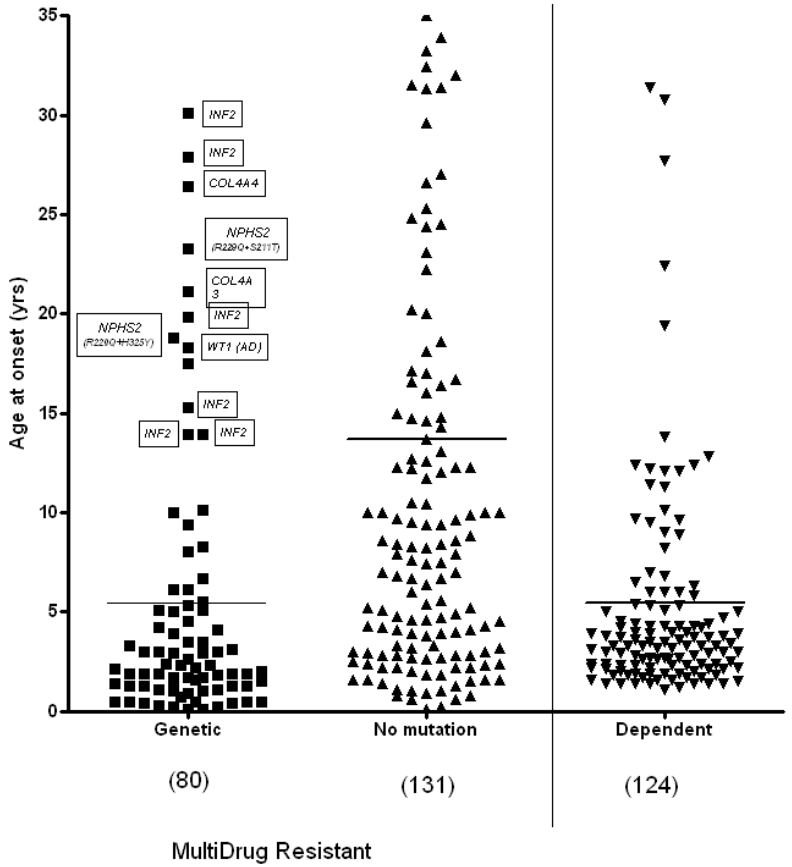
Onset	N°	Genetic/no mut.
0-3 yrs	97	52/45
4-6	33	11/22
7-10	31	5/26
11-20	32	7/23
> 21	38	5/35

N° 355

MultiDrug Dependent

N° 124

Onset	N°
0-3 yrs	75
4-6	27
7-10	8
11-20	10
> 21	5



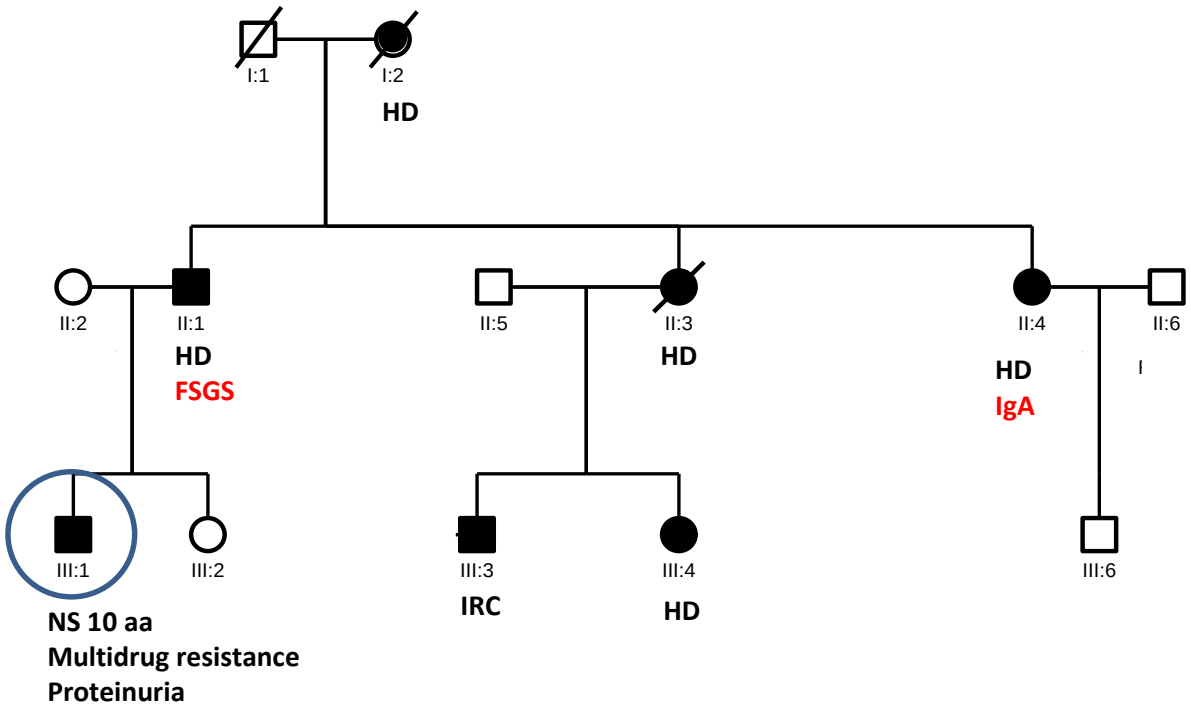
Gene Causing SRNS	Mode of Inheritance	Harward (1783)	PodoNet (514)	Florence (69)	ITAnet (568)	TOT (2934)	%
NPHS2	AR	177	138	5	55	375	38,9
NPHS1	AR	131	41	0	53	225	23,3
WT1	AD	85	48	0	30	163	16,9
PLCE1	AR	37	10	2	1	50	5,2
SMARCAL1	AR	16	12	0	2	30	3,1
LAMB2	AR	20	5	0	0	25	2,6
INF2	AD	9	4	0	11	24	2,5
TRPC6	AD	9	1	0	6	16	1,7
COQ6	AR	8	0	0	0	8	0,8
PTPRO	AR	0	6	0	0	6	0,6
LMX1B	AD	4	1	1	0	6	0,6
ITGA3	AR	5	0	0	0	5	0,5
MYO1E	AR	5	0	0	0	5	0,5
CUBN	AR	5	0	0	0	5	0,5
COQ2	AR	4	1	0	0	5	0,5
ADCK4	AR	3	1	0	0	4	0,4
CD2AP	AR	0	0	0	3	3	0,3
DGKE1	AR	2	0	0	0	2	0,2
PDSS2	AR	2	0	0	0	2	0,2
ACTN4	AD	0	0	2	0	2	0,2
ARHGAP24	AD	1	0	0	0	1	0,1
ARHGDIA	AR	1	0	0	0	1	0,1
CFH	AR	1	0	0	0	1	0,1
ITGB4	AR	1	0	0	0	1	0,1

Tot. **965/2934**

Multidrug dependence NGS panel (17 genes)

N° of patient	50
Median Age at Onset (yrs)	5.55 (1.1-12.8)
Median follow up (yrs)	12.7 (3.7-33.5)
Steroid	50 (100%)
MMF	8 (16%)
CYCLO	14 (28%)
CsA	48 (96%)
RTX	38 (76%)
Total Variants	5948
Filtered (MAF>=0.05)	86
Coverage mean	98.86 %
Uniformity	97.2%
Mean depth	258X

No deleteriuos Variant



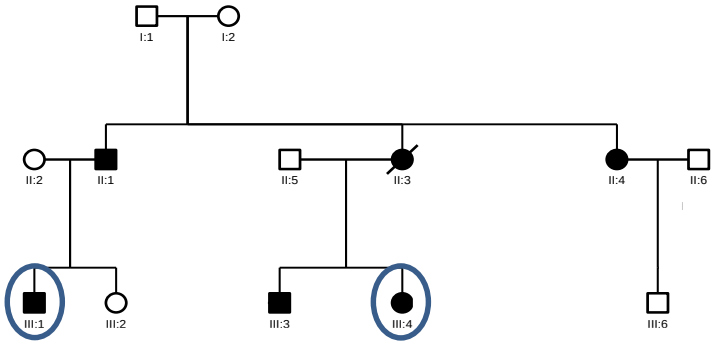
Pannello Sindrome Nefrosica
Ampliseq –IonTorrent
17 geni
Campione III:1
124 varianti identificate

.vfc on wANNOVAR

MAF >=0.01 per 1000G
ESP-6500
EXAC

Nessuna variante significativa

Whole Exome Sequencing
TruSeq Illumina v.2
HiSeq2000



Coverage medio >= 30X

	Reads (M)	Bases (G)	SNP totali	In/del totali	Dopo filtering
III:1	44.1	6.51	156275	10413	22
III:3	40.6	5.93	152498	10110	19

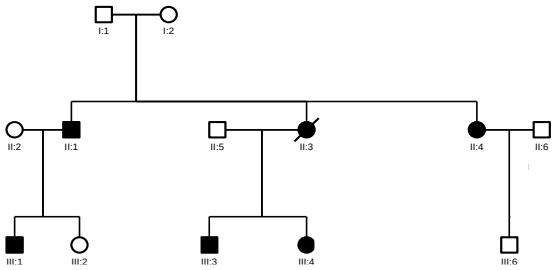
↓

Prioritizzazione ad espressione renale e concordanza nei due affetti

Chr2: 228009275C>T: *COL4A4*:NM_000092.4:c.72-1G>A HET

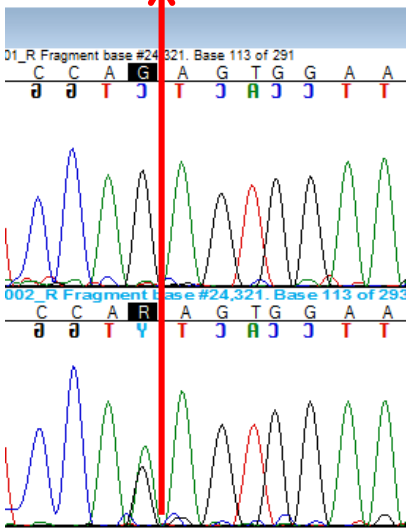
COL4A4: c.72-1G>A

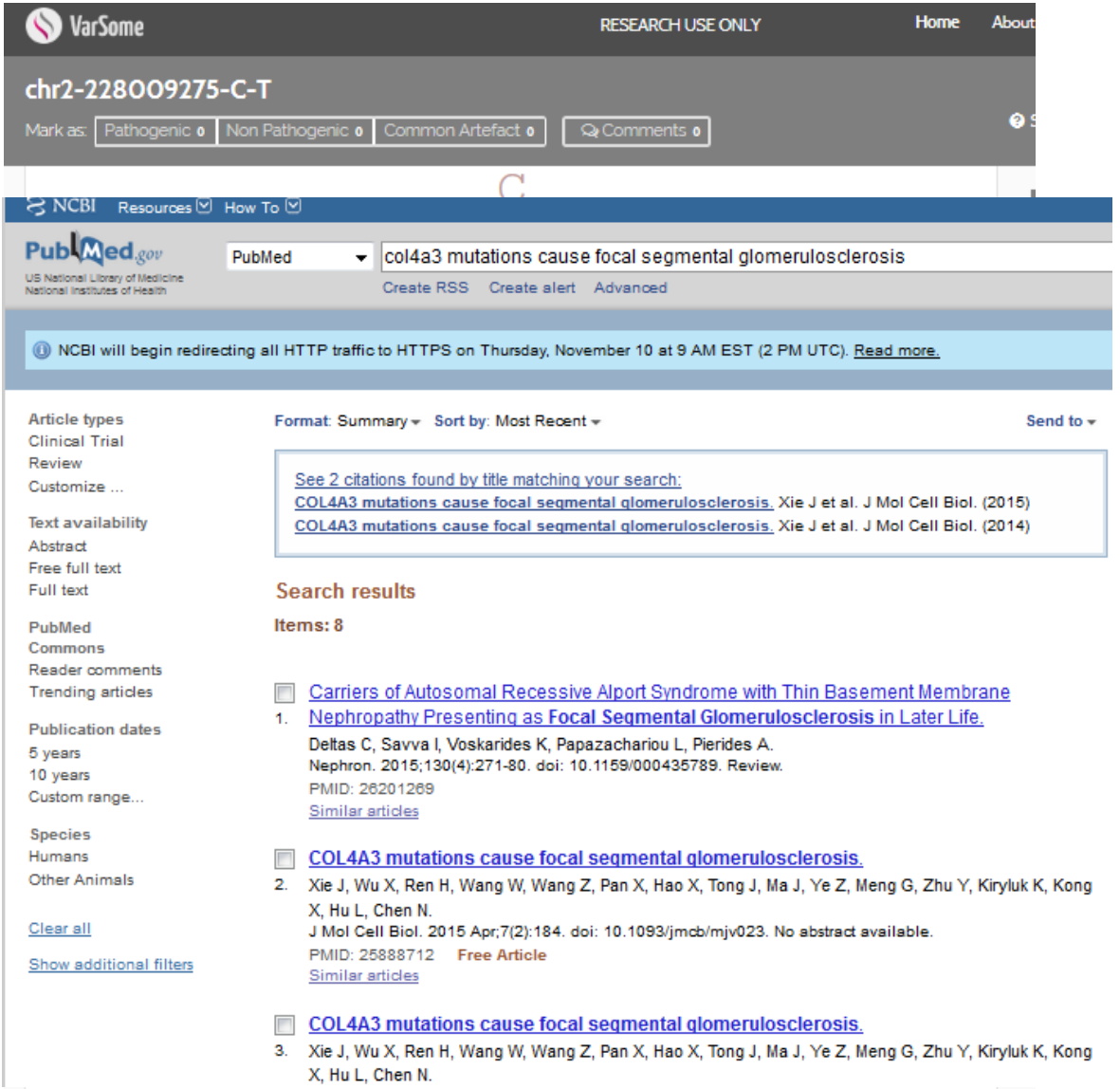
AR: Alport Syndrome
AD: Benignal Familial Hematuria



Intron 2 Exon 3

ccagAGTGGAA





ACTIN CYTOSKELETON AND SIGNALING

ACTN4	AD	Adult onset NS
MYH9	Risk allele	Adult onset NS
INF2	AD	Familial/sporadic NS; Charcot-Marie-Tooth
SYNPO	?	Adult onset NS
APOL1	Complex; AR	Adult onset NS
MYO1E	AR	Early or adult onset NS
ARHGAP24	AD	Adult onset NS
ARHGDIA	AR	CNS

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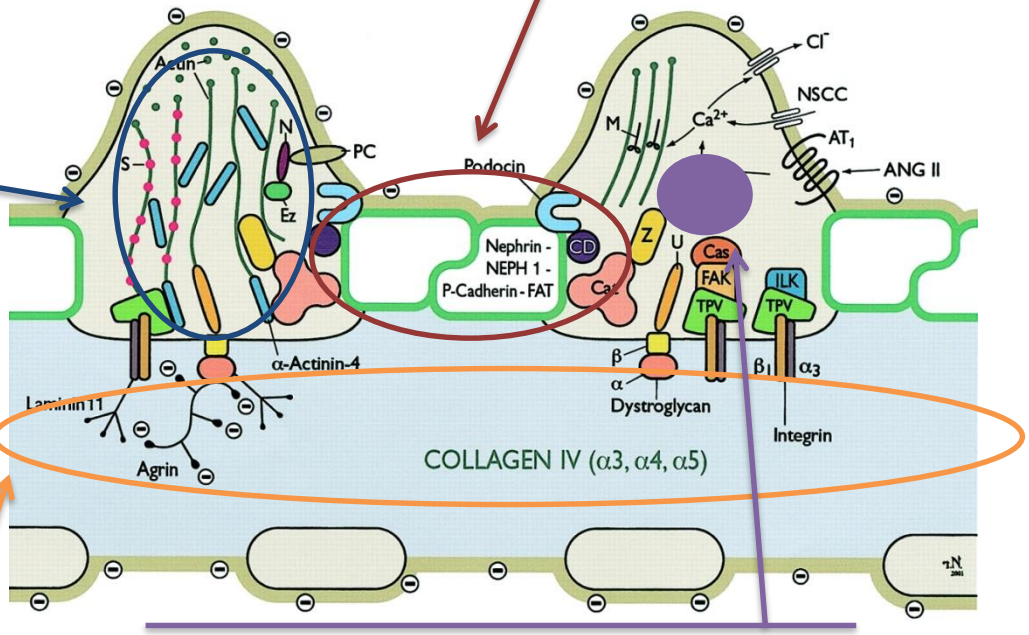
NPHS1	AR	CNS/NS
NPHS2	AR	CNS, NS – childhood and adult onset
CD2AP	AD-AR ?	Early-onset NS, HIV nephropathy
PLCE1	AR	Early-onset NS
TRPC6	AD	Adult onset NS
PTPRO	AR	Childhood-onset NS



GBM

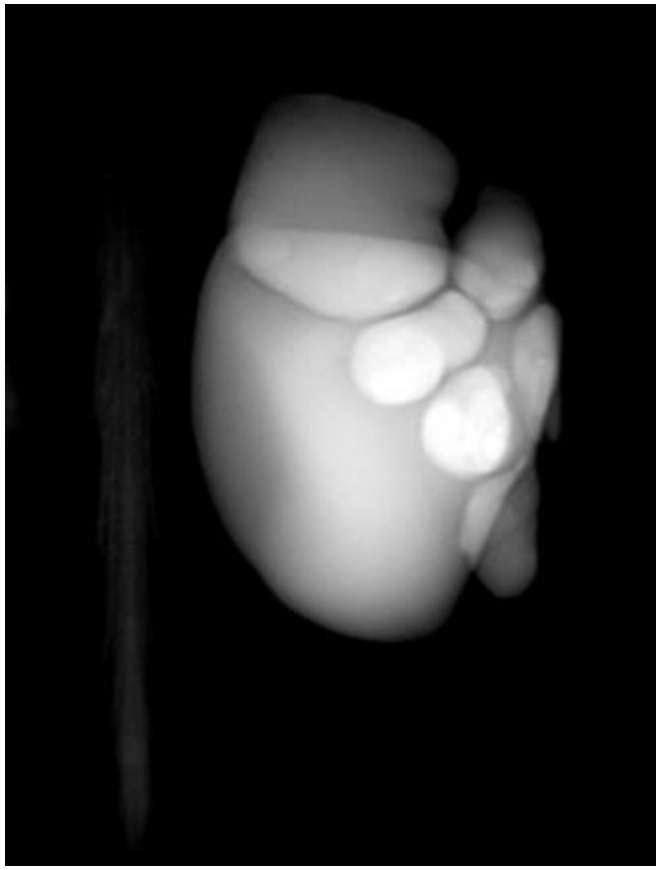
COL4A3	AR	Alport's disease
COL4A4	AR	Alport's disease
COL4A5	X-linked	Alport's disease

NUCLEAR PROTEINS

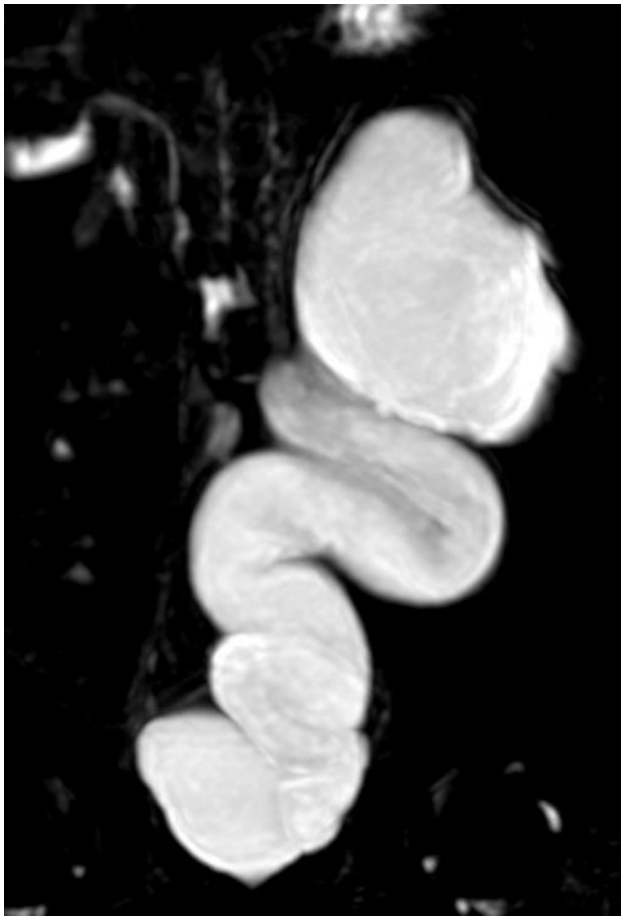
WT1	Sporadic; AD	Adult onset NS, Denys–Drash and Frasier Syndromes
LMX1B	AR	Nail–Patella Syndrome/NS only
SMARCAL1	AR	Schimke immuno-osseous dysplasia

CAKUT

Congenital **A**nomalies of the **K**idney and the **U**rinary **T**ract



SS FSE 40 mm
10 sec acq time

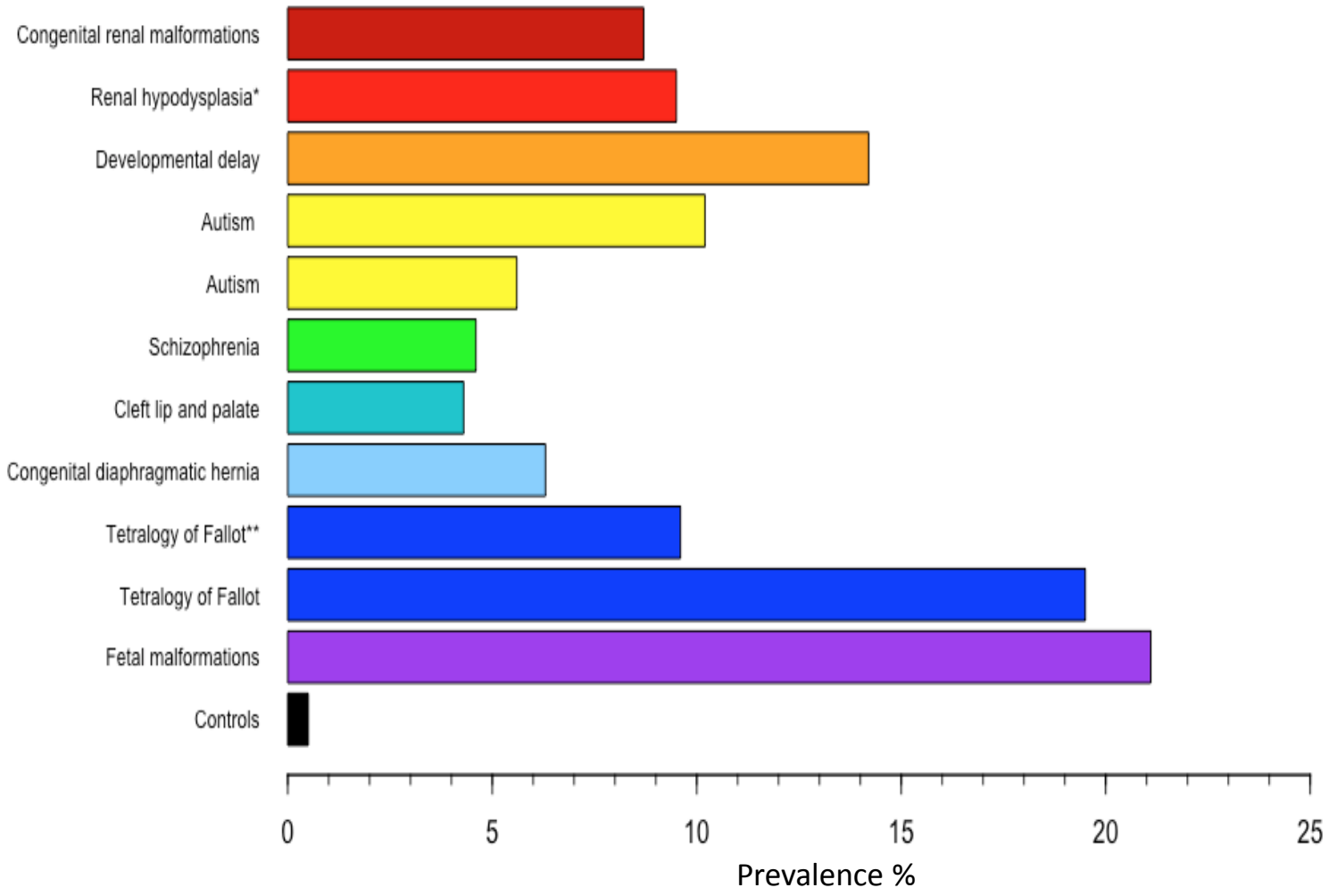


TSE T23D RT con ric.MIP e MPR

- **CNV**: copy number variations, i.e. the gain (duplication) or loss (deletion) of genomic DNA of a size ranging from 1 kilobase to several megabases. ~5 of human DNA is subject to variations in copy number across the genome

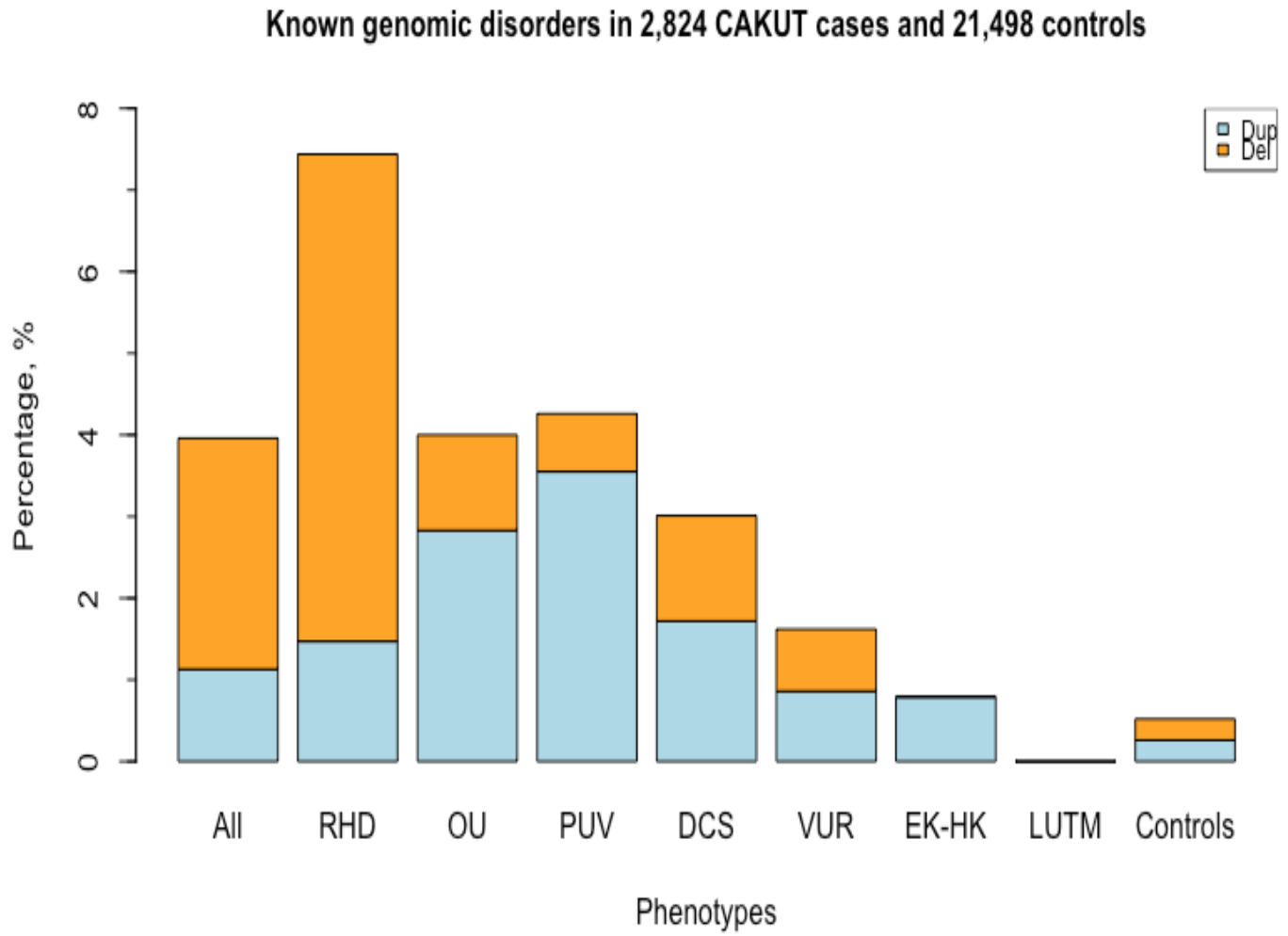
- **DNA microarray**: platforms used to genotype a large number of known SNPs at high density (0.5-2.5 millions across the genome) that can be used to infer CNVs

Prevalence of Known Genomic Disorders in Human Disease



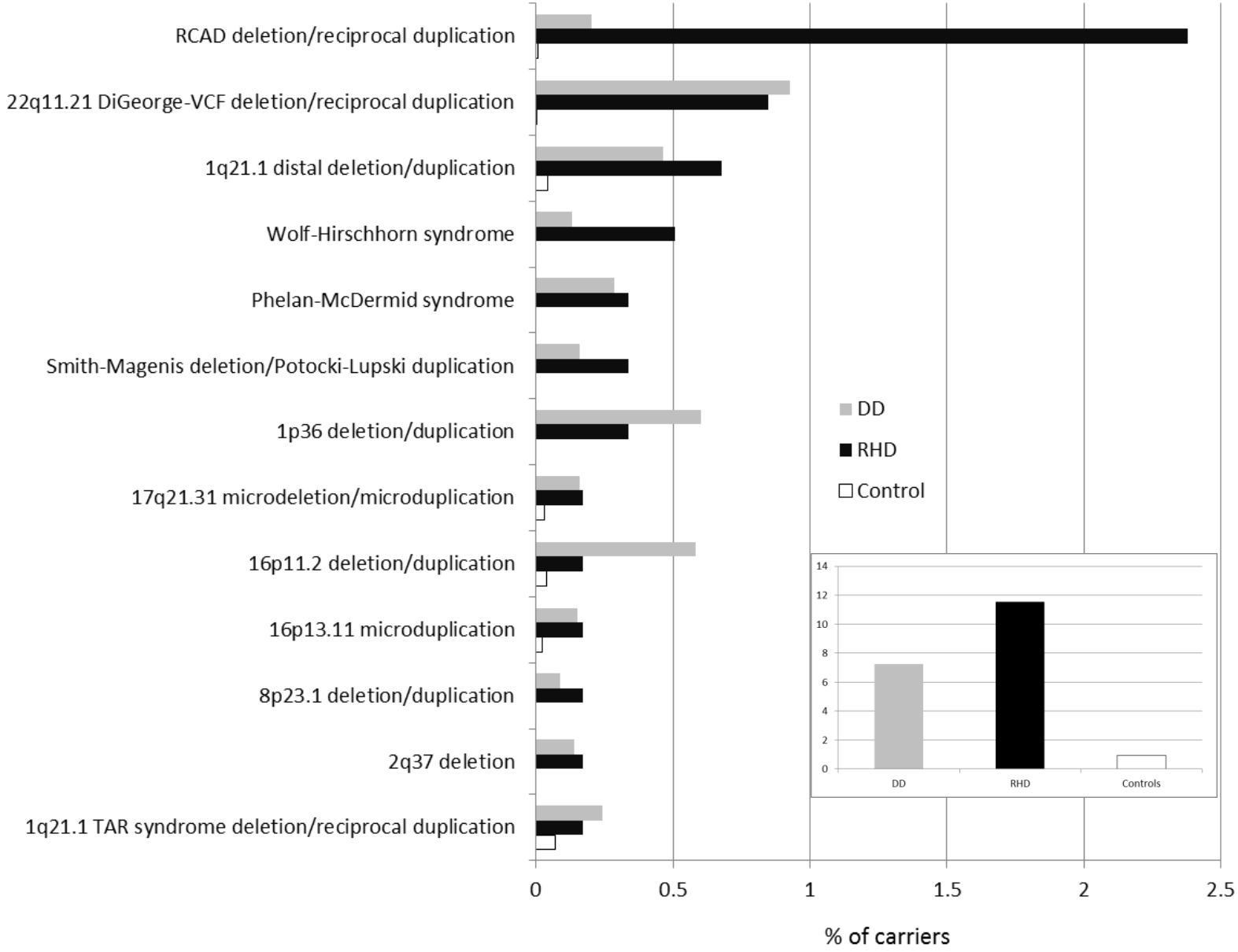
Sanna-Cherchi et al. *J Clin Invest in preparation*

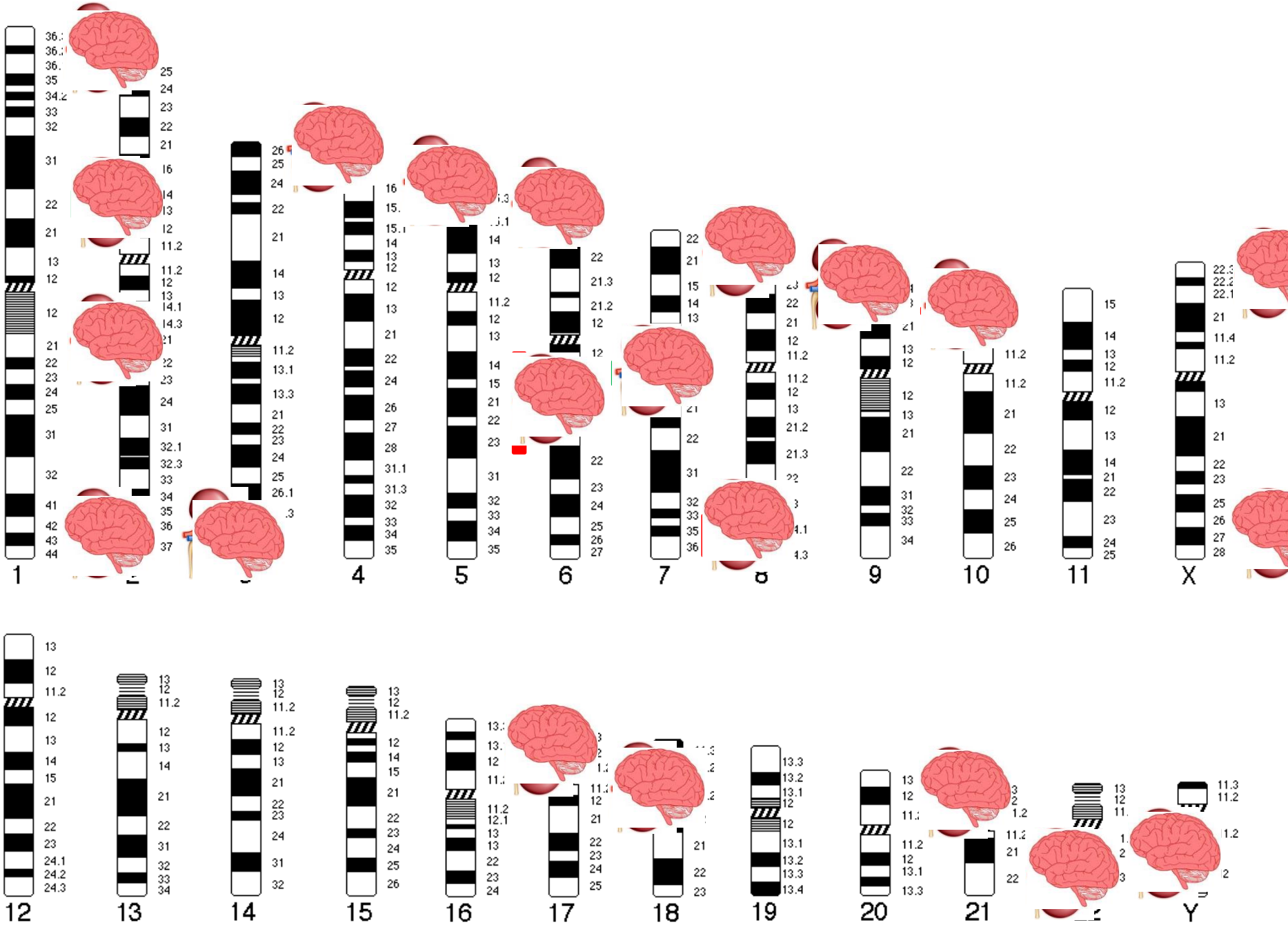
CNV analysis on a large cohort demonstrates that CAKUT categories have distinct genomic architecture



Sanna-Cherchi,
personal data

Genetic Overlap Between CAKUT and Developmental Delay




1
4
5
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X
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17
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19
20
21
Y

Extra Renal Manifestations

- About one-third of CAKUT patients present a coexisting congenital defect involving non-renal or non-urinary tract structures

- Most of CNVs that we identified in CAKUT affect the same loci found to be pathogenic in patients with Neurodevelopmental disorders

- Many children with CAKUT are diagnosed in utero or shortly after birth, therefore, it is critical to develop tools for risk stratification and therapy of late onset disease such as autism, intellectual disability, diabetes, and others.

Precision Medicine on CAKUT: Hypotheses

- Precise molecular diagnosis via DNA microarrays can significantly improve diagnosis, risk stratification, and clinical management for CAKUT patients

- Kidney malformations (detectable in utero) can act as sentinel for hidden diseases that manifest later and molecular diagnosis can significantly improve medical management for such patients

- Simone Sanna-Cherchi's Lab, Columbia University,
- Ali Gharavi's Lab, Columbia University, NY

-Gian Marco Ghiggeri
-Francesco Scolari

-Principal Collaborating sites

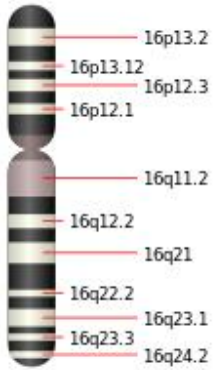
Ancona, Italy	Giovanni Frasca
Barcelona, Spain	JM Campistol, Lida Rodas Marin
Bari, Italy	Loreto Gesualdo, Mario Giordano, Milena Gigante
Belo Horizonte, Brazil	Ana Cristina Simoes y Silva
Brescia, Italy	Francesco Scolari, Claudia Izzi
Cagliari, Italy	Giuseppe Masnata
CHOP, Philadelphia	Hakon Hakonarson
CKiD Study	Bradley A. Warady, Susan L. Furth, Craig Wong
Duke University	Nicholas Katsanis, Yangfan (Phoebe) Liu
Harvard University	Friedhelm Hildebrandt, Asaf Vivante
Istanbul, Turkey	Yasar Caliskan
Milan, Italy	Daniele Cusi, G. Ardissino, Vinicio Goj
Messina, Italy	Givanni Conti, Domenico Santoro
Olomouc, Czech Republic	Hana Flogelova
Parma, Italy	Landino Allegri, Isabella Pisani, Mariarosa Maiorana
PRCM, Poland	Anna Materna-Kiryluk, Anna Latos-Bielenska
Skopje, Macedonia	Velibor Tasic, Zoran Gucev
Split, Croatia	Marijan Saraga, Mirna Saraga Babic
Trieste, Italy	Giuliano Boscutti
UCLA, Los Angeles	Patricia Weng
U. Michigan, Ann Arbor	Edgar Otto, Matthew Sampson
VUMC, Amsterdam	Rik Westland, Johanna van Wijk
Yale University	Richard Lifton

The Midwest Pediatric Nephrology Consortium (MWPNC)

PKD

- "In the beginning was the gene":

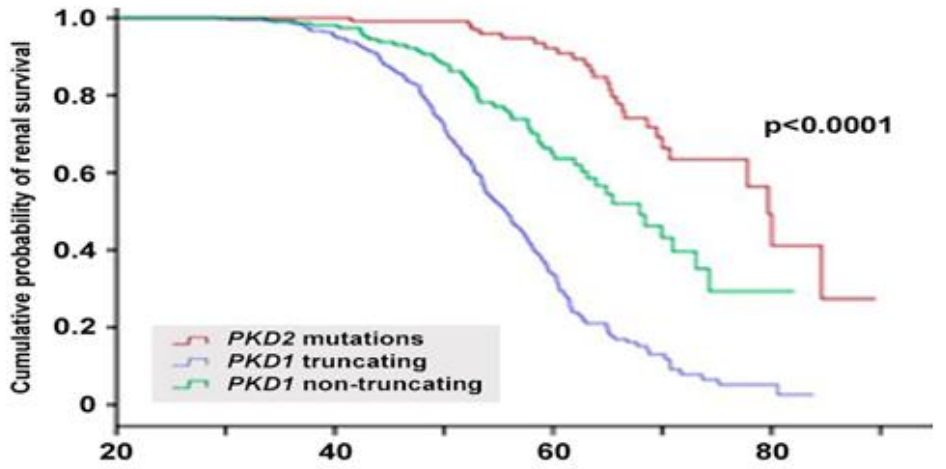
PKD gene mutation



ESRD

Le Meur Y, 2015

GENE LOCUS AND ALLELIC EFFECT ON PHENOTYPE



Patients at risk:						
PKD1 truncating	356	296	175	53	11	2
PKD1 non-truncating	172	144	134	48	15	1
PKD2 mutations	127	116	99	63	23	5

Mutation of *PKD2*:
Median age at ESRD: 77.8 yrs

Non truncating mutation of *PKD1*:
Median age at ESRD: 65.8 yrs

Truncating mutation of *PKD1*:
median age at ESRD: 55.1 yrs

Cornec-Le Gall E, JASN 2013

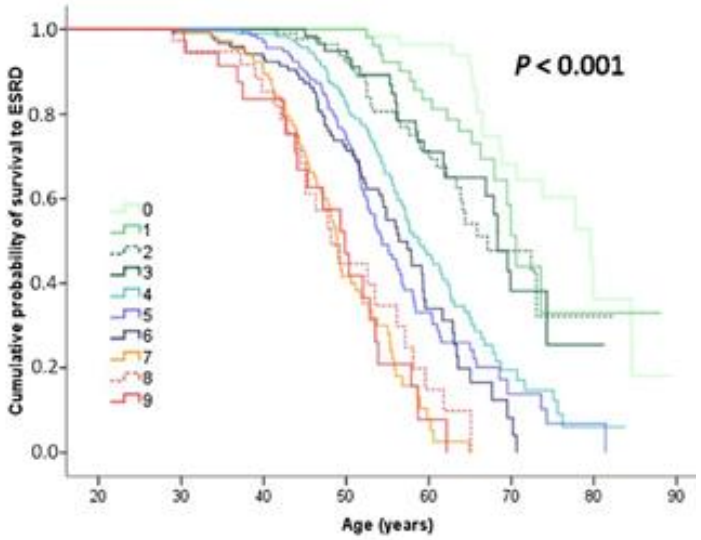
THE PROPKD SCORE:
A NEW ALGORITHM TO PREDICT RENAL SURVIVAL IN ADPKD

MULTIVARIATE COX ANALYSIS

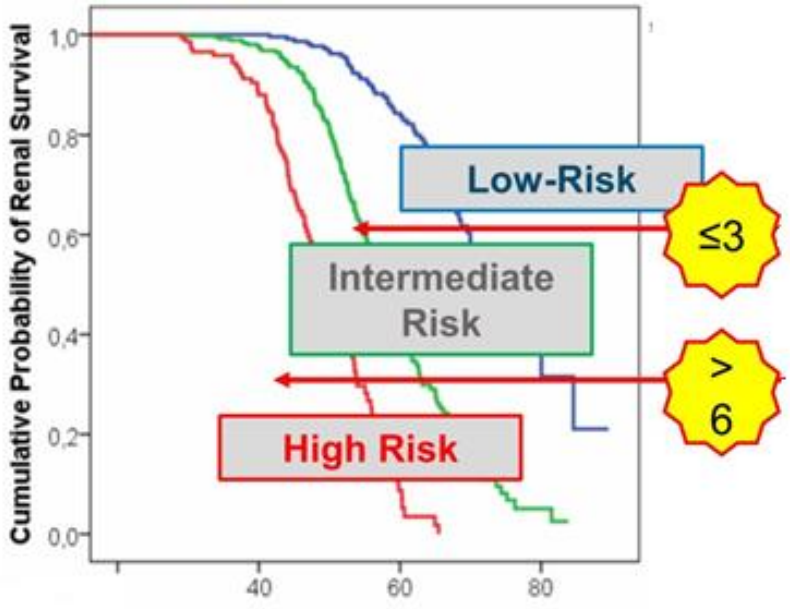
VARIABLE	PATIENTS (N)	HR (95% CI)	P VALUE	POINTS FOR PROPKD SCORE
FEMALE	541			0
MALE	432	1.55 (1.29-1.88)	<0.001	1
HYPERTENSION < 35 YR, NO	679			0
HYPERTENSION < 35 YR, YES	294	2.11 (1.71-2.61)	<0.001	2
≥1 UROLOGIC EVENT < 35 YR, NO	734			0
≥1 UROLOGIC EVENT < 35 YR, YES	239	1.73 (1.38-2.18)	<0.001	2
PKD2 MUTATION	186			0
PKD1 NON-TRUNCATING MUT.	239	2.27 (1.57-3.28)	0.002	2
PKD1 TRUNCATING MUTATION	548	4.75 (3.41-6.60)	<0.001	4

The PROPKD score and survival

RENAL SURVIVAL BASED ON PROPKD SCORE 0-9 POINTS



STRATIFICATION OF RISK OF PROGRESSION TO ESRD



Cornec-Le Gall E, 2015

NETWORK FOR RENAL RESEARCH

Ali Gharavi | **Simone Sanna-Cherchi**

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Cause monogeniche di nefronoftisi (ciliopatie)

Table 6 | **Monogenic causes of nephronophthisis-related ciliopathies**

Gene (alternative name)	Protein	Refs
NPHP1 (JBTS4)	Nephrocystin-1	154,155
INVS (NPHP2)	Inversin	156
NPHP3	Nephrocystin-3	157
NPHP4	Nephroretinin	158,159
IQCB1 (NPHP5)	IQ calmodulin-binding motif-containing protein 1	160
CEP290 (NPHP6)	Centrosomal protein 290 kDa	161
GLIS2 (NPHP7)	Zinc finger protein GLIS2	162
RPGRIP1L (NPHP8)	Protein fantom	163
NEK8 (NPHP9)	Serine/threonine-protein kinase Nek8	164
SDCCAG8 (NPHP10)	Serologically defined colon cancer antigen 8	63
TMEM67 (NPHP11)	Meckelin	165
TTC21B (NPHP12)	Tetratricopeptide repeat domain 21B	166
WDR19 (NPHP13)	WD repeat-containing protein 19	167
ZNF423 (NPHP14)	Zinc finger protein 423	168
CEP164 (NPHP15)	Centrosomal protein 164 kDa	168
ANKS6 (NPHP16)	Ankyrin repeat and sterile α motif domain containing protein 6	169

The table lists the 16 most-frequent monogenic causes of nephronophthisis-related ciliopathies. Monogenic (recessive) mutations in the following genes are less frequent causes of nephronophthisis-related ciliopathies (Meckel syndrome, Senior–Loken syndrome, Joubert syndrome and Bardet–Biedl syndrome): *XPNPEP3, ATXN10, FAN1, SLC41A1, CEP83, SLC12A3, CLCNKB, AGXT, GRHPR, HOGA1, PKHD1, INPP5E, TMEM216, AHI1, ARL13B, CC2D2A, OFD1, KIF7, TCTN1, TMEM237, CEP41, TSGA14, TMEM138, C5orf42, TMEM231, CSPP1, PDE6D, TBC1D32, SCLT1, MKS1, TCTN2, B9D1, B9D2, KIF14, BBS1, BBS2, ARL6, BBS4, BBS5, MKKS, BBS7, TTC8, PTHB1, C21orf58, TRIM32, C4orf24, WDPCP, LZTFL1, ALMS1, IFT122, WDR35, IFT140, C14ORF179, DYNC2H1, WDR34, WDR60, IFT80, IFT172, TRAF3IP1, NEK1, POC1A, EVC,* and *EVC2*.

95 geni

Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2015.205

Cause monogeniche di Nefrolitiasi

Table 7 | **Monogenic causes of urinary stone disease**

Gene	Protein	Disease entity	Mode of inheritance	Refs
ADCY10/SAC	Adenylate cyclase 10 (soluble)	Hypercalciuria, calcium oxalate nephrolithiasis	AD	170
AGXT	Alanine-glyoxylate aminotransferase	Primary hyperoxaluria, type 1	AR	171
APRT	Adenine phosphoribosyltransferase	Adenine phosphoribosyltransferase deficiency, urolithiasis (DHA stones), renal failure	AR	172
ATP6V0A4	ATPase, H^+ transporting, lysosomal V0 subunit a4	dRTA	AR	173
ATP6V1B1	ATPase, H^+ transporting, lysosomal 56/58kDa, V1 subunit B1	dRTA with deafness	AR	174
CA2	Carbonic anhydrase II	Osteopetrosis and dRTA or pRTA	AR	175
CASR	Calcium-sensing receptor	Hypocalcaemia with Bartter syndrome and/or hypocalcaemia	AD	176
CLCN5	H^+/Cl^- exchange transporter	Dent disease or nephrolithiasis, type 1	XR	177
CLCNKB	Chloride channel, voltage-sensitive Kb	Bartter syndrome, type 3	AR	178
CLDN16	Claudin 16	FHHNC	AR	179
CLDN19	Claudin 19	FHHNC with ocular abnormalities	AR	180
CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1	1,25-(OH) D-24 hydroxylase deficiency, infantile hypercalcaemia	AR	181
FAM20A	Pseudokinase FAM20A	Enamel-Renal syndrome, amelogenesis imperfecta and nephrocalcinosis	AR	182
GRHPR	Glyoxylate reductase/ hydroxypyruvate reductase	Primary hyperoxaluria, type 2	AR	183
HNF4A	Hepatocyte nuclear factor 4α	MODY, Fanconi syndrome and nephrocalcinosis	AD	184
HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	Primary hyperoxaluria, type 3	AR	185
HPRT1	Hypoxanthine phosphoribosyltransferase 1	Kelley–Seegmiller syndrome, partial HPRT deficiency, HPRT-related gout	XR	186
KCNJ1	ATP-sensitive inward rectifier potassium channel 1	Bartter syndrome, type 2	AR	187
OCRL	Inositol polyphosphate 5-phosphatase OCRL-1	Lowe syndrome/Dent disease 2	XR	188
SLC12A1	Solute carrier family 12, member 1	Bartter syndrome, type 1	AR	189
SLC22A12	Solute carrier family 22 (organic anion/urate transporter), member 12	Renal hypouricaemia, type 1	AD/AR	190
SLC2A9	Solute carrier family 2 (facilitated glucose transporter), member 9	Renal hypouricaemia, type 2	AD/AR	191
SLC34A1	Solute carrier family 34 (sodium phosphate), member 1	Hypophosphataemic nephrolithiasis/ osteoporosis-1, (NPHLOP1) or Fanconi renotubular syndrome 2	AD/AR	192
SLC34A3	Solute carrier family 34 (sodium phosphate), member 3	Hypophosphataemic rickets with hypercalciuria	AR	193
SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	Cystinuria, type A	AR	194
SLC4A1	Solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)	Primary distal renal tubular acidosis,	AD/AR	195
SLC7A9	solute carrier family 7 (glycoprotein associated amino acid transporter light chain, bo, + system), member 9	Cystinuria, type B	AD/AR	196
SLC9A3R1	Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Hypophosphataemic nephrolithiasis/ osteoporosis-2, (NPHLOP2)	AD	197
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor	Idiopathic hypercalciuria	AD	198
XDH	Xanthine dehydrogenase	Xanthinuria, type 1	AR	199

AD, autosomal dominant; AR, autosomal recessive; dRTA, distal renal tubular acidosis; FHHNC, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis; MODY, maturity onset diabetes of the young; pRTA, proximal renal tubular acidosis; XR, X-linked recessive.

30 geni

Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2015.205

Cause monogeniche di glomerulonefrite cronica

Table 5 | **Monogenic causes of chronic glomerulonephritis**

Gene	Protein	Disease	Refs
Autosomal recessive			
CFH	Complement factor H	MPGN	88
Autosomal dominant			
CFI	Complement factor I	MPGN	144
CFHR5	Complement factor H-related protein 5	MPGN	90,145–147
FN1	Fibronectin 1	GFND	148
Autosomal dominant or recessive			
COL4A3	Collagen type IV α3	Alport	149,150
COL4A4	Collagen type IV α4	Alport	149,150
CD46	Membrane cofactor protein (MCP)	MPGN	151
C3	Complment component 3	MPGN	89
X-linked			
COL4A5	Collagen type IV α5	Alport	152
COL4A6	Collagen type IV α6	Alport with LM	153

Alport: Alport syndrome; GFND: glomerulopathy with giant fibronectin deposits; LM: leiomyomatosis; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

10 geni

Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2015.205

Cause monogeniche di sindrome nefrosica steroido resistente

Table 4 | **Monogenic genes causes of SRNS**

Gene	Protein	Refs
Autosomal recessive		
*ADCK4**	AarF domain containing kinase 4	54
*ARHGDIA**	Rho GDP dissociation inhibitor 1	55
*CD2AP**	CD2-associated protein	75,121
*CFH**	Complement factor H	122
*COQ2**	Coenzyme Q2 4-hydroxybenzoate polyprenyltransferase	52,80
*COQ6**	Coenzyme Q6 monooxygenase	53
CRB2	Crumbs homolog 2	7
*CUBN**	Cubilin	123
*DGKE**	Diacylglycerol kinase epsilon	124
EMP2	Epithelial membrane protein 2	79
FAT1	Protocadherin Fat 1	F.H. unpublished
*ITGA3**	Integrin α3	125
*ITGB4**	Integrin β4	126
KANK1	KN motif and ankyrin repeat domain containing proteins 1	56
KANK2	KN motif and ankyrin repeat domain containing proteins 2	56
KANK4	KN motif and ankyrin repeat domain containing proteins 4	56
*LAMB2**	Laminin β2	78
MTTL1	Mitochondrially encoded tRNA leucine 1	127
*MYO1E**	MYO1E variant protein	128
*NPHS1**	Nephrin	14
*NPHS2**	Podocin	74
NUP93	Nuclear pore complex protein Nup93	F.H. unpublished
NUP107	Nuclear pore complex protein Nup107	129
NUP205	Nuclear pore complex protein Nup205	F. H. unpublished
*PDSS2**	Decaprenyl-diphosphate synthase subunit 2	130
*PLCE1**	Phospholipase C epsilon 1	58
*PTPRO**	Receptor-type tyrosine-protein phosphatase O	131
*SCARB2**	Lysosome membrane protein 2	132
*SMARCAL1**	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1	133
WDR73	WD repeat domain 73	134–136
XPO5	Exportin 5	F. H. unpublished
Autosomal dominant		
*ACTN4**	Actinin α4	76
ANLN	Anillin, actin binding protein	137
*ARHGAP24**	Rho GTPase activating protein 24	138
*INF2**	Inverted formin-2	77
*LMX1B**	LIM homeobox transcription factor 1β	139
MYH9	Myosin heavy chain 9	140
*TRPC6**	Short transient receptor potential channel 6	141,142
*WT1**	Wilms tumor 1	143

*Sequenced by our group[44].

39 geni

Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2015.205

GASLINI

CAKUT

Table 3 | **Monogenic causes of CAKUT**

Gene	Protein	Refs
Autosomal dominant		
BMP4	Bone morphogenetic protein 4	92
CHD1L	Chromodomain helicase DNA binding protein 1-like	93
DSTYK	Dual serine/threonine and tyrosine protein kinase	39
EYA1	Eyes absent homolog 1	94
GATA3	GATA binding protein 3	95,96
HNF1B	HNF1 homeobox B	97
MUC1	Mucin 1	98
PAX2	Paired box 2	99
RET	Proto-oncogene tyrosine-protein kinase receptor Ret	100
ROBO2	Roundabout, axon guidance receptor, homolog 2 (*Drosophila*)	101
SALL1	Sal-like protein 1 (also known as spalt-like transcription factor 1	102
SIX1	SIX homeobox 1, 2 and 5	103
SIX2	SIX homeobox 2	92
SIX5	SIX homeobox 5	104
SOX17	Transcription factor SOX-17	105
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	106
TBX18	T-box transcription factor TBX18	17
TNXB	Tenascin XB	107
UMOD	Uromodulin	108
UPK3A	Uroplakin 3A	109
WNT4	Protein Wnt-4	110–112
Autosomal recessive		
ACE	Angiotensin I-converting enzyme	113
AGT	Angiotensinogen	113
AGTR1	Angiotensin II receptor, type 1	113
CHRM3	Muscarinic acetylcholine receptor M3	114
FGF20	Fibroblast growth factor 20	115
FRAS1	Extracellular matrix protein FRAS1	116
FREM1	FRAS1 related extracellular matrix proteins 1	9
FREM2	FRAS1 related extracellular matrix proteins 2	9
GRIP1	Glutamate receptor interacting protein 1	9
HPSE2	Inactive heparanase 2	117
ITGA8	Integrin α8	118
LRIG2	Leucine-rich repeats and immunoglobulin-like domains 2	119
REN	Renin	113
TRAP1	Heat shock protein 75 (also known as TNF receptor-associated protein 1)	6
X-linked		
KAL1	Anosmin 1	120

36 geni

Vivante, A. & Hildebrandt, F. (2015) Exploring the genetic basis of early-onset chronic kidney disease *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2015.205