Supplementary Material

Integration of Genetic Testing and Pathology for the Diagnosis of Adults with FSGS

*Tony Yao[1,2], *Khalil Udwan, MD PhD[1,2], Rohan John MD[3], Akanchaya Rana, MD[1,2,4], Amirreza Haghighi, MD[1], Lizhen Xu, PhD[5], Saidah Hack, BSc[1,2], Heather N. Reich, MD PhD[1,2,4,6], Michelle Hladunewich, MD MSc[7], Daniel Cattran, MD[1,2,4,6], Andrew D. Paterson, MD[4,6,8,9], +York Pei, MD MSc[1,2,4,6], +Moumita Barua, MD[1,2,4,6]

*, + These authors contributed equally to this work

[1]Division of Nephrology, University Health Network, Toronto, Canada

[2]Toronto General Hospital Research Institute, Toronto General Hospital, Toronto, Canada

[3]Department of Pathology, University Health Network, Toronto, Canada

[4]Institute of Medical Sciences, University of Toronto, Canada

[5]The Centre for Applied Genomics, The Hospital for Sick Children's, Toronto, Canada

[6]Department of Medicine, University of Toronto, Canada

[7]Division of Nephrology, Sunnybrook Health Sciences Center, Toronto, Canada

[8]Genome and Genome Biology, The Hospital for Sick Children's, Toronto, Canada

[9]Epidemiology & Biostatistics, Dalla Lana School of Public Health, University of Toronto

Correspondence:

Dr. Moumita Barua

200 Elizabeth Street, 8NU-855

Toronto General Hospital

Toronto, ON

M5G 2C4

416-340-4800 ext 8007

(F) 416-340-3999

moumita.barua@uhn.ca

Table of Contents:

Supplementary Table 1. Additional Baseline Clinical Characteristics of the Sequenced Cohort.

	Percentage (%) of Available Data	Number of Patients
Age of onset of kidney disease (years) (% of available data)		161
0-12	10	17
12-18	6	9
>18	84	135
Proteinuria at onset		126
Dipstick positive	32	40
300 mg-2 g/ 24 hours	12	15
> 2 g/24 hours	56	71
Nadir plasma albumin (g/dl) (% of available data)		128
>35	43	56
30-34	20	25
25-29	13	17
20-24	8	10
<19	16	20
FSGS histologic subtype		
Not otherwise specified	80	126
Tip	8	126
Perihilar	7	126
Collapsing	2	126
Cellular	1	126
Inadequate to classify	2	126
Progression to kidney failure from disease onset (years) (% of patients with kidney failure)		71
< 5 years	24	17
5-10 years	31	22
> 10 years	45	32
	Percentage (%) of Available Data	Total Number of Available Patients
Patients with reportedly normal creatinine clearance at the onset of disease	65	103
Patients with family history of kidney disease	16	193
History of smoking	43	127
Frequent NSAID use	12	121

193 individuals from 179 families had exome sequencing performed but data was not available for all participants. Number of individuals in which data is available or satisfying the criteria is indicated in the last column. NSAID = non-steroid anti-inflammatory drug.

Supplementary Table 2. List of Genes Associated with FSGS and Related Phenotypes.

Gene	Inheritance	Accession ID	Mean Depth of Coverage across All Samples
FSGS/steroid-resistant nephrotic syndrome			
ACTN4	AD	NM_004924	57X
ADCK4	AR	NM_024876	54X
ALG1	AR	NM_019109	59X
ALG13	XLR	NM_018466	49X
ANLN	AD	NM_018685	83X
APOL1	assoc.	NM_003661	94X
ARHGAP24	AD	NM_031305	87X
ARHGDIA	AR	NM_004309	70X
AVIL	AR	NM_006576	79X
CD151	AR	NM_004357	54X
CD2AP	AD/AR	NM_012120	62X
CFH	AR	NM_000186	103X
COL4A3	AD/AR	NM_000091	61X
COL4A4	AD/AR	NM_000092	63X
COL4A5	X-linked	NM_033380	35X
COQ2	AR	NM_015697	59X
COQ6	AR	NM_182476	67X
CRB2	AR	NM_173689	44X
CUBN	AR	NM_001081	77X
DGKE	AR	NM_003647	75X
E2F3	AD	NM_001949	74X
EMP2	AR	NM_001424	53X
INF2	AD	NM_032714	45X
ITGA3	AR	NM_002204	73X
ITGB4	AR	NM_000213	64X
KANK1	AR	NM_015158	82X
KANK2	AR	NM_015493	71X
KANK4	AR	NM_181712	75X
LAGE3	AR	NM_006014	29X
LAMA5	AR	NM_005560	41X
LAMB2	AR	NM_002292	82X
LMNA	AD	NM_005572	39X
LMX1B	AD	NM_002316	47X
MAGI2	AR	NM_012301	67X

MYH9	AD	NM_002473	60X
MYO1E	AR	NM_004998	78X
NPHS1	AR	NM_004646	55X
NPHS2	AR	NM_014625	70X
NUP107	AR	NM_020401	75X
NUP205	AR	NM_015135	85X
NUP93	AR	NM_014669	85X
NXF5	XLR	NM_032946	82X
OCRL	XLR	NM_000276	67X
OSGEP	AR	NM_017807	77X
PAX2	AD	NM_003990	77X
PDSS2	AR	NM_020381	71X
PLCE1	AR	NM_016341	92X
PMM2	AR	NM_000303	84X
PODXL	AD	NM_005397	61X
PTPRO	AR	NM_030667	80X
SCARB2	AR	NM_005506	68X
SGPL1	AR	NM_003901	82X
SMARCAL1	AR	NM_014140	80X
SYNPO	AD	NM_007286	56X
TP53RK	AR	NM_033550	47X
TPRKB	AR	NM_016058	49X
TRPC6	AD	NM_004621	75X
WDR73	AR	NM_032856	79X
WT1	AD	NM_024426	47X
XPO5	AR	NM_020750	84X
ZMPSTE24	AR	NM_005857	88X
CAKUT			
BMP4	AD	NM_130850	82X
BMP7	AR	NM_001719	54X
CHD1L	AD	NM_004284	79X
DSTYK	AD	NM_015375	78X
EYA1	AD	NM_172059	84X
FGF20	AR	NM_019851	75X
FOXC1	AD	NM_001453	23X
FRAS1	AD/AR	NM_025074	78X
FREM2	AD/AR	NM_207361	102X
GATA3	AD	NM_002051	83X
GREB1L	AD	NM_001142966	88X
GRIP1	AR	NM_021150	79X
HNF1B	AD	NM_000458	64X

ITGA8	AR	NM_003638	75X
RET	AD	NM_020630	62X
ROBO2	AD	NM_002942	73X
SALL1	AD	NM_002968	86X
SIX1	AD	NM_005982	67X
SIX5	AD	NM_175875	26X
SLIT2	AR	NM_004787	74X
SOX17	AD	NM_022454	43X
SRGAP1	AD	NM_020762	81X
TNXB	AD	NM_032470	36X
TRAP1	AR	NM_016292	73X
UPK3A	AD	NM_006953	48X
WNT4	AD	NM_030761	86X
Nephronophthisis			
ANKS6	AR	NM_173551	49X
CCDC41	AR	NM_016122	62X
CEP164	AR	NM_014956	53X
CEP290	AR	NM_025114	52X
DCDC2	AR	NM_016356	89X
GLIS2	AR	NM_032575	50X
IFT172	AR	NM_015662	66X
INVS	AR	NM_183245	93X
IQCB1	AR	NM_001023571	56X
MAPKBP1	AR	NM_014994	70X
NEK8	AR	NM_178170	75X
NPHP1	AR	NM_000272	81X
NPHP3	AR	NM_153240	74X
NPHP4	AR	NM_015102	62X
RPGRIP1L	AR	NM_015272	80X
SDCCAG8	AR	NM_006642	76X
TMEM67	AR	NM_153704	50X
TTC21B	AD/AR	NM_024753	68X
WDR19	AR	NM_025132	85X
ZNF423	AD/AR	NM_015069	109X
Other			
CLCN5	XLR	NM_000084	66X
UMOD	assoc.	NM_003361	57X

Supplementary Table 3. Likely Pathogenic Variants in *COL4A* Genes.

Patient # (Family ID)	Sex	Ethnicity	Age at Disease Onset	Age at kidney failure	Exon (Intron) Number	Nucleotide Change	Protein Effect	Allele Frequency	Zygosity	References
Likely Pathogenic *COL4A3* Variants										
2378 (s)	M	EUR	22	23	29	c.2172delA	Gly724fs	0	Het	
7939 (s)	F	EUR	29	n/a (33)	1	c.84delC	Ser28fs	0	Het	
Likely Pathogenic *COL4A4* Variants										
7505 (F29)	F	EAS	24	n/a (40)	10	c.603G>A	Trp201stop	0	Het	
2526 (s)	M	EUR	Unk	45	8	c.509G>A	Gly170Glu	0	Het	[1]
2566 (s)	M	EUR	21	53	(25)	c.1988-2A>C	Disrupts splice acceptor	0	Het	
2687 (s)	F	EUR	23	42	(26)	c.2057-1G>A	Disrupts splice acceptor	0	Het	
Likely Pathogenic *COL4A5* Variants										
2545 (s)	F	EUR	Unk	Unk	(9)	c.545_546+2delAAgt	Affects splicing	0	Het	

The following minor allele frequency (MAF) cut-offs as determined in gnomAD (http://gnomad.broadinstitute.org/) were used for dominant and recessive disease genes respectively: 0.00005 and 0.005 (accessed 2018 Feb 22). (F) designates family pedigree number while (s) indicates a sporadic case. Het indicates heterozygous. References indicate previously reported pathogenic variants affecting the same codon. Age at kidney failure was indicated as n/a for patients without kidney failure, followed by their age at time of analysis in parentheses. Unk indicates that data were unavailable. EUR indicates European while EAS indicates East Asian. The *COL4A5* mutation in 2545 was predicted to affect splicing at the wild-type donor site by Human Splicing Finder 3.1 (http://www.umd.be/HSF3/).

Supplementary Table 4. Likely Pathogenic Variants in non-*COL4A* Genes.

Patient # (Family ID)	Sex	Ethnicity	Age at Disease Onset	Age at kidney failure	Gene Symbol	Inheritance	Exon (Intron) Number	Nucleotide Change	Protein Effect	Allele Frequency	Zygosity	References
Likely Pathogenic Podocyte Gene Variants												
2202 (F2)	F	EUR	11	12	*TRPC6*	AD	2	c.326G>A	Gly109Asp	0	Het	[2]
2195 (F2)	F	EUR	26	32	*TRPC6*	AD	2	c.326G>A	Gly109Asp	0	Het	[2]
2469 (F3)	F	EUR	24	47	*PODXL*	AD	7	c.1376_1379del	Lys459fs	0	Het	
2470 (F3)	F	EUR	7	23	*PODXL*	AD	7	c.1376_1379del	Lys459fs	0	Het	
2504 (s)	F	EUR	27	36	*TRPC6*	AD	2	c.523C>T	Arg175Trp	0	Het	[3]
2572 (s)	M	EUR	17	24	*INF2*	AD	4	c.542T>C	Val181Ala	0	Het	[4]
7939 (s)	F	EUR	29	n/a (33)	*LMX1B*	AD	6	c.879delG	Leu293fs	0	Het	
Likely Pathogenic CAKUT Gene Variants												
1791 (s)	M	EUR	21	Unk	*BMP4*	AD	4	c.774dupA	Pro259fs	0	Het	
2653 (s)	F	EUR	28	37	*PAX2*	AD	3	c.369_370insTA	Ile123fs	0	Het	
7535 (s)	F	EUR	Unk	Unk	*EYA1*	AD	14	c.1318C>T	Arg440Trp	2.44E-05	Het	[5]
Likely Pathogenic Variants in Other Genes												
7019 (s)	M	EUR	Unk	Unk	*CLCN5*	AR	10	c.1535G>T	Gly512Val	0	Hemi	[6]
7276 (s)	M	EUR	27	n/a (32)	*LAMA5*	AR	(45)	c.6065-1G>T	Disrupts splice acceptor	0	Homo	
7902 (s)	F	EUR	33	n/a (43)	*CEP290*	AR	54	c.7346C>A	Ser2449stop	0	Homo	

The following minor allele frequency (MAF) cut-offs as determined in gnomAD (http://gnomad.broadinstitute.org/) were used for dominant and recessive disease genes respectively: 0.00005 and 0.005 (accessed 2018 Feb 22). (F) designates family pedigree number while (s) indicates a sporadic case. Het indicates heterozygous, hemi indicates hemizygous, and homo indicates homozygous. References indicate previously reported pathogenic variants affecting the same codon. Age at kidney failure was indicated as n/a for patients without kidney failure, followed by their age at time of analysis in parentheses. Unk indicates that data were unavailable. EUR indicates European. 2195 and 2202 are mother and daughter; 2469 and 2470 are mother and daughter.

Supplementary Table 5. Possibly Pathogenic Variants.

Patient # (Family ID)	Sex	Ethnicity	Age at Disease Onset	Age at ESRD	Gene Symbol	Inheritance	Exon (Intron) Number	Nucleotide Change	Protein Effect	Allele Frequency	Zygosity	References
Possibly Pathogenic Podocyte Gene Variants												
7482 (F28)	M	EAS	28	n/a (36)	*TRPC6*	AD	2	c.643C>T	Arg215Trp	8.15E-06	Het	[7]
2475 (s)	F	EUR	29	32	*WT1*	AD	8	c.1312C>T	Leu438Phe	0	Het	
6699 (s)	F	EUR	32	n/a (50)	*WT1*	AD	10	c.1502G>A	Arg501His	0	Het	
7276 (s)	M	EUR	27	n/a (32)	*INF2*	AD	3	c.500A>C	His167Pro	0	Het	
7938 (s)	M	EUR	33	n/a (53)	*WT1*	AD	7	c.1099G>T	Asp367Tyr	0	Het	
Possibly Pathogenic CAKUT Gene Variants												
2583 (s)	M	EUR	23	42	*PAX2*	AD	4	c.413T>A	Ile138Asn	0	Het	
2639 (s)	M	EAS	18	36	*PAX2*	AD	3	c.275C>T	Thr92Met	0	Het	
Potentially Compound Heterozygous Variants												
2698 (s)	F	Admixed	51	68	*CD2AP*	AR	8	c.902A>T	Lys301Met	1.77E-04	Het	[8]
							3	c.274G>A	Ala92Thr	0	Het	
2708 (s)	M	Admixed	40	Unk	*ANKS6*	AR	6	c.1322A>G	Gln441Arg	6.83E-04	Het	[9]
							10	c.1883C>T	Ser628Phe	2.26E-04	Het	
2758 (s)	M	EUR	4	n/a (20)	*NUP93*	AR	11	c.1162C>T	Arg388Trp	8.23E-04	Het	[10]
							17	c.2065T>A	Phe689Ile	0	Het	
7596 (s)	F	EUR	2	n/a (19)	*CUBN*	AR	45	c.6928_6934delTAACCTC	Glu2310Cysfs	1.77E-04	Het	[11]
							51	c.7968_7969delinsGTTATATAAGGTATAACA	Leu2656_Pro2657delinsPheValIleProTyrIleThr	3.61E-05	Het	

The following minor allele frequency (MAF) cut-offs as determined in gnomAD (http://gnomad.broadinstitute.org/) were used for dominant and recessive disease genes respectively: 0.00005 and 0.005 (accessed 2018 Feb 22). (F) designates family pedigree number while (s) indicates a sporadic case. Het indicates heterozygous. References indicate previous reports of the variant. Age at kidney failure was indicated as n/a for patients without kidney failure, followed by their age at time of analysis in parentheses. Unk indicates that data were unavailable. EUR indicates European while EAS indicates East Asian.

Supplementary Table 6. Previously Reported Variants with Uncertain Pathogenic Significance.

Patient # (Family ID)	Sex	Ethnicity	Age at Disease Onset	Age at Kidney Failure	Gene Symbol	Inheritance	Exon (Intron) Number	Nucleotide Change	Protein Effect	Allele Frequency	Zygosity	References
1613 (F1)	M	EUR	24	42	*NUP93*	AR	11	c.1162C>T	Arg388Trp	8.23E-04	Het	[10]
2517 (F4)	M	Admixed	Unk	14	*ZMPSTE24*	AR	7	c.794A>G	Asn265Ser	1.22E-05	Het	[12]
6463 (F13)	F	EUR	Unk	Unk	*TTC21B*	AR	14	c.1697A>G	His566Arg	6.68E-04	Het	[13]
5772 (s)	F	Admixed	44	61	*NPHS1*	AR	12	c.1610C>T	Thr537Met	9.68E-04	Het	[14]
7291 (s)	M	Admixed	38	n/a (50)	*COQ2*	AR	5	c.890A>G	Tyr297Cys	4.11E-06	Het	[15]
7596 (s)	F	EUR	2	n/a (19)	*NPHS1*	AR	14	c.1868G>T	Cys623Phe	3.61E-05	Het	[14]
7982 (s)	M	EUR	40	n/a (64)	*NPHP3*	AR	(8)	c.2694-2_2694-1delAG	Disrupts splice acceptor	2.78E-04	Het	[16]

The following minor allele frequency (MAF) cut-offs as determined in gnomAD (http://gnomad.broadinstitute.org/) were used for dominant and recessive disease genes respectively: 0.00005 and 0.005 (accessed 2018 Feb 22). (F) designates family pedigree number while (s) indicates a sporadic case. Het indicates heterozygous. References indicate previous reports of the variant. Age at kidney failure was indicated as n/a for patients without kidney failure, followed by their age at time of analysis in parentheses. Unk indicates that data were unavailable. EUR indicates European. 2517 has an additional pathogenic variant in *LMX1B* (c.668G>A, p.R223Q). 7596 has additional possibly pathogenic variants in *CUBN* (c.6928_6934delTAACCTC, p.E2310Cfs; c.7968_7969delinsGTTATATAAGGTATAACA, p.L2656_P2657delinsFVIPYIT).

Supplementary Table 7. Additional Clinical Characteristics for Patient Subgroups.

	COL4A (n=12)	Other genetic (n=12)	Non-proven genetic (n=169)
Age of onset of kidney disease (years)			
0-12	10	12	10
12-18	0	13	6
>18	90	75	84
Ethnicity			
European	92	50	64
African	0	0	4
East Asian	0	25	12
Admixed	8	25	20
Proteinuria at onset			
Dipstick positive	25	38	32
300 mg-2 g/ 24 hours	13	12	12
> 2 g/24 hours	62	50	56
Nadir plasma albumin (g/dl)			
>35	57	27	44
30-34	14	43	18
25-29	29	15	12
20-24	0	15	8
<19	0	0	18
Normal creatinine clearance at disease onset	67	83	77
History of smoking	50	25	46
Frequent NSAID use	14	0	12
FSGS histologic subtype			
Not otherwise specified	100	50	77
Tip	0	0	9
Perihilar	0	0	8
Collapsing	0	25	2
Cellular	0	0	1
Inadequate	0	25	3
Kidney failure	46	44	50
Number of years to kidney failure from diagnosis			
< 5 years	0	60	23
5-10 years	50	40	29
> 10 years	50	0	48
Kidney transplant (% of transplant in patients with kidney failure)	100	75	54
Recurrence of disease after kidney transplant (within the first year)	0	0	13
Graft failure after one year	20	67	32

All patients in the *COL4A* subgroup received a kidney transplant, which was significantly different from the no proven genetic basis group (p=0.05). Numbers shown are percentages of available data. Total number of biopsies for each subgroup: COL4A (9), other genetic (4), non-proven genetic (113).

Supplementary Table 8. Tables demonstrating ages at disease onset and estimated mean survival/age of kidney failure by subgroup, with sexes analyzed separately.

			95% CI	
	Age of onset / all cohort	**Std error**	Lower	Upper
COL4A	36	3	29	42
Genetic	26	5	17	37
No proven genetic	34	1	32	37

			95% CI	
	Kidney failure / all cohort	**Std error**	Lower	Upper
COL4A	58	5	49	69
Genetic	43	6	31	55
No proven genetic	62	2	58	66

			95% CI	
	Age of onset / females	**Std error**	Lower	Upper
COL4A	27	4	19	35
Genetic	24	6	12	36
No proven genetic	36	3	31	41

			95% CI	
	Kidney failure / females	**Std error**	Lower	Upper
COL4A	48	4	40	56
Genetic	NA	NA	NA	NA
No proven genetic	64	3	57	70

			95% CI	
	Age of onset / males	**Std error**	Lower	Upper
COL4A	36	4	27	44
Genetic	27	7	14	40
No proven genetic	34	2	30	37

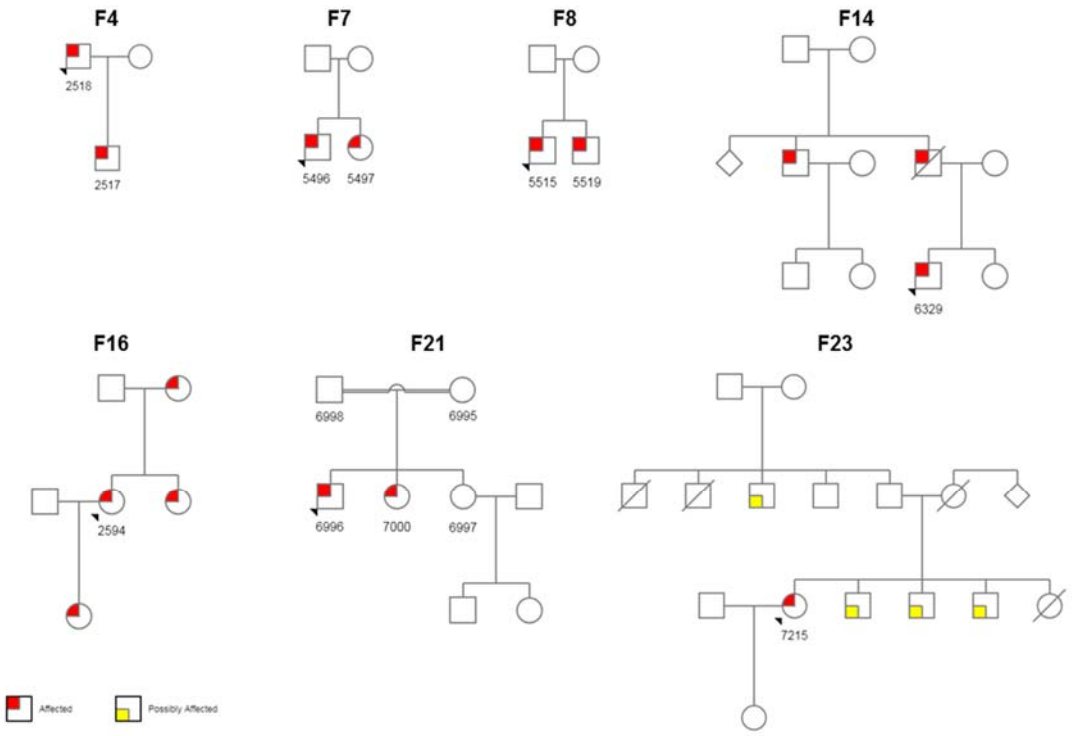
			95% CI	
	Kidney failure / males	**Std error**	Lower	Upper
COL4A	66	0	66	66
Genetic	33	8	17	48
No proven genetic	63	3	57	70

Genetic refers to other genetic causes not including *COL4A*. For *COL4A* subgroup, only one male patient developed kidney failure at last follow up. No females in the other genetic group developed kidney failure at last follow up. There were no statistically significant differences between males and females in any pairwise comparison. Std error = standard error; CI = confidence interval; NA = not applicable.

Supplementary Table 9. Clinical characteristics of *COL4A*, other genetic cause and no proven genetic cause subgroups.

	COL4A (12)	Other genetic (12)	No proven genetic (169)
% male	5/12	8/12	98/169
Mean age of onset of kidney disease	36	26	34
% with hematuria	6/10	2/8	20/70
% of patients with family history of kidney disease	5/11	4/9	19/155
% partial remission	2/7	3/10	25/95
% complete remission	0/7	0/10	19/95
% no remission	1/7	2/10	14/95
% unknown status of remission	4/7	5/10	37/95
% kidney failure	5/11	4/9	63/127
% with only global glomerulosclerosis on light microscopy	1/9	2/4	10/113
% glomerular basement membrane abnormalities on electron microscopy	5/9	1/4	30/113
% with >50% podocyte foot process effacement on electron microscopy	9/9	3/4	81/113
Number of patients where pathology report with electron microscopy description is available	9	4	113
Mean age at kidney failure (years)	58	43	62
% kidney transplant in patients with kidney failure	5/5	3/4	34/63
% of recurrence of disease after kidney transplant (within the first year)	0/5	0/3	4/31

Absolute numbers presented. Denominator represents number of individuals for which data is available.



Supplementary Figure 1. Pedigrees of families with definitely pathogenic variants. In F21, 6996 has a likely pathogenic variant (*NPHS1* R976S) while other samples have not been tested yet. In all other families shown, individuals with ID's are known to have the respective pathogenic variant. Pedigree information is not available for F9. Arrows indicate probands.

SUPPLEMENTARY REFERENCES

1. Morinière, V, Dahan, K, Hilbert, P, Lison, M, Lebbah, S, Topa, A, Bole-Feysot, C, Pruvost, S, Nitschke, P, Plaisier, E, Knebelmann, B, Macher, M-A, Noel, L-H, Gubler, M-C, Antignac, C, Heidet, L: Improving Mutation Screening in Familial Hematuric Nephropathies through Next Generation Sequencing. *J Am Soc Nephrol,* 25**:** 2740-2751, 2014.
2. Santín, S, Ars, E, Rossetti, S, Salido, E, Silva, I, García-Maset, R, Giménez, I, Ruíz, P, Mendizábal, S, Nieto, JL, Peña, A, Camacho, JA, Graga, G, Cobo, MÁ, Bernis, C, Ortiz, A, de Pablos, AL, Sánchez-Moreno, A, Pintos, G, Mirapeix, E, Fernández-Llama, P, Ballarín, J, Torra, R: TRPC6 mutational analysis in a large cohort of patients with focal segmental glomerulosclerosis. *Nephrol Dial Transplant,* 24**:** 3089-3096, 2009.
3. Hofstra, JM, Lainez, S, van Kuijk, WHM, Schoots, J, Baltissen, MPA, Hoefsloot, LH, Knoers, NV, Berden, JHM, Bindels, RJM, van der Vlag, J, Hoenderop, JGJ, Wetzels, JFM, Nijenhuis, T: New TRPC6 gain-of-function mutation in a non-consanguineous Dutch family with late-onset focal segmental glomerulosclerosis. *Nephrol Dial Transplant,* 28**:** 1830-1838, 2013.
4. Barua, M, Brown, EJ, Charoonratana, VT, Genovese, G, Sun, H, Pollak, MR: Mutations in the INF2 gene account for a significant proportion of familial but not sporadic focal and segmental glomerulosclerosis. *Kidney Int,* 83**:** 316-322, 2013.
5. Li, Y, Manaligod, JM, Weeks, DL: EYA1 mutations associated with the branchio-oto-renal syndrome result in defective otic development in Xenopus laevis. *Biology of the Cell,* 102**:** 277-292, 2010.
6. Lloyd, SE, Gunther, W, Pearce, SH, Thomson, A, Bianchi, ML, Bosio, M, Craig, IW, Fisher, SE, Scheinman, SJ, Wrong, O, Jentsch, TJ, Thakker, RV: Characterisation of renal chloride channel, CLCN5, mutations in hypercalciuric nephrolithiasis (kidney stones) disorders. *Human Molecular Genetics,* 6**:** 1233-1239, 1997.
7. Mallett, AJ, McCarthy, HJ, Ho, G, Holman, K, Farnsworth, E, Patel, C, Fletcher, JT, Mallawaarachchi, A, Quinlan, C, Bennetts, B, Alexander, SI: Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders. *Kidney Int,* 92**:** 1493-1506, 2017.
8. Gigante, M, Pontrelli, P, Montemurno, E, Roca, L, Aucella, F, Penza, R, Caridi, G, Ranieri, E, Ghiggeri, GM, Gesualdo, L: CD2AP mutations are associated with sporadic nephrotic syndrome and focal segmental glomerulosclerosis (FSGS). *Nephrol Dial Transplant,* 24**:** 1858-1864, 2009.
9. Hoff, S, Halbritter, J, Epting, D, Frank, V, Nguyen, TM, van Reeuwjik, J, Boehlke, C, Schell, C, Yasunaga, T, Helmstädter, M, Mergen, M, Filhol, E, Boldt, K, Horn, N, Ueffing, M, Otto, EA, Eisenberger, T, Elting, MW, van Wijk, JA, Bockenhauer, D, Sebire, NJ, Rittig, S, Vyberg, M, Ring, T, Pohl, M, Pape, L, Neuhaus, TJ, Elshakhs, NA, Koon, SJ, Harris, PC, Grahammer, F, Huber, TB, Kuehn, EW, Kramer-Zucker, A, Bolz, HJ, Roepman, R, Saunier, S, Walz, G, Hildebrandt, F, Bergmann, C, Lienkamp, SS: ANKS6 is a central component of a nephronophthisis module linking NEK8 to INVS and NPHP3. *Nature genetics,* 45**:** 951-956, 2013.
10. Braun, DA, Sadowski, CE, Kohl, S, Lovric, S, Astrinidis, SA, Pabst, WL, Gee, HY, Ashraf, S, Lawson, JA, Shril, S, Airik, M, Tan, W, Schapiro, D, Rao, J, Choi, WI, Hermle, T, Kemper, MJ, Pohl, M, Ozaltin, F, Konrad, M, Bogdanovic, R, Büscher, R, Helmchen, U, Serdaroglu, E, Lifton, RP, Antonin, W, Hildebrandt, F: Mutations in nuclear pore genes

NUP93, NUP205 and XPO5 cause steroid-resistant nephrotic syndrome. *Nature genetics,* 48**:** 457-465, 2016.

11. Sadowski, CE, Lovric, S, Ashraf, S, Pabst, WL, Gee, HY, Kohl, S, Engelmann, S, Vega-Warner, V, Fang, H, Halbritter, J, Somers, MJ, Tan, W, Shril, S, Fessi, I, Lifton, RP, Bockenhauer, D, El Desoky, S, Kari, JA, Zenker, M, Kemper, MJ, Mueller, D, Fathy, HM, Soliman, NA, SRNS Study Group, Hildebrandt, F: A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. *J Am Soc Nephrol,* 26**:** 1279-1289, 2015.
12. Agarwal, AK, Zhou, XJ, Hall, RK, Nicholls, K, Bankier, A, Van Esch, H, Fryns, JP, Garg, A: Focal segmental glomerulosclerosis in patients with mandibuloacral dysplasia owing to ZMPSTE24 deficiency. *Journal of Investigative Medicine,* 54**:** 208-213, 2006.
13. Davis, EE, Zhang, Q, Liu, Q, Diplas, BH, Davey, LM, Hartley, J, Stoetzel, C, Szymanska, K, Ramaswami, G, Logan, CV, Muzny, DM, Young, AC, Wheeler, DA, Cruz, P, Morgan, M, Lewis, LR, Cherukuri, P, Maskeri, B, Hansen, NF, Mullikin, JC, Blakesley, RW, Bouffard, GG, NISC Comparative Sequencing Program, Gyapay, G, Rieger, S, Tönshoff, B, Kern, I, Soliman, NA, Neuhaus, TJ, Swoboda, KJ, Kayserili, H, Gallagher, TE, Lewis, RA, Bergmann, C, Otto, EA, Saunier, S, Scambler, PJ, Beales, PL, Gleeson, JG, Maher, ER, Attié-Bitach, T, Dollfus, H, Johnson, CA, Green, ED, Gibbs, RA, Hildebrandt, F, Pierce, EA, Katsanis, N: TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum. *Nature genetics,* 43**:** 189-196, 2011.
14. Santín, S, García-Maset, R, Ruíz, P, Giménez, I, Zamora, I, Peña, A, Madrid, A, Camacho, JA, Fraga, G, Sánchez-Moreno, A, Cobo, MÁ, Bernis, C, Ortiz, A, De Pablos, AL, Pintos, G, Justa, ML, Hidalgo-Barquero, E, Fernández-Llama, P, Ballarín, J, Ars, E, Torra, R, FSGS Spanish Study Group: Nephrin mutations cause childhood- and adult-onset focal segmental glomerulosclerosis. *Kidney Int,* 76**:** 1268-1276, 2009.
15. Diomedi-Camassei, F, Di Giandomenico, S, Santorelli, FM, Caridi, G, Piemonte, F, Montini, G, Ghiggeri, GM, Murer, L, Barisoni, L, Pastore, A, Muda, AO, Valente, ML, Bertini, E, Emma, F: COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. *J Am Soc Nephrol,* 18**:** 2773-2380, 2007.
16. Schueler, M, Halbritter, J, Phelps, IG, Braun, DA, Otto, EA, Porath, JD, Gee, HY, Shendure, L, O'Roak, BJ, Lawson, JA, Nabhan, MM, Soliman, NA, Doherty, D, Hildebrandt, F: Large-scale targeted sequencing comparison highlights extreme genetic heterogeneity in nephronophthisis-related ciliopathies. *Journal of Medical Genetics,* 53**:** 208-214, 2016.
17. Gast, C, Pengelly, RJ, Lyon, M, Bunyan, DJ, Seaby, EG, Graham, N, Venkat-Raman, G, Ennis, S: Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. *Nephrol Dial Transplant,* 31**:** 961-970, 2016.
18. Storey, H, Savige, J, Sivakumar, V, Abbs, S, Flinter, FA: COL4A3/COL4A4 Mutations and Features in Individuals with Autosomal Recessive Alport Syndrome. *J Am Soc Nephrol,* 24**:** 1945-1954, 2013.
19. Pescucci, C, Mari, F, Longe, I, Vogiatzi, P, Caselli, R, Scala, E, Abaterusso, C, Gusmano, R, Seri, M, Miglietti, N, Bresin, E, Renieri, A: Autosomal-dominant Alport syndrome: natural history of a disease due to COL4A3 or COL4A4 gene. *Kidney Int,* 65**:** 1598-1603, 2004.
20. Heidet, L, Arrondel, C, Forestier, L, Cohen-Solal, L, Mollet, G, Gutierrez, B, Stavrou, C, Gubler, M-C, Antignac, C: Structure of the human type IV collagen gene COL4A3 and mutations in autosomal Alport syndrome. *J Am Soc Nephrol,* 12**:** 97-106, 2001.

21. Buzza, M, Dagher, H, Yan Wang, Y, Wilson, D, Babon, JJ, Cotton, RG, Savige, J: Mutations in the COL4A4 gene in thin basement membrane disease. *Kidney Int,* 63**:** 447-453, 2003.
22. Dagher, H, Yan Wang, Y, Fassett, R, Savige, J: Three novel COL4A4 mutations resulting in stop codons and their clinical effects in autosomal recessive Alport syndrome. *Hum Mutat,* 20**:** 321-322, 2002.
23. Malone, AF, Phelan, PJ, Hall, G, Cetincelik, U, Homstad, A, Alonso, A, Jiang, R, Lindsey, T, Wu, G, Sparks, MA, Smith, SR, Webb, NJA, Kalra, P, Adeyemo, A, Shaw, AS, Conlon, PJ, Jennette, JC, Howell, DN, Winn, MP, Gbadegesin, RA: Rare hereditary COL4A3/COL4A4 variants may be mistaken for familial focal segmental glomerulosclerosis. *Kidney Int,* 86**:** 1253-1259, 2014.
24. Mencarelli, MA, Heidet, L, Storey, H, van Geel, M, Knebelmann, B, Fallerini, C, Miglietti, N, Antonucci, MF, Cetta, F, Sayer, JA, van den Wijngaard, A, Yau, S, Mari, F, Bruttini, M, Ariani, F, Dahan, K, Smeets, B, Antignac, C, Flinter, FA, Renieri, A: Evidence of digenic inheritance in Alport syndrome. *Journal of Medical Genetics,* 52**:** 163-174, 2015.
25. Barker, DF, Pruchno, CJ, Jiang, X, Atkin, CL, Stone, EM, Denison, JC, Fain, PR, Gregory, MC: A mutation causing Alport syndrome with tardive hearing loss is common in the western United States. *American Journal of Medical Genetics,* 58**:** 1157–1165, 1996.
26. Ma, J, Pan, X, Wang, Z, Wang, Y, Feng, X, Ren, H, Zhang, W, Chen, X, Wang, W, Chen, N: Twenty-one novel mutations identified in the COL4A5 gene in Chinese patients with X-linked Alport's syndrome confirmed by skin biopsy. *Nephrology Dialysis Transplantation,* 26**:** 4003-4010, 2011.
27. Nagel, M, Nagorka, S, Gross, O: Novel COL4A5, COL4A5, and COL4A3 mutations in Alport syndrome. *Human Mutation,* 26**:** 60, 2005.
28. Barker, DF, Denison, JC, Atkin, CL, Gregory, MC: Efficient detection of Alport syndrome COL4A5 mutations with multiplex genomic PCR-SSCP. *American Journal of Medical Genetics,* 98**:** 148-160, 2001.
29. Hashimura, Y, Nozu, K, Kaito, H, Nakanishi, K, Fu, XJ, Ohtsubo, H, Hashimoto, F, Oka, M, Ninchoji, T, Ishimori, S, Morisada, N, Matsunoshita, N, Kamiyoshi, N, Yoshikawa, N, Iijima, K: Milder clinical aspects of X-linked Alport syndrome in men positive for the collagen IV α5 chain. *Kidney International,* 85**:** 1208-1213, 2014.
30. Boye, E, Flinter, FA, Zhou, J, Tryggvason, K, Bobrow, M, Harris, A: Detection of 12 novel mutations in the collagenous domain of the COL4A5 gene in Alport syndrome patients. *Human Mutation,* 5**:** 198-204, 1995.
31. Martin, P, Heiskari, N, Zhou, J, Leinone, A, Tumelius, T, Hertz, JM, Barker, DF, Gregory, MC, Atkin, CL, Styrkarsdottir, U, Neumann, H, Springate, J, Shows, T, Pettersson, E, Tryggvason, K: High mutation detection rate in the COL4A5 colllagen gene in suspected Alport syndrome using PCR and direct DNA sequencing. *Journal of the American Society of Nephrology,* 9**:** 2291-2301, 1998.
32. Plant, KE, Green, PM, Vetrie, D, Flinter, FA: Detection of mutations in COL4A5 in patients with Alport syndrome. *Human Mutation,* 13**:** 124-132, 1999.
33. Renieri, A, Bruttini, M, Galli, L, Zanelli, P, Neri, T, Rossetti, S, Turco, A, Heiskari, N, Zhou, J, Gusmano, R, Massella, L, Banfi, G, Scolari, F, Sessa, A, Rizzoni, G, Tryggvason, K, Pignatti, PF, Savi, M, Ballabio, A, De Marchi, M: X-linked Alport syndrome: an SSCP-based mutation survey over all 51 exons of the COL4A5 gene. *American Journal of Medical Genetics,* 58**:** 1192-1204, 1996.

34. Strasser, K, Hoefele, J, Bergmann, C, Büscher, AK, Büscher, R, Hoyer, PF, Weber, S: COL4A5-associated X-linked Alport syndrome in a female patient with early inner ear deafness due to a mutation in MYH9. *Nephrology Dialysis Transplantation,* 27**:** 4236-4240, 2012.
35. Weber, S, Strasser, K, Rath, S, Kittke, A, Beicht, S, Alberer, M, Lange-Sperandio, B, Hoyer, PF, Benz, MR, Ponsel, S, Weber, LT, Klein, H-G, Hoefele, J: Identification of 47 novel mutations in patients with Alport syndrome and thin basement membrane nephropathy. *Pediatric Nephrology,* 31**:** 941-955, 2016.
36. Adam, J, Connor, TMF, Wood, K, Lewis, D, Naik, R, Gale, DP, Sayer, JA: Genetic testing can resolve diagnostic confusion in Alport syndrome. *Clinical Kidney Journal,* 7**:** 197-200, 2014.
37. Inoue, Y, Nishio, H, Shirakawa, T, Nakanishi, K, Nakamura, H, Sumino, K, Nishiyama, K, Iijima, K, Yoshikawa, N: Detection of mutations in the COL4A5 gene in over 90% of male patients with X-linked Alport's syndrome by RT-PCR and direct sequencing. *American Journal of Kidney Diseases,* 34**:** 854-862, 1999.
38. Moyano Crespo, GD, Torres, AI, Mukdsi, JH: Crescentic and necrotising glomerulonephritis: a rare histological manifestation of Alport syndrome. *Journal of Clinical Pathology,* 68**:** 581-583, 2015.
39. Pont-Kingdon, G, Sumner, K, Gedge, F, Miller, C, Denison, JC, Gregory, MC, Lyon, E: Molecular testing for adult type Alport syndrome. *BMC Nephrology,* 10**:** 38, 2009.
40. Dreyer, SD, Morello, R, German, MS, Zabel, B, Winterpacht, A, Lunstrum, GP, Horton, WA, Oberg, KC, Lee, B: LMX1B transactivation and expression in nail–patella syndrome. *Human Molecular Genetics,* 9**:** 1067-1074, 2000.
41. Ghoumid, J, Petit, F, Holder-Espinasse, M, Jourdain, A-S, Guerra, J, Dieux-Coeslier, A, Figeac, M, Porchet, N, Manouvrier-Hanu, S, Escande, F: Nail–Patella Syndrome: clinical and molecular data in 55 families raising the hypothesis of a genetic heterogeneity. *European Journal of Human Genetics,* 24**:** 44-50, 2016.
42. Hamlington, JD, Jones, C, McIntosh, I: Twenty-two Novel LMX1B Mutations Identified in Nail Patella Syndrome (NPS) Patients. *Human Mutation,* 18**:** 458, 2001.
43. Knoers, NV, Bongers, EM, Beersum, SE, Lommen, EJ, van Bokhoven, H, Hol, FA: Nail-patella syndrome: identification of mutations in the LMX1B gene in Dutch families. *J Am Soc Nephrol,* 11**:** 1762-1766, 2000.
44. McIntosh, I, Dreyer, SD, Clough, MV, Dunston, JA, Eyaid, Wa, Roig, CM, Montgomery, T, Ala-Mello, S, Kaitila, I, Winterpacht, A, Zabel, B, Frydman, M, Cole, WG, Francomano, CA, Lee, B: Mutation Analysis of LMX1B Gene in Nail-Patella Syndrome Patients. *Am J Hum Genet,* 63**:** 1651-1658, 1998.
45. Ashraf, S, Gee, HY, Woerner, S, Xie, LX, Vega-Warner, V, Lovric, S, Fang, H, Song, X, Cattran, DC, Avila-Casado, C, Paterson, AD, Nitschké, P, Bole-Feysot, C, Cochat, P, Esteve-Rudd, J, Haberberger, B, Allen, SJ, Zhou, W, Airik, R, Otto, EA, Barua, M, Al-Hamed, MH, Kari, JA, Evans, J, Bierzynska, A, Saleem, MA, Böckenhauer, D, Kleta, R, El Desoky, S, Hacihamdioglu, DO, Gok, F, Washburn, J, Wiggins, RC, Choi, M, Lifton, RP, Levy, S, Han, Z, Salviati, L, Prokisch, H, Williams, DS, Pollak, M, Clarke, CF, Pei, Y, Antignac, C, Hildebrandt, F: ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. *Journal of Clinical Investigation,* 123**:** 5179-5189, 2013.

46. Boyer, O, Nevo, F, Plaisier, E, Funalot, B, Gribouval, O, Benoit, G, Cong, EH, Arrondel, C, Tête, M-J, Montjean, R, Richard, L, Karras, A, Pouteil-Noble, C, Balafrej, L, Bonnardeaux, A, Canaud, G, Charasse, C, Dantal, J, Deschenes, G, Deteix, P, Dubourg, O, Petiot, P, Pouthier, D, Leguern, E, Guiochon-Mantel, A, Broutin, I, Gubler, M-C, Saunier, S, Ronco, P, Vallat, J-M, Alonso, MA, Antignac, C, Mollet, G: INF2 Mutations in Charcot–Marie–Tooth Disease with Glomerulopathy. *New England Journal of Medicine,* 365**:** 2377-2388, 2011.
47. Kari, JA, Montini, G, Bockenhauer, D, Brennan, E, Rees, L, Trompeter, RS, Tullus, K, van't Hoff, W, Waters, A, Ashton, E, Lench, N, Sebire, NJ, Marks, SD: Clinico-pathological correlations of congenital and infantile nephrotic syndrome over twenty years. *Pediatr Nephrol,* 29**:** 2173-2180, 2014.
48. Lovric, S, Fang, H, Vega-Warner, V, Sadowski, CE, Gee, HY, Halbritter, J, Ashraf, S, Saisawat, P, Soliman, NA, Kari, JA, Otto, EA, Hildebrandt, F: Rapid Detection of Monogenic Causes of Childhood-Onset Steroid-Resistant Nephrotic Syndrome. *Clinical Journal of the American Society of Nephrology,* 9**:** 1109-1116, 2014.
49. Machuca, E, Benoit, G, Nevo, F, Tête, M-J, Gribouval, O, Pawtowski, A, Brandström, P, Loirat, C, Niaudet, P, Gubler, M-C, Antignac, C: Genotype-phenotype correlations in non-Finnish congenital nephrotic syndrome. *Journal of the American Society of Nephrology,* 21**:** 1209-1217, 2010.
50. Philippe, A, Nevo, F, Esquivel, EL, Reklaityte, D, Gribouval, O, Tête, M-J, Loirat, C, Dantal, J, Fischbach, M, Pouteil-Noble, C, Decramer, S, Hoehne, M, Benzing, T, Charbit, M, Niaudet, P, Antignac, C: Nephrin Mutations Can Cause Childhood-Onset Steroid-Resistant Nephrotic Syndrome. *J Am Soc Nephrol,* 19**:** 1871-1878, 2008.
51. Yang, F, Chen, Y, Zhang, Y, Qiu, L, Chen, Y, Zhou, J: Novel NPHS1 gene mutations in a Chinese family with congenital nephrotic syndrome. *Journal of Genetics,* 95**:** 161-166, 2016.
52. Boyer, O, Woerner, S, Yang, F, Oakeley, EJ, Linghu, B, Gribouval, O, Tête, M-J, Duca, JS, Klickstein, L, Damask, AJ, Szustakowski, JD, Heibel, F, Matignon, M, Baudouin, V, Chantrel, F, Champigneulle, J, Martin, L, Nitschké, P, Gubler, M-C, Johnson, KJ, Chibout, S-D, Antignac, C: LMX1B Mutations Cause Hereditary FSGS without Extrarenal Involvement. *J Am Soc Nephrol,* 24**:** 1216-1222, 2013.
53. Hall, G, Lane, B, Chryst-Ladd, M, Wu, G, Lin, J-J, Qin, X, Hauser, ER, Gbadegesin, RA: Dysregulation of WTI (−KTS) is Associated with the Kidney-Specific Effects of the LMX1B R246Q Mutation. *Scientific Reports,* 7**:** 39933, 2017.
54. Isojima, T, Harita, Y, Furuyama, M, Sugawara, N, Ishizuka, K, Horita, S, Kajiho, Y, Miura, K, Igarashi, T, Hattori, M, Kitanaka, S: LMX1B mutation with residual transcriptional activity as a cause of isolated glomerulopathy. *Nephrol Dial Transplant,* 29**:** 81-88, 2014.
55. Berdeli, A, Mir, S, Yavascan, O, Serdaroglu, E, Bak, M, Aksu, N, Oner, A, Anarat, A, Donmez, O, Yildiz, N, Sever, L, Tabel, Y, Dusunsel, R, Sonmez, F, Cakar, N: NPHS2 (podicin) mutations in Turkish children with idiopathic nephrotic syndrome. *Pediatr Nephrol,* 22**:** 2031-2040, 2007.
56. Karle, SM, Uetz, B, Ronner, V, Glaeser, L, Hildebrandt, F, Fuchshuber, A: Novel Mutations in NPHS2 Detected in Both Familial and Sporadic Steroid-Resistant Nephrotic Syndrome. *J Am Soc Nephrol,* 13**:** 388-393, 2002.

57. Hinkes, B, Vlangos, C, Heeringa, S, Mucha, B, Gbadegesin, RA, Liu, J, Hasselbacher, K, Ozaltin, F, Hildebrandt, F: Specific podocin mutations correlate with age of onset in steroid-resistant nephrotic syndrome. *J Am Soc Nephrol,* 19**:** 365-371, 2008.
58. Kerti, A, Csohány, R, Szabó, A, Árkossy, O, Sallay, P, Morinière, V, Vega-Warner, V, Nyírő, G, Lakatos, O, Szabó, T, Lipska, BS, Schaefer, F, Antignac, C, Reusz, G, Tulassay, T, Tory, K: NPHS2 p.V290M mutation in late-onset steroid-resistant nephrotic syndrome. *Pediatr Nephrol,* 28**:** 751-757, 2013.
59. Tabatabaeifar, M, Schlingmann, K-P, Litwin, M, Emre, S, Bakkaloglu, A, Mehls, O, Antignac, C, Schaefer, F, Weber, S, Group, ET: Functional analysis of BMP4 mutations identified in pediatric CAKUT patients. *Pediatr Nephrol,* 24**:** 2361-2368, 2009.
60. Weber, S, Taylor, JC, Winyard, P, Baker, KF, Sullivan-Brown, J, Schild, R, Knüppel, T, Zurowska, AM, Caldas-Alfonso, A, Litwin, M, Emre, S, Ghiggeri, GM, Bakkaloglu, A, Mehls, O, Antignac, C, Network, E, Schaefer, F, Burdine, RD: SIX2 and BMP4 mutations associate with anomalous kidney development. *J Am Soc Nephrol,* 19**:** 891-903, 2008.