Supplemental Material Table of Contents

Supplemental Table 1. Clinical profile of all the patients included in the study.

Patient	Gender	Ethnicity	Age at onset (years)	Histology	Clinical onset				Response to CNIs	Response to RASi	Remission	CKD stage at last follow-up	Post-transplant recurrence	Age at phenotyping (years)
					Proteinuria	Albumine g/dl	Dyslipidemia	Oedema						
Case 1	F	Senegalese	3.4	FSGS	4.2 mg/mg	2.6	No	No	-	Yes	P	ESKD	-	10
Case 2	F	European	26.2	FSGS	5 mg/mg	3	Yes	No	-	Yes	P	III	-	27.2
Case 3	F	European	11.8	MCD	2.5 mg/mg	3	NA	NA	No	Yes	P	I	-	20.7
Case 4	F	European	3.6	FSGS	60 mg/m^2/h	NA	NA	No	-	No	N	I	-	16
Case 5	M	European	4.7	MCD	3.8 mg/mg	3.3	No	No	-	No	N	I	-	15.7
Case 6	F	European	6	FSGS	NA	NA	NA	NA	-	Yes	P	ESKD	-	20.9
Case 7	M	European	0.8	FSGS	111 mg/m^2/h	NA	NA	No	-	Yes	P	I	-	4.8
Case 8	F	European	9.7	FSGS	6.5 mg/mg	1.7	Yes	Yes	No	No	N	IV	-	10.8

Case 9	M	European	22	FSGS	NA	NA	NA	No	-	Yes	P	III	-	23.4
Case 10	F	European	9	NP	48 mg/m^2/h	NA	NA	NA	-	Yes	P	III	-	14
Case 11	F	European	16.5	FSGS	NA	NA	NA	NA	-	Yes	P	II	-	17.8
Case 12	F	Latino	1.9	NP	8 mg/mg	NA	No	No	-	No	N	ESKD	-	3.8
Case 13	M	European	1.6	FSGS	10 mg/mg	3.1	No	No	No	No	N	II	-	6
Case 14	M	European	2.9	MCD	NA	NA	NA	NA	-	No	N	I	-	4
Case 15	M	European	1.6	FSGS	292 mg/m^2/h	1.6	Yes	No	No	No	N	II	-	6.6
Case 16	M	European	5	MCD	61.3 mg/m^2/h	NA	No	No	-	Yes	P	II	-	7.5
Case 17	M	Tunisian	7.5	FSGS	22.3 mg/mg	1.9	Yes	Yes	No	Yes	P	ESKD	-	9.5
Case 18	M	European	3.9	MCD	5 mg/mg	1.8	Yes	Yes	No	No	P	I	-	5

Case 19	M	European	1.2	FSGS	45 mg/mg	2	Yes	Yes	-	No	N	ESKD	No	1.2
Case 20	M	European	6.4	FSGS	7.6 mg/mg	1.8	Yes	Yes	-	No	N	ESKD	No	7
Case 21	F	European	5	FSGS	5.2 mg/mg	2	Yes	No	No	No	N	ESKD	-	15
Case 22	M	European	0.2	MCD	8 mg/mg	2	NA	No	No	No	N	ESKD	-	13
Case 23	M	European	3	FSGS	450 $mg/m^2/h$	2.1	NA	Yes	No	No	N	ESKD	No	21
Case 24	M	European	0.02	FSGS	NA	NA	NA	Yes	-	No	N	ESKD	No	22
Case 25	F	European	0.4	NP	36 mg/mg	2	Yes	Yes	-	No	N	ESKD	No	1
Case 26	M	European	29	FSGS	12 mg/mg	2.6	Yes	NA	-	-	N	III	-	33
Case 27	F	European	11.3	FSGS	5 mg/mg	3.4	NA	No	No	No	N	ESKD	-	15

Case 28	M	European	2.8	MCD	97 mg/m2/h	2.5	Yes	No	No	No	N	I	-	10
Case 29	F	European	4	NP	7 mg/mg	2.2	Yes	No	Yes	Yes	P	I	-	4
Case 30	M	European	6	FSGS	NA	NA	NA	No	-	-	N	ESKD	-	18
Case 31	M	European	13	FSGS	3.4 mg/mg	2.8	Yes	Yes	-	No	N	ESKD	No	18
Case 32	F	European	0.3	DMS	NA	NA	NA	Yes	-	No	N	ESKD	No	14
Case 33	F	European	7.7	FSGS	15 mg/mg	1.4	Yes	Yes	No	No	N	ESKD	No	12
Case 34	F	European	3.8	FSGS	10 mg/mg	2.4	Yes	Yes	No	No	N	ESKD	No	4
Case 35	F	European	1.6	FSGS	8 mg/mg	2.3	Yes	Yes	-	-	N	ESKD	No	2
Case 36	F	European	1	NP	35.2 mg/mg	1.3	Yes	No	-	No	N	ESKD	No	1

Case 37	M	European	8.6	FSGS	4.7 mg/mg	3.4	Yes	No	-	-	N	III	-	9
Case 38	M	European	2.5	MCD	5.3 mg/mg	2.7	No	Yes	-	Yes	C	I	-	3.5
Case 39	M	European	0.4	FSGS	41 mg/mg	2.3	Yes	Yes	-	Yes	C	I	-	1
Case 40	F	European	3.4	FSGS	3 mg/mg	1.8	Yes	Yes	-	Yes	C	I	-	8
Case 41	F	European	2.6	FSGS	9.3 mg/mg	2.4	Yes	Yes	No	Yes	C	I	-	4
Case 42	M	European	2.6	FSGS	3 mg/mg	1.9	Yes	Yes	Yes	Yes	C	I	-	3
Case 43	F	European	2.8	FSGS	2.7 mg/mg	3.4	Yes	No	-	Yes	P	I	-	3
Case 44	M	European	2.7	FSGS	40 mg/mg	1.2	Yes	Yes	Yes	-	C	I	-	3
Case 45	M	European	2.6	FSGS	4.8 mg/mg	2.2	NA	Yes	No	No	P	II	-	13

Case 46	F	European	7.9	MCD	20.1 mg/mg	1.7	Yes	Yes	Yes	No	C	I	-	8
Case 47	M	European	5	MCD	NA	NA	NA	NA	Yes	-	C	-	-	11
Case 48	M	European	5.11	MCD	2 mg/mg	2.7	Yes	No	-	No	P	I	-	7
Case 49	M	European	13	FSGS	12.4 mg/mg	2.1	Yes	Yes	-	No	N	I	-	13.5
Case 50	F	European	6	MCD	4 mg/mg	2.3	Yes	Yes	-	No	P	I	-	10
Case 51	M	European	6	FSGS	4 mg/mg	1.9	Yes	Yes	Yes	Yes	P	ESKD	No	10
Case 52	F	European	13	MCD	3 mg/mg	2.7	Yes	No	No	No	N	III	-	13
Case 53	F	European	13	FSGS	4.4 mg/mg	3	Yes	No	No	No	N	ESKD	No	20

Case 54	M	European	12	FSGS	8 mg/mg	1.5	Yes	Yes	No	No	N	ESKD	Yes	21
Case 55	F	Maroccan	0.8	DMS	3.5 mg/mg	2.2	Yes	Yes	-	No	N	ESKD	No	5
Case 56	F	European	2	FSGS	NA	NA	NA	NA	-	No	N	III	-	18
Case 57	F	European	9	FSGS	3.3 mg/mg	2.1	NA	Yes	No	No	N	III	-	16
Case 58	F	European	3.5	FSGS	5 mg/mg	1.1	Yes	Yes	No	No	N	ESKD	Yes	16
Case 59	F	European	6	MCD	3 mg/mg	1.8	No	No	No	No	N	ESKD	Yes	8
Case 60	M	European	2.3	FSGS	7 mg/mg	2.1	Yes	Yes	No	No	N	ESKD	Yes	10
Case 61	M	European	29.6	FSGS	NA	NA	NA	NA	-	-	N	ESKD	-	32
Case 62	M	European	26	FSGS	NA	NA	NA	NA	-	-	N	ESKD	No	27
Case 63	F	European	4.6	FSGS	9.8 mg/mg	3	Yes	No	No	No	N	ESKD	No	9

Case 64	F	European	14.2	FSGS	2.8 mg/mg	4.3	No	No	No	No	N	ESKD	No	21
Case 65	M	European	5	NP	8 mg/mg	1.9	Yes	Yes	-	-	C	I	-	5
Case 66	M	European	6.1	MCD	6.1 mg/mg	1.2	Yes	Yes	Yes	Yes	C	I	-	6.1
Case 67	F	European	1.5	NP	NA	NA	NA	NA	-	-	C	I	-	1.5
Case 68	M	European	2.9	NP	4 mg/mg	2.2	Yes	NA	-	-	C	I	-	2.9
Case 69	M	European	1.9	NP	31.5 mg/mg	2.3	Yes	Yes	No	-	C	I	-	1.9
Case 70	M	European	3.2	NP	5.9 mg/mg	2.6	NA	NA	-	-	C	I	-	3.2
Case 71	M	European	3	NP	13.8 mg/mg	2.2	Yes	Yes	Yes	-	C	I	-	3
Case 72	M	Tunisian	9.2	NP	7 mg/mg	1.3	Yes	No	-	-	C	I	-	9.2
Case 73	M	European	10	NP	4 mg/mg	2.4	Yes	Yes	-	-	C	I	-	10
Case 74	F	European	2.9	NP	12.9 mg/mg	2.4	Yes	NA	Yes	-	C	I	-	2.9

Case 75	F	European	3.2	MCD	11 mg/mg	1.4	Yes	Yes	Yes	-	C	I	-	3.2
Case 76	M	European	3.9	NP	25 mg/mg	2.3	No	No	-	-	C	I	-	3.9
Case 77	F	European	3.3	NP	13.6 mg/mg	1.9	Yes	Yes	Yes	-	C	I	-	3.3
Case 78	M	European	3.4	NP	13 mg/mg	1.9	Yes	Yes	-	-	C	I	-	3.4
Case 79	M	European	9.2	NP	6 mg/mg	3.1	NA	Yes	Yes	-	C	I	-	9.2
Case 80	M	European	7.7	NP	6 mg/mg	1.5	NA	Yes	-	-	C	I	-	7.7
Case 81	M	European	2.5	NP	19.4 mg/mg	2.6	NA	NA	Yes	-	C	I	-	2.5
Case 82	M	European	5.7	NP	5 mg/mg	2.4	Yes	Yes	-	-	C	I	-	5.7
Case 83	M	Moroccan	4	NP	34.1 mg/mg	2.4	Yes	NA	Yes	-	C	I	-	4
Case 84	F	Senegalese	7.5	NP	44.2 mg/mg	2.4	No	No	-	-	C	I	-	7.5
Case 85	F	Chinese	3	NP	29.1 mg/mg	0.9	NA	Yes	Yes	-	C	I	-	3

Case 86	M	Chinese	10.3	MCD	12.6 mg/mg	1.5	Yes	NA	No	-	C	I	-	10.3
Case 87	M	European	7.8	NP	23.5 mg/mg	2	NA	NA	Yes	-	C	I	-	7.8
Case 88	M	European	3	NP	2.1 mg/mg	1.7	Yes	Yes	-	-	C	I	-	3
Case 89	M	European	3.4	NP	28.2 mg/mg	2	Yes	Yes	Yes	-	C	I	-	3.4
Case 90	M	European	6.5	NP	23.2 mg/mg	1.1	NA	Yes	Yes	-	C	I	-	6.5
Case 91	F	European	3.6	NP	16.8 mg/mg	1.9	Yes	Yes	Yes	-	C	I	-	3.6
Case 92	M	European	11.6	NP	12.4 mg/mg	1.7	Yes	Yes	No	-	C	I	-	11.6
Case 93	M	European	3.5	NP	3 mg/mg	3.4	NA	NA	Yes	-	C	I	-	3.5
Case 94	F	Moroccan	3.2	NP	42 mg/mg	0.9	Yes	Yes	Yes	-	C	I	-	3.2
Case 95	F	Cape Verdean	11	MCD	3.5 mg/mg	3.4	NA	NA	-	-	C	I	-	11
Case 96	F	European	4.5	NP	26.3 mg/mg	2.7	NA	NA	Yes	-	C	I	-	4.5

Case 97	M	European	10.6	NP	NA	NA	NA	No	-	-	C	I	-	10.6
Case 98	M	European	5.2	NP	8 mg/mg	1.7	Yes	Yes	-	-	C	I	-	5.2
Case 99	F	European	2	NP	7.2 mg/mg	2.6	Yes	Yes	Yes	-	C	I	-	2
Case 100	F	European	2.9	NP	13.4 mg/mg	2	NA	Yes	-	-	C	I	-	2.9
Case 101	F	Senegalese	7.3	NP	6 mg/mg	2.2	NA	Yes	Yes	Yes	C	I	-	7.3
Case 102	F	Senegalese	8.2	NP	5 mg/mg	2.4	NA	Yes	Yes	-	C	I	-	8.2
Case 103	F	European	3.5	NP	9.2 mg/mg	1.6	Yes	Yes	-	-	C	I	-	3.5
Case 104	F	European	2.1	NP	46.1 mg/mg	2.1	Yes	Yes	Yes	-	C	I	-	2.1
Case 105	M	European	4.1	NP	20.5 mg/mg	1	Yes	Yes	-	-	C	I	-	4.1
Case 106	M	European	2.1	NP	22.4 mg/mg	1.6	Yes	Yes	-	-	C	I	-	2.1
Case 107	M	European	6	NP	2.2 mg/mg	1.2	Yes	Yes	-	-	C	I	-	6

Case 108	F	European	6.6	FSGS	18.5 mg/mg	2.2	Yes	No	-	-	C	I	-	6.6
Case 109	M	Albanian	8.8	NP	18.9 mg/mg	2.1	NA	Yes	Yes	-	C	I	-	8.8
Case 110	M	Chinese	11.1	NP	5.4 mg/mg	3.4	NA	Yes	Yes	-	C	I	-	11.1
Case 111	M	Chinese	4.5	NP	3.3 mg/mg	2	Yes	Yes	Yes	-	C	I	-	4.5

F, female; M, male; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; DMS, diffuse mesangial sclerosis; NP, not performed; -, therapy not performed; C, complete remission; N, no remission; P, partial remission; CNIs, calcineurin inhibitors; RASi, inhibitors of the renin-angiotensin-aldosterone system; CKD, chronic kidney disease; ESKD, end stage kidney disease.

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Supplemental Table 2. Panel of 298 genes analyzed with whole-exome sequencing.

Gene	Locus	OMIM	Reference
ACE	chr17:61554422-61575741	+ 106180	1
AGT	chr1:230838272-230850336	+ 106150	1
AGTR1	chr3:148415658-148460790	* 106165	1
AGTR2	chrX:115301958-115306225	* 300034	1
AIFM3	chr22: 21319396-21335649	* 617298	2
ALG1	chr16: 5083703-5137380	* 605907	3
ALG8	chr11: 77811982-77850706	* 608103	4
BMP4	chr14:54416455-54421270	* 112262	1
BMP7	chr20:55743809-55841707	* 112267	5
CDC5L	chr6:44355251-44418161	* 602868	5
CHD1L	chr1:146714291-146767447	* 613039	1
CHD7	chr8: 61591337-61779465	* 608892	6
CHRM3	chr1: 239549865-240078750	* 118494	1
CRKL	chr22: 21271714-21308037	* 602007	2
DCHS1	chr11: 6642556-6677085	* 603057	7
DCHS2	chr4: 155153399-155412930	* 612486	8
DNAJB11	chr3: 186285192-186315061	* 611341	9
DSTYK	chr1:205111631-205180727	* 612666	1
DZIP1L	chr3: 137780832-137834660	* 617570	10
E2F3	chr6:20402398-20493941	* 600427	11
EXT1	chr8: 118806729-119124092	* 608177	12
EYA1	chr8:72109668-72268979	* 601653	13
FAT1	chr4: 187508937-187647876	* 600976	14
FAT3	chr11: 92085262-92629618	* 612483	8
FAT4	chr4: 126237554-126414087	* 612411	15
FGF20	chr8:16850334-16859674	* 605558	1
FGFR1	chr8:38268656-38325363	* 136350	8
FGFR2	chr10:123237844-123357972	* 176943	16
FOXI1	chr5: 169532901-169536727	* 601093	17
FOXP1	chr3:71003844-71633140	* 605515	18
FRAS1	chr4:78978724-79465423	* 607830	1
FREM1	chr9: 14734664-14910993	* 608944	1
FREM2	chr13:39261173-39461267	* 608945	1
GANAB	chr11: 62392298-62414104	* 104160	4
GATA3	chr10:8096667-8117164	* 131320	5
GDNF	chr5: 37812779-37839788	* 600837	19
GLI3	chr7:42000548-42276618	* 165240	20
GRIP1	chr12:66741211-67072925	* 604597	1
HNF1B	chr17:36046434-36105096	* 189907	1
HPSE2	chr10:100216834-100995632	* 613469	21
ITGA8	chr10: 15555948-15762124	* 604063	22
ITGB1	chr10: 33189247-33294720	* 135630	23
LRIG2	chr1:113615831-113667342	* 608869	24
LRP4	chr11:46878419-46940193	* 604270	8
LRP5	chr11: 68080077-68216743	* 603506	4
MUC1	chr1:155158300-155162706	* 158340	1
NRIP1	chr21: 16333556-16437321	* 602490	25
OSR1	chr2:19551246-19558372	* 608891	26
PAX2	chr10:102505468-102589697	* 167409	1
PBX1	chr1: 164524821-164868533	* 176310	27
PKD1	chr16: 2138711-2185899	* 601313	4
PKD2	chr4: 88928820-88998929	* 173910	4
PRKCSH	chr19: 11546109-11561783	* 177060	4
REN	chr1:204123944-204135465	* 179820	1
RET	chr10:43572517-43625797	* 164761	1
ROBO2	chr3:77089294-77699114	* 602431	1

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SALL1	chr16:51169886-51185183	* 602218	1
SALL4	chr20:50400583-50419048	* 607343	28
SEC61B	chr9: 101984346-101992897	* 609214	4
SEC63	Chr6: 108188960-108279393	* 608648	4
SHH	chr7:155595558-155604967	* 600725	29
SIX1	chr14:61111417-61116155	* 601205	1
SIX2	chr2:45232324-45236542	* 604994	1
SIX5	chr19:46268043-46272497	* 600963	1
SLIT2	chr4:20255235-20620788	* 603746	30
SNAP29	chr22:21213271-21245506	* 604202	2
SOX17	chr8:55370495-55373456	* 610928	1
SOX9	chr17:70117161-70122560	* 608160	31
SPRY2	chr13: 80910111-80915086	* 602466	1
TBX18	chr6: 85397069-85474237	* 604613	1
TBX3	chr12:115108059-115121969	* 601621	1
TNXB	chr6: 32008931-32083111	* 600985	1
TRAP1	chr16:3708038-3767598	* 606219	1
UMOD	chr16:20344373-20364037	* 191845	1
UPK3A	chr22:45680868-45691755	* 611559	1
USF2	chr19:35759896-35770718	* 600390	1
ACTN4	chr19:39138327-39221170	* 604638	1
ADCK4	chr19:41197434-41222790	* 615567	1
ANLN	chr7:36429432-36493400	* 616027	1
APOL1	chr22:36649117-36663577	* 603743	1
ARHGAP24	chr4:86396284-86923823	* 610586	1
ARHGDIA	chr17:79825597-79829282	* 601925	1
CD151	chr11:832952-838834	* 602243	1
CD2AP	chr6:47445525-47594994	* 604241	1
CDK20	chr9: 90581356-90589668	* 610076	32

COQ2	chr4:84184979-84205964	* 609825	1
COQ6	chr14:74416955-74429813	* 614647	1
CRB2	chr9:126118448-126141032	* 609720	1
DGKE	chr17:54911460-54946036	* 601440	1
DLC1	chr8: 12940870-13373167	* 604258	32
EMP2	chr16:10622279-10674539	* 602334	1
GPC3	chrX:132669776-133119673	* 300037	33
GPC5	chr13:92050935-93519487	* 602446	34
INF2	chr14:105155943-105185947	* 610982	35
ITGA3	chr17:48133340-48167848	* 605025	36
ITGB4	chr17:73717516-73753899	* 147557	36
ITSN1	chr21: 35014706-35272165	* 602442	32
ITSN2	chr2: 24425733-24583583	* 604464	32
KANK2	chr19: 11274943-11308467	* 614610	1
KANK4	chr1: 62702651-62785085	* 614612	1
MAGI2	chr7: 77646393-79082890	* 606382	37
MYH9	chr22:36677324-36784063	* 160775	38
MYO1E	chr15:59428564-59665071	* 601479	1
NPHS1	chr19:36316274-36342739	* 602716	1
NPHS2	chr1:179519677-179545084	* 604766	1
NUP107	chr12:69080514-69136785	* 607617	1
NUP205	chr7:135242667-135333505	* 614352	1
NUP93	chr16: 56764017-56878797	* 614351	1
NXF5	chrX:101087085-101112549	* 300319	39
PDSS2	chr6:107473761-107780779	* 610564	1
PLCE1	chr10:95753746-96088146	* 608414	1
PODXL	chr7:131185023-131241376	* 602632	40
PTPRO	chr12:15475487-15750335	* 600579	1
SCARB2	chr4:77079894-77135035	* 602257	1
SGPL1	chr10: 72575717-72640930	* 603729	41

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SMARCAL1	chr2:217277473-217347772	* 606622	1
SYNPO	chr5:150020220-150038792	* 608155	11
TENC1	chr12:53440753-53458156	* 607717	32
TRPC6	chr11:101322296-101454659	* 603652	1
WT1	chr11:32409325-32457087	* 607102	1
XPO5	chr6: 43490072-43543812	* 607845	1
ADAMTS13	chr9:136287120-136324508	* 604134	42
C3	chr19:6677846-6720662	* 120700	1
CD46	chr1:207925383-207968861	* 120920	1
CFB	chr6: 31895475-31919861	* 138470	43
CFH	chr1:196621008-196716634	* 134370	1
CFHR1	chr1:196743930-196763203	* 134371	43
CFHR2	chr1: 196788898-196928356	* 600889	43
CFHR3	chr1:196743930-196763203	* 605336	43
CFHR4	chr1: 196819371-196888102	* 605337	43
CFHR5	chr1: 196946667-196978804	* 608593	43
CFI	chr4:110661848-110723335	* 217030	1
PLG	chr6: 161123270-161174347	* 173350	44
THBD	chr20:23026270-23030301	* 188040	45
AGXT	chr2: 241807896-241819919	* 604285	1
COL4A1	chr13: 110801318-110959496	* 120130	46
CREBBP	chr16:3775056-3930121	* 600140	47
DHCR7	chr11:71145457-71159477	* 602858	48
DIS3L2	chr2:232826293-233201908	* 614184	49
DLL4	chr15:41221531-41231258	* 605185	50
FGF10	chr5: 44303646-44389808	* 602115	51
GLA	chrX: 100652791-100662913	* 300644	52
GRHPR	chr9: 37422663-37436987	* 604296	53
HOGA1	chr10: 99344080-99372559	* 613597	54
JAG1	chr20:10618332-10654694	* 601920	55
KAL1	chr6:20534688-21232634	* 300836	1
KANK1	chr9: 470291-746105	* 607704	1
KCNJ10	chr1: 160007257-160040038	* 602208	56
LMX1B	chr9:129376748-129463311	* 602575	1
NARS2	chr11: 78147007-78285919	* 612803	57
NEU1	chr6: 31825436-31830683	* 608272	58
NOTCH2	chr1:120454176-120612317	* 600275	59
OCRL	chrX: 128673826-128726538	* 300535	13
PEX1	chr7: 92116334-92157845	* 602136	60
PMM2	chr16:8891670-8943194	* 601785	61
ROR2	chr9: 94325373-94712444	* 602337	62
TFAP2A	chr6: 10393419-10419892	* 107580	63
TSC1	chr9: 135766735-135820020	* 605284	64
TSC2	chr16: 2097466-2138716	* 191092	64
VIPAS39	chr14: 77893018-77924295	* 613401	65
VPS33B	chr15: 91541646-91565833	* 608552	66
WDR73	chr15:85186012-85197521	* 616144	1
WNT4	chr1:22443798-22469519	* 603490	1
WNT5A	chr3: 55499743-55523973	* 164975	67
VHL	chr3: 10182692-10193904	* 608537	68
ZMPSTE24	chr1:40723779-40759856	* 606480	14
AHI1	chr6: 135604670-135818914	* 608894	1
ALDOB	chr9:104182860-104198105	* 612724	69
ALMS1	chr2: 73612886-73837920	* 606844	70
ANKS6	chr9: 101493611-101559247	* 615370	1
ARL13B	chr3: 93698983-93774512	* 608922	1
ARL6	chr3: 97483365-97519953	* 608845	1
ATXN10	chr22: 46067678-46241187	* 611150	1

B9D1	chr17: 19240867-19281495	* 614144	1
B9D2	chr19: 41860326-41870078	* 611951	1
BBS1	chr11: 66278077-66301098	* 209901	1
BBS2	chr16: 56500748-56554195	* 606151	1
BBS4	chr15: 72978527-73030817	* 600374	1
BBS5	chr2: 170335688-170382432	* 603650	1
BBS7	chr4: 122745595-122791652	* 607590	1
C14ORF179/ IFT43	chr14: 76368479-76550928	* 614068	1
C4ORF24/ BBS12	chr4: 123653857-123666097	* 610683	1
C5ORF42	chr5: 37106330-37249530	* 614571	1
CC2D2A	chr4: 15471489-15603180	* 612013	1
CEP164	chr11: 117185273-117283984	* 614848	1
CEP290	chr12: 88442793-88535993	* 610142	1
CEP41	chr7: 130033612-130082274	* 610523	1
CEP83/ CCDC41	chr12: 94700225-94853764	* 615847	71
DYNC2H1	chr11: 102980160-103350591	* 603297	1
EVC	chr4: 5712924-5830772	* 604831	1
EVC2	chr4: 5544499-5711275	* 607261	1
FAN1	chr15: 31196055-31235311	* 613534	72
GLIS2	chr16: 4364762-4389598	* 608539	73
IFT122	chr3: 129158968-129239198	* 606045	1
IFT140	chr16: 1560428-1662111	* 614620	1
IFT172	chr2: 27667238-27712656	* 607386	1
IFT80	chr3: 159974774-160117668	* 611177	1
INPP5E	chr9: 139323071-139334274	* 613037	1
INVS	chr9: 102861538-103063282	* 243305	73
IQCB1	chr3: 121488610-121553926	* 609237	74
KIF14	chr1: 200520628-200589862	* 611279	1
KIF7	chr15: 90152020-90198682	* 611254	1

LZTFL1	chr3: 45864808-45957534	* 606568	1
MKKS	chr20: 10381657-10414870	* 604896	1
MKS1	chr17: 56282803-56296966	* 609883	1
NEK1	chr4: 170314426-170533780	* 604588	13
NEK8	chr17: 27052915-27070473	* 609799	13
NPHP1	chr2: 110879888-110962643	* 607100	13
NPHP3	chr3: 132276986-132441303	* 608002	13
NPHP4	chr1: 5922871-6052533	* 607215	13
OFD1	chrX:13752832-13787480	* 300170	13
PDE6D	chr2: 232597135-232650982	* 602676	1
PKHD1	chr6: 51480098-51952423	* 606702	1
POC1A	chr3: 52109269-52188706	* 614783	1
PTHB1/BBS9	chr7: 33168856-33645680	* 607968	1
RPGRIP1L	chr16: 53631595-53737850	* 610937	1
SCLT1	chr4: 129786076-130014764	* 611399	1
SDCCAG8	chr1: 243419320-243663394	* 613524	1
TBC1D32	chr6: 121400640-121655891	* 615867	1
TCTN1	chr12: 111051832-111087235	* 609863	1
TCTN2	chr12: 124155660-124192948	* 613846	1
TMEM138	chr11: 61129473-61136981	* 614459	1
TMEM216	chr11: 61159159-61166335	* 613277	1
TMEM231	chr16: 75572015-75590184	* 614949	1
TMEM237	chr2: 202484907-202508293	* 614423	1
TMEM67	chr8: 94767072-94831462	* 609884	1
TRIM32	chr9: 119449581-119463579	* 602290	1
TTC21B	chr2:166729872-166810348	* 612014	1
TTC8	chr14: 89290497-89344335	* 608132	1
WDPCP	chr2: 63348518-64054977	* 613580	1
WDR19	chr4: 39184024-39287430	* 608151	1

WDR34	chr9: 131395940-131419066	* 613363	1
WDR35	chr2: 20110021-20189892	* 613602	1
WDR60	chr7: 158649269-158749438	* 615462	1
XPNPEP3	chr22: 41253081-41363838	* 613553	1
ZNF423	chr16: 49521435-49891830	* 604557	1
AQP2	chr12: 50344524-50352664	* 107777	13
AQP6	chr12: 50360977-50370922	* 601383	74
ATP6V0A4	chr7:138391040-138484305	* 605239	1
ATP6V1B1	chr2:71163012-71192536	* 192132	1
ATP6V1C2	chr2:10861775-10925236	* 618070	75
AVP	chr20: 3063202-3065370	* 192340	13
AVPR2	chrX: 153167985-153172620	* 300538	13
BCS1L	chr2: 219523487-219528166	* 603647	76
BSND	chr1: 55464606-55476556	* 606412	13
CA2	chr8: 86376081-86393722	* 611492	13
CASR	chr3: 121902530-122005342	* 601199	13
CLCN5	chrX: 49687225-49863892	* 300008	13
CLCNKA	chr1: 16345370-16360545	* 602024	13
CLCNKB	chr1: 16370272-16383803	* 602023	13
CLDN16	chr3: 190040330-190129932	* 603959	13
CLDN19	chr1: 43198764-43205925	* 610036	13
CNNM2	chr10:104678050-104849978	* 607803	13
COG6	chr13: 40229764-40365802	* 606977	77
COQ9	chr16: 57481337-57495187	* 612837	78
CTNS	chr17: 3,539,762-3,564,836	* 606272	79
CUBN	chr10:16865965-17171816	* 602997	80
CUL3	chr2: 225334867-225450110	* 603136	13
EGF	chr4: 110834040-110933422	* 131530	13
EHHADH	chr3: 184908412-184999778	* 607037	81
FXYD6-FXYD2	chr11: 117690878-117747382	* 606683 * 601814	82
G6PC	chr17: 41052814-41065386	* 613742	83
HNF4A	chr20: 42984340-43061485	* 600281	84
KCNJ1	chr11:128706210128737268	* 600359	1
KLHL3	chr5: 136953189-137071779	* 605775	13
MRPS22	chr3: 138724648-139076065	* 605810	85
NR3C2	chr4: 148999913-149365850	* 600983	86
OSGEP	chr14: 20914570-20923264	* 610107	87
RRM2B	chr8: 103216730-103251346	* 604712	88
SCNN1A	chr12: 6456009-6486896	* 600228	13
SCNN1B	chr16: 23289552-23392620	* 600760	14
SCNN1G	chr16: 23194036-23228204	* 600761	13
SLC12A1	chr15: 48483861-48596275	* 600839	13
SLC12A3	chr16: 56899119-56949762	* 600968	13
SLC2A2	chr3: 170714137-170744539	* 138160	13
SLC34A1	chr5: 176806236-176825849	* 182309	13
SLC36A2	chr5: 150694539-150727151	* 608331	89
SLC3A1	chr2: 44502599-44548633	* 104614	13
SLC4A1	chr17: 42325753-42345509	+ 109270	13
SLC4A4	chr4: 72053003-72437804	* 603345	13
SLC4A5	chr2: 74443369-74570541	* 606757	13
SLC4A8	chr12: 51785101-51902980	* 605024	13
SLC4A9	chr5: 139739787-139754728	* 610207	13
SLC5A2	chr16: 31494323-31502181	* 182381	13
SLC6A18	chr5: 1225470-1246304	* 610300	89
SLC6A19	chr5: 1201710-1225232	* 608893	89
SLC6A20	chr3: 45796942-45838027	* 605616	89
SLC7A7	chr14:23242431-23299029	* 603593	13
SLC7A9	chr19: 33321415-33360672	* 604144	13
TP53RK	chr20: 45313004-45318418	* 608679	90

TRPM6	chr9:77337411-77503010	* 607009	13
WNK1	chr12: 861759-1020618	* 605232	13
WNK4	chr17: 40932696-40948954	* 601844	13
COL4A3	chr2:228029281-228179508	* 120070	1
COL4A4	chr2:227867427-228029275	* 120131	1
COL4A5	chrX:107683074-107940775	* 303630	1
LAMB2	chr3:49158548-49170599	* 150325	1
FN1	chr2: 216225163-216300895	* 135600	91

Supplemental Table 3. List of pathogenic variants based on the ACMG score.

Patient	Gene	MOI	Nucleotide change	Amino acid change	Zygosity	PVS1	PS1	PS2	PS3	PS4	PM1	PM2	PM3	PM4	PM5	PM6	PP1	PP2	PP3	PP4	PP5	Variant Class
Case 1	*COL4A4*	AR	c.1445C>G	p.Pro482Arg	Hom	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	Likely Pathogenic
	APOL1	AR	c.1024A>G c.1152T>G c.1164_1169delTTATAA	p.Ser342Gly p.Ile384Met p.Asn388_Tyr389del	Het Het Het	N N N	N N N	N N N	Y Y Y	N N N	Y Y Y	N N N	Y Y Y	N N Y	N N N	N N N	N N N	N N N	Y Y Y	Y Y Y	Y Y Y	Pathogenic Pathogenic Pathogenic
Case 2	*COL4A4*	AR	c.3289+1G>A c.2590G>A	/ p.Gly864Arg	Het Het	Y N	N N	N N	Y N	Y Y	N Y	Y Y	Y Y	N N	N Y	N N	N N	N N	Y Y	Y Y	Y Y	Pathogenic Pathogenic
Case 3	*COL4A3*	AR	c.4421T>C c.1831G>A	p.Leu1474Pro p.Gly611Arg	Het Het	N N	N N	N N	N N	N Y	N Y	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic
Case 4	*COL4A5*	XLD	c.1912G>A	p.Gly638Ser	Het	N	N	N	N	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	N	Pathogenic
Case 5	*COL4A5*	XLD	c.991G>A	p.Gly331Ser	Hem	N	N	N	N	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	N	Pathogenic
Case 6	*COL4A5*	XLD	c.3197G>A	p.Gly1066Asp	Het	N	N	N	N	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	N	Pathogenic
Case 7	*LAMB2*	AR	c.4868G>A c.1931G>A	p.Gly1623Asp p.Arg644His	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N N	Pathogenic Pathogenic
Case 8	*GLA*	XL	c.937G>T	p.Asp313Tyr	Het	N	N	N	N	Y	N	N	N	N	Y	N	Y	Y	N	Y	N	Likely Pathogenic
Case 9	*FAT1*	AR	c.6823G>A	p.Asp2275Asn	Hom	N	N	N	N	Y	N	Y	Y	N	N	N	N	N	Y	Y	N	Pathogenic
Case 10	*FAT4*	AR	c.11265A>T c.11953T>A	p.Glu3755Asp p.Tyr3985Asn	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N N	Pathogenic Pathogenic
Case 11	*PAX2*	AD	c.239C>T	p.Pro80Leu	Het	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic

Case 12	*PAX2*	AD	c.410+1G>A		Het	Y	N	Y	N	Y	N	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic
Case 13	*CLCN5*	XLR	c.749G>A	p.Gly250Asp	Hem	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	Y	Y	N	Pathogenic
Case 14	*CLCN5*	XLR	c.608C>G	p.Ser203Trp	Hem	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	Y	Y	N	Pathogenic
Case 15	*CLCN5*	XLR	c.781G>A	p.Gly261Arg	Hem	N	N	N	N	Y	N	Y	N	N	Y	N	N	N	Y	Y	N	Pathogenic
Case 16	*CTNS*	AR	c.198_218del arr[GRCh37] 17p13.2 (3505485_3560005) x1	p.Ile67_Pro73del	Het Het	N Y	N N	N N	N N	Y Y	N N	Y Y	Y Y	Y N	N N	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic
Case 17	*LMX1b*	AD	c.764C>T	p.Ala255Val	Het	N	N	N	Y	Y	N	Y	N	N	N	N	Y	N	Y	Y	N	Pathogenic
Case 18	*KANK1*	AR	c.971A>G c.200G>A	p.Tyr324Cysp.Arg67Gln	Het Het	N N	N N	Y N	N N	Y Y	N N	Y N	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N N	Pathogenic Likely Pathogenic
Case 19	*NPHS2*	AR	c.413G>A c.467_468dupT	p.Arg138Gln p.Leu156PhefsTer10	Het Het	N Y	N N	N N	Y N	N N	N N	Y Y	Y Y	N Y	Y N	N N	N N	N N	Y Y	Y Y	Y Y	Pathogenic Pathogenic
Case 20	*NPHS2*	AR	c.104dupG c.1143delC	p.Arg36ProfsTer33 p.Met382CysfsTer?	Het Het	Y Y	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N N	Pathogenic Pathogenic
Case 21	*NPHS2*	AR	c.686G>A c.911C>T	p.Arg229Gln p.Ser304Phe	Het Het	N N	N N	N N	Y N	N Y	Y N	N Y	Y Y	N N	Y N	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic
Case 22	*NPHS2*	AR	c.479A>G c.855_856delAA	p.Asp160Gly p.Arg286ThrfsTer16	Het Het	N Y	N Y	N N	N N	Y N	N N	Y Y	Y Y	N N	Y N	N N	N N	N N	Y Y	Y Y	Y Y	Pathogenic Pathogenic
Case 23	*NPHS2*	AR	c.365G>C c.416T>C	p.Trp122Ser p.Leu139Pro	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	Y Y	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic
Case 24	*NPHS2*	AR	c.538G>A	p.Val180Met	PatUPD	Y	N	N	N	Y	N	Y	N	N	N	N	N	N	Y	Y	Y	Pathogenic
Case 25	*NPHS2*	AR	c.419delG	p.Gly140AspfsTer41	Hom	Y	N	N	N	N	N	Y	Y	N	N	N	N	N	Y	Y	Y	Pathogenic
Case 26	*NPHS2*	AR	c.686G>A c.883G>A	p.Arg229Gln p.Ala295Thr	Het Het	N N	N N	N N	Y N	N Y	Y N	N Y	Y Y	N N	Y N	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic

Case 27	*NPHS2*	AR	c.946C>T c.686G>A	p.Pro316Ser p.Arg229Gln	Het Het	N N	N N	N N	N Y	Y N	N Y	Y N	Y Y	N N	N Y	N N	N N	N N	Y Y	Y Y	N Y	Pathogenic Pathogenic
Case 28	*NPHS2*	AR	c.467T>C c.855_856delAA	p.Leu156Ser p.Arg286ThrfsTer16	Het Het	N Y	N Y	N N	N N	Y N	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N Y	Pathogenic Pathogenic
Case 29	*NPHS1*	AR	c.2928G>T c.2299C>T	p.Arg976Ser p.Pro767Ser	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	Y N	Pathogenic Pathogenic
Case 30	*ANLN*	AD	c.745A>G	p.Asn249Asp	Het	N	N	N	N	Y	N	Y	N	N	N	N	Y	N	Y	Y	N	Likely Pathogenic
Case 31	*PLCE1*	AR	c.325_326delAT c.4570_4572delATG	p.Leu110GlufsTer13 p.Met1524del	Het Het	Y N	N N	N N	N N	Y Y	N N	Y Y	Y Y	N Y	N N	N N	Y Y	N N	Y Y	Y Y	N N	Pathogenic Pathogenic
Case 32	*PLCE1*	AR	c.4327G>A c.2038C>T	p.Gly1443Arg p.Gln680Ter	Het Het	N Y	N N	N N	N N	Y Y	N N	Y Y	Y Y	N N	N N	N N	N N	N N	Y Y	Y Y	N N	Pathogenic Pathogenic
Case 33	*ACTN4*	AD	c.782T>A	p.Val261Glu	Het	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic
Case 34	*ACTN4*	AD	c.464T>C	p.Ile155Thr	Het	N	N	Y	N	Y	N	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic
Case 35	*WT1*	AD	c.1388C>T	p.Ser463Phe	Het	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic
Case 36	*WT1*	AD	c.1384C>T	p.Arg462Trp	Het	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic
Case 37	*WT1*	AD	c.1300C>T	p.Arg434Cys	Het	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	Y	Y	N	Pathogenic

ACMG, American College of Medical Genetics and Genomics; MOI, model of inheritance; AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive; XLD, X-linked dominant; PatUPD, paternal uniparental isodisomy; Hom, homozygous; Het, heterozygous; Hem, hemizygous; N, no; Y, yes.

PVS1: *Null variant (nonsense, frameshift, canonical +/− 1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease.*

PS1: *Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.*

PS2: *De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.*

PS3: *Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.*

PS4: *The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.*

PM1: *Located in a mutational hot spot and/or critical and well-established functional domain.*

PM2: *Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC.*

PM3: *For recessive disorders, detected in trans with a pathogenic variant.*

PM4: *Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.*

PM5: *Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.*

PM6: *Assumed de novo, but without confirmation of paternity and maternity.*

PP1: *Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.*

PP2: *Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.*

PP3: *Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc).*

PP4: *Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.*

PP5: *Reputable source recently reports variant as pathogenic but the evidence is not available to the laboratory to perform an independent evaluation.*

Supplemental Table 4. List of variants of Unknown significance based on the ACMG score.

	Gene	MOI	Nucleotide change	Amino acid change	Zygosity	PVS 1	PS1	PS2	PS3	PS4	PM1	PM2	PM3	PM4	PM5	PM6	PP1	PP2	PP3	PP4	PP5	BA1	BS1	BS2	BS3	BS4	BP1	BP2	BP3	BP4	BP5	BP6	BP7	Variant Class
Case 55	*SIX5*	AD	c.811G>A	p.Asp271Asn	Het	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	Y	Y	N	N	N	N	N	Y	N	Y	N	VUS
Case 56	*SOX17*	AD	c.181C>G	p.Arg61Gly	Het	N	N	N	N	Y	N	Y	N	N	N	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	P
Case 57	*CUBN*	AR	c.3604G>A c.8203G>T	p.Ala1202Thr p.Asp2735Tyr	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	N N	N N	N N	N N	N N	N N	Y Y	Y Y	N N	N N	N N	N N	N N	N N	N N	N N	N N	N N	N N	N N	N N	LP LP
Case 58	*TRPC6*	AD	c.172C>T	p.Arg58Trp	Het	N	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	Y	N	VUS
Case 59	*NPHP4*	AR	c.2230G>A c.3329C>T	p.Val744Met p.Ala1110Val	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	N N	N N	N N	N N	N N	N N	Y Y	Y Y	N N	N N	N N	N Y	N N	N N	N N	N N	N N	N N	N N	N Y	N N	LP VUS
Case 60	*CUBN*	AR	c.5911C>A	p.Pro1971Thr	Hom	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	Y	N	VUS
Case 61	*COL4A4*	AR	c.2276C>T c.3871C>G	p.Pro759Leu p.Pro1291Ala	Het Het	N N	N N	N N	N N	Y Y	N N	Y Y	N N	N N	N N	N N	N N	N N	Y Y	Y Y	N N	N N	N N	Y Y	N N	N N	N N	N N	N N	N N	N N	Y Y	N N	VUS VUS
Case 62	*COQ2*	AR	c.64A>T c.879G>C	p.Arg22Term p.Trp293Cys	Het Het	Y N	N N	N N	N N	N Y	N N	N Y	Y Y	Y N	N N	N N	N N	N N	N Y	Y Y	N N	Y N	Y N	Y N	N N	N N	N N	N N	N N	Y N	N N	Y N	N N	VUS P
Case 63	*CEP290* *NPHP4*	AR AR	c.6401T>C c.1991A>G c.1852G>A	p.Ile2134Thr p.Asp664Gly p.Glu618Lys	Het Het Het	N N N	N N N	N N N	N N N	Y Y Y	N N N	N N N	N Y N	N N N	N N N	N N N	N N N	N N N	Y Y Y	Y Y Y	Y N N	N N N	Y Y Y	Y Y Y	N N N	N N N	N N N	N N N	N N N	N N N	N N N	N N N	N N N	VUS VUS VUS
Case 64	*FRAS1* *FREM2*	AR AR	c.160G>C c.6623T>C c.685C>T	p.Asp54His p.Leu2208Pro p.Arg229Cys	Het Het Het	N N N	N N N	N N N	N N N	Y Y Y	N N N	N Y Y	Y Y Y	N N N	N N N	N N N	N N N	N N N	N Y Y	Y Y Y	N N N	N N N	N N N	Y N N	N N N	N N N	N N N	N N N	N N N	Y N N	N N N	Y N N	N N N	VUS P P

ACMG, American College of Medical Genetics and Genomics; MOI, model of inheritance; AR, autosomal recessive; AD, autosomal dominant; Hom, homozygous; Het, heterozygous; N, no; Y, yes; LP, likely Pathogenic, P, pathogenic; VUS; variant of uncertain significance.

PVS1: *Null variant (nonsense, frameshift, canonical +/− 1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease.*

PS1: *Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.*

PS2: *De novo (both maternity and paternity confirmed) in a patient with the disease and no family history.*

PS3: *Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product.*

PS4: *Prevalence of the variant in affected individuals significantly increased compared to the prevalence in controls.*

PM1: *Located in a mutational hot spot and/or critical and well-established functional domain.*

PM2: *Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes or ExAC.*

PM3: *For recessive disorders, detected in trans with a pathogenic variant.*

PM4: *Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants.*

PM5: *Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.*

PM6: *Assumed de novo, but without confirmation of paternity and maternity.*

PP1: *Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease.*

PP2: *Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.*

PP3: *Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc).*

PP4: *Patient's phenotype or family history highly specific for a disease with a single genetic etiology.*

PP5: *Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation.*

BA1: *Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, or ExAC.*

BS1: *Allele frequency is greater than expected for disorder.*

BS2: *Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age.*

BS3: *Well-established in vitro or in vivo functional studies showing no damaging effect on protein function or splicing.*

BS4: *Lack of segregation in affected members of a family.*

BP1: *Missense variant in a gene for which primarily truncating variants are known to cause disease.*

BP2: *Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder or observed in cis with a pathogenic variant in any inheritance pattern.*

BP3: *In-frame deletions/insertions in a repetitive region without a known function.*

BP4: *Multiple lines of computational evidence suggesting no impact on gene or gene product (conservation, evolutionary, splicing impact, etc).*

BP5: *Variant found in a case with an alternate molecular basis for disease.*

BP6: *Reputable source recently reports variant as benign, but the evidence not available to the laboratory to perform an independent evaluation.*

BP7: *A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved. Variants should be classified as of Uncertain Significance if other criteria are unmet or the criteria for benign and pathogenic are contradictory*

Supplemental Table 5. Genetic profile of patients included in the study.

Patient	Gender	Ethnicity	PATHOGENIC VARIANTS									
			Gene	**MOI**	**OMIM**	**Nucleotide change**	**Amino acid change**	**Inheritance**	**gnomAD allele frequency**	**In-house control cohort** (300 WES)	**ACMG score[25] (Variant class)**	**Reference**
Case 1	F	Senegalese	*COL4A4* *APOL1*	AR AR	* 120131 * 603743	c.1445C>G c.1445C>G c.1024A>G c.1152T>G c.1164_1169delTTATAA	p.Pro482Arg p.Pro482Arg p.Ser342Gly p.Ile384Met p.Asn388_Tyr389del	mat pat mat mat pat	NP 0.22630 0.22600 0.14040	NP NP NP NP	Likely Pathogenic Pathogenic Pathogenic Pathogenic	-ND -92 -92 -92
Case 2	F	European	*COL4A4*	AR	* 120131	c.3289+1G>A c.2590G>A	 p.Gly864Arg	mat pat	NP NP	NP NP	Pathogenic Pathogenic	-93 -94
Case 3	F	European	*COL4A3*	AR	* 120070	c.4421T>C c.1831G>A	p.Leu1474Pro p.Gly611Arg	mat pat	0.00489 NP	NP NP	Pathogenic Pathogenic	-95 -ND
Case 4	F	European	*COL4A5*	XLD	* 303630	c.1912G>A	p.Gly638Ser	mat	0.00000	NP	Pathogenic	-96
Case 5	M	European	*COL4A5*	XLD	* 303630	c.991G>A	p.Gly331Ser	mat	NP	NP	Pathogenic	-ND
Case 6	F	European	*COL4A5*	XLD	* 303630	c.3197G>A	p.Gly1066Asp	mat	NP	NP	Pathogenic	-ND
Case 7	M	European	*LAMB2*	AR	* 150325	c.4868G>A c.1931G>A	p.Gly1623Asp p.Arg644His	mat pat	NP 0.00023	NP NP	Pathogenic Pathogenic	-ND -ND
Case 8	F	European	*GLA*	XLR/XLD	* 300644	c.937G>T	p.Asp313Tyr	pat	0.004458	NP	Likely Pathogenic	-97
Case 9	M	European	*FAT1*	AR	* 600976	c.6823G>A c.6823G>A	p.Asp2275Asn p.Asp2275Asn	mat pat	0.00003	NP	Pathogenic	-ND

Case 10	F	European	*FAT4*	AR	* 612411	c.11265A>T c.11953T>A	p.Glu3755Asp p.Tyr3985Asn	pat mat	NP NP	NP NP	Pathogenic Pathogenic	-ND -ND
Case 11	F	European	*PAX2*	AD	* 167409	c.239C>T	p.Pro80Leu	*de novo*	NP	NP	Pathogenic	-98
Case 12	F	Latino	*PAX2*	AD	* 167409	c.410+1G>A		*de novo*	NP	NP	Pathogenic	-ND
Case 13	M	European	*CLCN5*	XLR	* 300008	c.749G>A	p.Gly250Asp	mat	NP	NP	Pathogenic	-ND
Case 14	M	European	*CLCN5*	XLR	* 300008	c.608C>G	p.Ser203Trp	NA	NP	NP	Pathogenic	-ND
Case 15	M	European	*CLCN5*	XLR	* 300008	c.781G>A	p.Gly261Arg	mat	NP	NP	Pathogenic	-99
Case 16	M	European	*CTNS*	AR	* 606272	c.198_218del arr[GRCh37] 17p13.2 (3505485_3560005)x1	p.Ile67_Pro73del *(CTNS included in deleted region, protein absent)*	mat pat	0.00003	NP NP	Pathogenic	-79 -ND
Case 17	M	Tunisian	*LMX1b*	AD	* 602575	c.764C>T	p.Ala255Val	pat	NP	NP	Pathogenic	-100
Case 18	M	European	*KANK1*	AR	* 607704	c.971A>G c.200G>A	p.Tyr324Cys p.Arg67Gln	*de novo* mat	0.00002 0.00628	NP NP	Pathogenic Likely Pathogenic	-ND -ND
Case 19	M	European	*NPHS2*	AR	* 604766	c.413G>A c.467_468dupT	p.Arg138Gln p.Leu156PhefsTer10	mat pat	0.00115 0.00083	NP NP	Pathogenic Pathogenic	-101 -102
Case 20	M	European	*NPHS2*	AR	* 604766	c.104dupG c.1143delC	p.Arg36ProfsTer33 p.Met382CysfsTer?	mat pat	NP NP	NP NP	Pathogenic Pathogenic	-103 -100
Case 21	F	European	*NPHS2*	AR	* 604766	c.686G>A c.911C>T	p.Arg229Gln p.Ser304Phe	mat pat	0.03591 NP	NP NP	Pathogenic Pathogenic	-104 -100

Case 22	M	European	*NPHS2*	AR	* 604766	c.479A>G c.855_856delAA	p.Asp160Gly p.Arg286ThrfsTer16	mat pat	0.00000 0.00014	NP NP	Pathogenic Pathogenic	-103 -103
Case 23	M	European	*NPHS2*	AR	* 604766	c.365G>C c.416T>C	p.Trp122Ser p.Leu139Pro	mat pat	0.00000 NP	NP NP	Pathogenic Pathogenic	-105 -ND
Case 24	M	European	*NPHS2*	AR	* 604766	c.538G>A c.538G>A	p.Val180Met p.Val180Met	patUPD	0.00000	NP	Pathogenic	-103
Case 25	F	European	*NPHS2*	AR	* 604766	c.419delG c.419delG	p.Gly140AspfsTer40 p.Gly140AspfsTer40	mat pat	NP	NP	Pathogenic	-103
Case 26	M	European	*NPHS2*	AR	* 604766	c.686G>A c.883G>A	p.Arg229Gln p.Ala295Thr	mat pat	0.03591 NP	NP NP	Pathogenic Pathogenic	-104 -106
Case 27	F	European	*NPHS2*	AR	* 604766	c.946C>T c.686G>A	p.Pro316Ser p.Arg229Gln	pat mat	NP 0.03591	NP NP	Pathogenic Pathogenic	-36 -104
Case 28	M	European	*NPHS2*	AR	* 604766	c.467T>C c.855_856delAA	p.Leu156Ser p.Arg286ThrfsTer16	pat mat	NP 0.00014	NP NP	Pathogenic Pathogenic	-ND -103
Case 29	F	European	*NPHS1*	AR	* 602716	c.2928G>T c.2299C>T	p.Arg976Ser p.Pro767Ser	pat mat	0.00007 0.00001	NP NP	Pathogenic Pathogenic	-107 -108
Case 30	M	European	*ANLN*	AD	* 616027	c.745A>G	p.Asn249Asp	pat	NP	NP	Likely Pathogenic	-ND
Case 31	M	European	*PLCE1*	AR	* 608414	c.325_326delAT c.4570_4572delATG	p.Leu110GlufsTer13 p.Met1524del	pat mat	0.00000 NP	NP NP	Pathogenic Pathogenic	-ND -ND
Case 32	F	European	*PLCE1*	AR	* 608414	c.4327G>A c.2038C>T	p.Gly1443Arg p.Gln680Ter	pat mat	NP NP	NP NP	Pathogenic Pathogenic	-100
Case 33	F	European	*ACTN4*	AD	* 604638	c.782T>A	p.Val261Glu	*de novo*	NP	NP	Pathogenic	-100
Case 34	F	European	*ACTN4*	AD	* 604638	c.464T>C	p.Ile155Thr	*de novo*	NP	NP	Pathogenic	-100
Case 35	F	European	*WT1*	AD	* 607102	c.1388C>T	p.Ser463Phe	*de novo*	NP	NP	Pathogenic	-ND

Case 36	F	European	*WT1*	AD	* 607102	c.1384C>T	p.Arg462Trp	*de novo*	0.00000	NP	Pathogenic	-109
Case 37	M	European	*WT1*	AD	* 607102	c.1300C>T	p.Arg434Cys	*de novo*	0.00000	NP	Pathogenic	-109

M, male; F, female; mat, maternal; pat, paternal; NP, not present; ND, not described; MOI, model of inheritance; AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive; XLD, X-linked dominant; patUPD, paternal uniparental isodisomy; WES, whole-exome sequencing, ACMG, American College of Medical Genetics and Genomics. Sequence variant nomenclature follow the last update of HGVS (110).

Supplemental Methods

DNA extraction

Peripheral blood DNA was extracted using QIAamp Mini Kit (QIAGEN®, Hilden, Germany), according to manufacturer's instructions, and quantified by NanoDROP 2000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA).

DNA library preparation

To construct DNA libraries we used a strategy based on enzymatic fragmentation to produce dsDNA fragments followed by End repair, A-tailing, adapter ligation and library amplification (Kapa Biosystems, Wilmington, MA). Libraries were hybridized with the protocol SeqCap EZ Exome v3 (Nimblegen, Roche, Basel, Switzerland) and sequenced with NextSeq500 (Illumina Inc., San Diego, CA).

Assembly, Variant Calling

The reads were aligned with the human reference hg19 genome using Burrows-Wheeler Aligner (BWA) (111), mapped and analyzed with the IGV software (Integrative Genome Viewer, 2013 Broad Institute) (112). Downstream alignment processing (i.e. alignment sorting, indexing, deduplication and base quality score recalibration) was performed with the Genome Analysis Toolkit Unified Genotyper Module (GATK) (113) SAMtools (114) and Picard Tools (http://picard.sourceforge.net/). The GATK Unified Genotyper was used to obtain a set of single nucleotide variants (SNV) and indel calls. We performed a hard filtering of called variants based on four criteria: i) the variant confidence (QUAL), that is the Phred-scaled posterior probability of the variant to be homozygous reference; ii) the Quality by Depth (QD), that is the variant confidence divided by the unfiltered depth; iii) the unfiltered depth (DP), that is the number of reads spanning the variant site, and iiii) the strand bias (FS), measured as the Phred-scaled p-value using Fisher's Exact Test to detect strand bias (the variation being seen on only either the forward or the reverse strand) in the reads. We excluded the variant calls for which at least one of these filters was true: QD < 5.0, DP < 5, FS > 60.0, QUAL < 30.0. Variants were annotated using Annovar tool (115) to obtain information such as variant frequency in different populations and the predictions of the variant effect using different methods (SIFT, Polyphen2, MutationTaster, MutationAssessor, FATHMM and FATHMM MKL). A variant effect consensus was obtained by categorizing the variant effects obtained for each method in deleterious and non-deleterious, then counting the number of deleterious effects to prioritize variants.

In order to estimate copy number variants (CNVs) we used a normalized read count approach implemented in-house: in detail, for each patient we estimated the average depth of coverage (aDOC) of every considered region using the program samtools depth (114). The output has been passed to an awk command to compute the average coverage for the region, as well as the percentage of base pairs with a depth of coverage of at least 1, 5, 10, 20 or 30. The bash function to perform this task is reported below:

```
function trancheCov
{
    bam=$1
coord=$2
samtools depth -r $coord -a -a $bam |\
awk -v coord=$coord -F "\t" '{
if($3>=30){thirty++;twenty++;ten++;five++;one++}
else if($3>=20){twenty++;ten++;five++;one++}
```

```
else if($3>=10){ten++;five++;one++}
else if($3>=5){five++;one++}
else if($3>=1){one++}
mysum+=$3; tot++}
END{printf
"%s\t%s\t%s\t%s\t%s\t%s\t%s\n",coord,mysum/tot,100*one/tot,100*five/tot,100*ten/t
ot,100*twenty/tot,100*thirty/tot}'
}
```

Where $coord is the coordinate string as reported in the bed file, and $bam is the indexed bam file of the corresponding patient.

Then we derived, for each patient, a normalized depth of coverage (nDOC), obtained by dividing the aDOC values of each region for the sum of aDOC over the considered regions.

In order to detect CNVs, finally, we compared for each region the nDOC values of every patients, computing the Median Absolute Deviation (MAD) to identify outliers in patients having low/high nDOC values.

The ratio between the nDOC values of the outliers and the median (R) indicates the type of CNVs: double deletion (R=0), single-copy deletion (R=0.5) and duplication (R>=1.5).

Variant interpretation strategy

Variants were filtered *in silico* for a panel of 298 genes (Supplemental Table 2) known to be associated with chronic kidney disease (CKD). A team of nephrologists, clinician scientists and geneticists performed variants prioritization.

Variants were classified and scored in agreement with the interpretation guidelines of the American College of Medical genetics and Genomics (ACMG) (Supplemental Table 3) (116).

In details, we selected only non-synonymous, short insertion/deletion or splice-site variants (30 bp splice acceptor, 30 bp splice donor) with the following characteristics (Figure 2):

- Variants not present or with a minor allele frequency ≤ 0.01 for autosomal recessive (AR) and with a minor allele frequency ≤0.001 for autosomal dominant (AD)-transmitted genes in population database "1000 Genomes Project", "Exome Variant Server", dbSNP147, ExAC, gnomAD. We used manual inspection for the p.[Arg229Gln] variant in *NPHS2* when segregating with variants localized in exon 7 and 8, as previously reported (104) and for *APOL1* G1 and G2 variants (92).
- Variants not present or with a minor allele frequency ≤ 0.01 for AR and with a minor allele frequency ≤ 0.001 for AD-transmitted genes in "in-house" exome control cohort (300 exomes) of unrelated subjects analyzed for non-renal diseases referred to the Medical Genetic Unit of the Meyer Children's Hospital (Florence, Italy).
- Variants predicted as damaging by at least 3 *in silico* tools (Polyphen-2, SIFT, Mutation Taster, Mutation Assessor, FATHMM, FATHMM MKL).
- Variants correctly segregating within the family or representing *de novo* variants.

Variants were classified as pathogenic if they fitted all the criteria and were consistent with the clinical phenotype of the patient and family carriers after reverse phenotyping (Figure 2). After the interpretation, the candidate variants were validated by Sanger sequencing. If no pathogenic variant was identified filtering for the 298 genes associated with CKD, we extended the analysis to all the exome.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS, Inc., Evanston, IL). Kaplan-Meier estimates for SRNS patients were used to generate an overall 10 years kidney survival curve, starting point disease onset and ending point end-stage kidney disease development or censoring. Differences among groups were assessed by log-rank test. Between-group comparisons were performed using one-way ANOVA for normally distributed variables. A p-value <0.05 was considered statistically significant.

Web resources

1000 Genomes Project, http:// www.1000genomes.org

Exome Variant Server of the NHLBI Exome Sequencing Project (ESP), http://evs.gs.washington.edu/ews

dbSNP147, https://www.ncbi.nlm.nih.gov/projects/SNP/

ExAC, http://exac.broadinstitute.org

gnomAD, http://gnomad.broadinstitute.org/

Human Gene Mutation Database (HGMD), http://www.hgmd.cf.ac.uk/ac/index.php

Clinvar database, http://www.ncbi.nlm.nih.gov/clinvar/

Polyphen-2, http://genetics.bwh.harvard.edu/pph2/

SIFT, http://sift.jcvi.org/

Mutation Taster, http://www.mutationtaster.org/

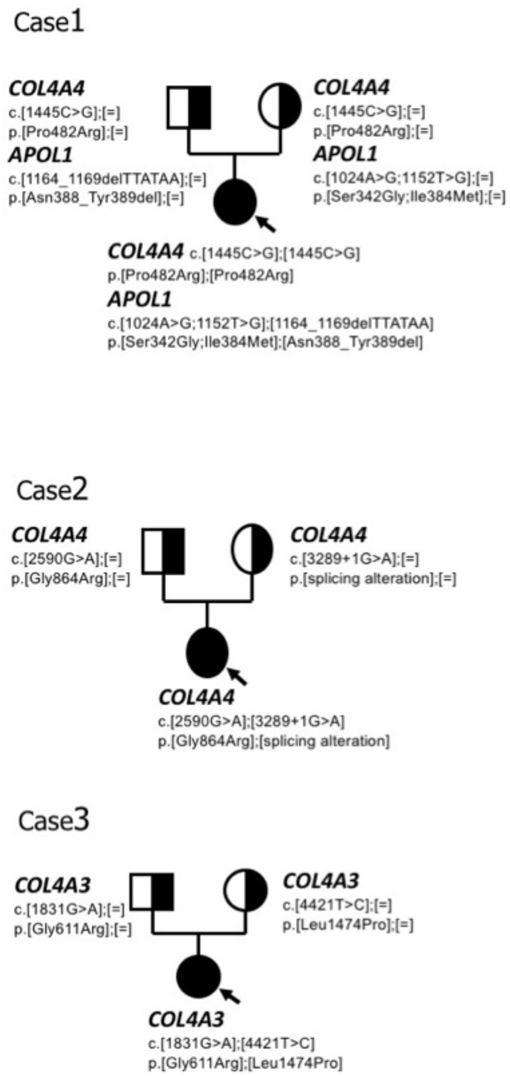
Mutation Assessor, http://www.ngrl.org.uk/Manchester/page/mutation-assessor

FATHMM, http://fathmm.biocompute.org.uk/

FATHMM MKL, http://fathmm.biocompute.org.uk/fathmmMKL.ht

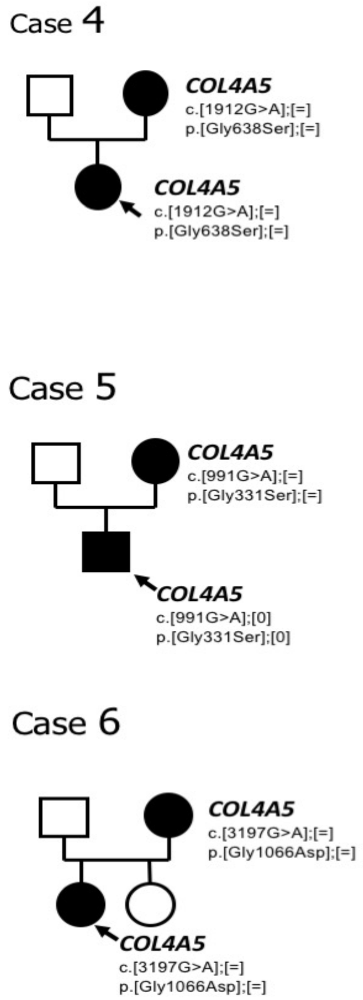
Case Reports

Case 1-3. These three patients showed steroid-resistant nephrotic syndrome, diagnosed and treated accordingly in 2 (cases 1 and 2) or 3 (case 3) different European nephrology centers and referred to our hospital on an average of 6 years after the clinical onset. Kidney biopsies had shown focal segmental glomerulosclerosis (cases 1 and 2), or minimal change disease (case 3) without raising the suspect of Alport syndrome, even after performing electron microscopy. In addition, all 3 patients had been checked for sensorineural hearing loss at diagnosis of nephrotic syndrome with normal findings. Case 1 developed sensorineural hearing loss later on, when rechecked upon whole exome sequencing assessment eight years after onset of nephrotic syndrome, while cases 2 and 3 still showed no sensorineural hearing loss ten years after onset of nephrotic syndrome. Case 3 was treated with steroids, cyclosporine, tacrolimus, and mycophenolate mofetil, without any response to treatment. Whole exome sequencing identified pathogenic variants in *COL4A4* in cases 1-2, and in *COL4A3* in case 3, as described in a previous report with distinct mutations (117, 118). Heterozygous parents showed microscopic hematuria without or with a mild proteinuria (300-500 mg/day) on reverse phenotyping. Parents



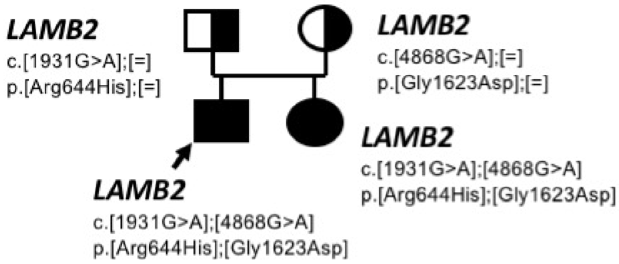
of case 1 were not consanguineous but came from an inbred population of an African village. Case 1 also carried *APOL1* G1/G2 risk alleles (92) explaining her rapid progression to end-stage kidney disease (7 years after onset).

Case 4-6. These patients showed steroid-resistant nephrotic syndrome and no signs of Alport syndrome at biopsy, being diagnosed with focal segmental glomerulosclerosis or (cases 4 and 6) or minimal change disease (case 5) without raising the suspect of Alport syndrome, even after performing electron microscopy. Steroid-resistant nephrotic syndrome diagnosis was confirmed in 3 different European nephrology centers for cases 4 and 6, who were referred to our hospital on average 13 years after onset of nephrotic syndrome. Whole exome sequencing identified pathogenic variants in *COL4A5* inherited from the respective mothers. Reverse phenotyping revealed that the mother of case 4 had no renal involvement but had sensorineural hearing loss while the mother of case 5 had microscopic hematuria.

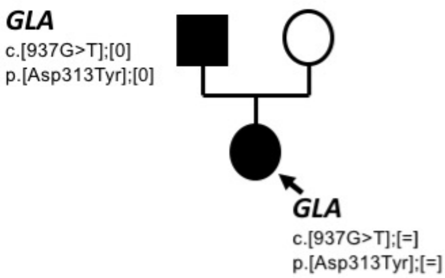


In case 6, the mother had developed during pregnancy a nephrotic syndrome that regressed after delivery with a mild residual proteinuria.

Case 7. This patient was diagnosed with steroid-resistant nephrotic syndrome in another pediatric nephrology center and referred to our Hospital for a second opinion on cyclosporine treatment. The biopsy showed focal segmental glomerulosclerosis. Whole exome sequencing revealed compound heterozygous pathogenic missense variants in *LAMB2*. *LAMB2* deletion causes Pierson syndrome, a condition that includes steroid-resistant nephrotic syndrome, but missense mutations are associated with isolated kidney involvement (119). The patient had an older sister previously treated for mesangioproliferative glomerulonephritis in another adult nephrology center that carried the same *LAMB2* variants.

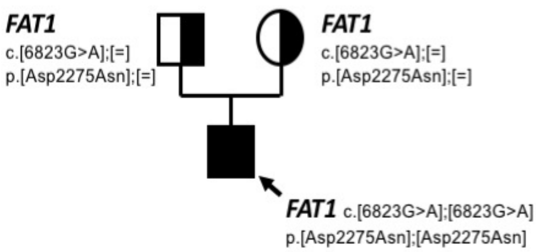


Case 8. This patient showed a severe isolated steroid-resistant nephrotic syndrome diagnosed in another Italian pediatric nephrology center, with focal segmental glomerulosclerosis at biopsy. After steroid treatment, she received cyclosporine, mycophenolate mofetil, tacrolimus, rituximab and even plasmapheresis without any response. She was referred to our hospital for a second opinion one year after the onset of nephrotic syndrome. Our clinical assessment confirmed idiopathic steroid-resistant nephrotic syndrome. Whole exome sequencing revealed the "D313Y" variant in *GLA* (97, 120), a pseudodeficiency allele causative for organ-specific Fabry disease, often with distinct organ involvement in different members of the same family (97). Reverse phenotyping showed lysosomal accumulation and vacuolization in podocytes with evidence of few very small concentric lamellar bodies in the podocytes in the kidney biopsy (97). The variant was inherited from the apparently healthy father who showed decreased α-Gal A activity and was diagnosed

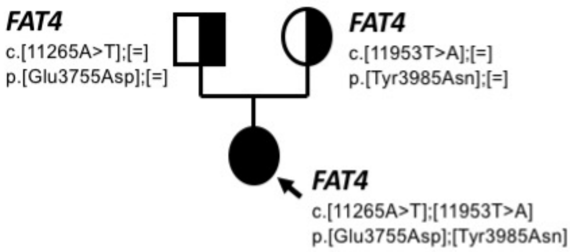


with sensorineural hearing loss only upon reverse phenotyping. sensorineural hearing loss is reported in 60% of subjects with Fabry disease, particularly hemizygous males (121).

Case 9. This patient was diagnosed with nephrotic syndrome in another nephrology center and referred to our hospital for a second opinion one year after. He had history of cluster headache. Kidney biopsy showed focal segmental glomerulosclerosis with tubular atrophy. Genetic testing revealed homozygous pathogenic variants in *FAT1*, inherited by non-consanguineous healthy parents from an inbred Italian village, consistently with a recent report (14).

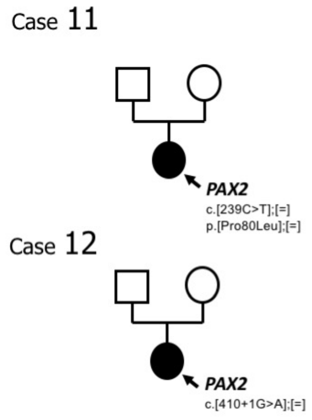


Case 10. This patient showed nephrotic proteinuria (3-4 g/day). Renal ultrasound scanning at onset was unremarkable. She showed compound heterozygous pathogenic variants in *FAT4*, a well-known gene of congenital abnormalities of the kidney and urinary tract (CAKUT), causing kidney hypodysplasia. Reverse phenotyping with renal scintigraphy revealed a left renal hypodysplasia (15).

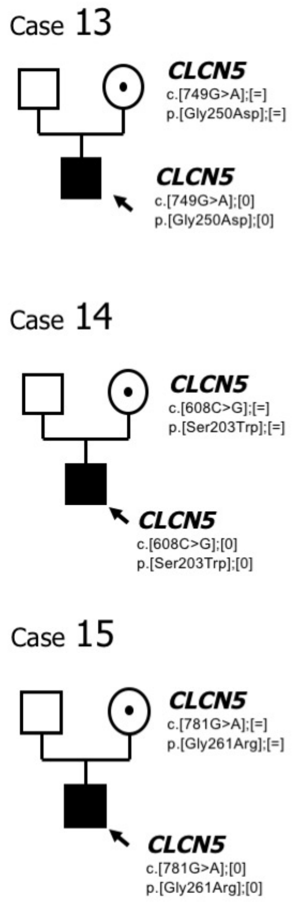


Case 11-12. These patients were diagnosed with idiopathic nephrotic syndrome in another nephrology center and referred to our hospital for a second opinion 2 years after the diagnosis of nephrotic syndrome. Case 11 showed focal segmental

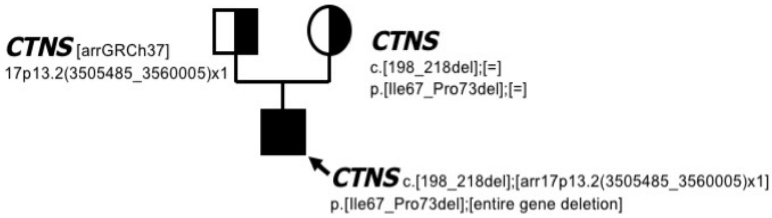
glomerulosclerosis at biopsy. In both cases, whole exome sequencing revealed *de novo* pathogenic variant in *PAX2* (98). Reverse phenotyping confirmed that they were affected by isolated focal segmental glomerulosclerosis. Consistently, deletions of *PAX2* are associated with the renal-coloboma syndrome, while missense mutations, are associated with isolated focal segmental glomerulosclerosis and steroid-resistant nephrotic syndrome (122).



Cases 13-15. These patients showed nephrotic syndrome and focal segmental glomerulosclerosis (cases 13 and 15) or minimal change disease (case 14) at biopsy. Kidney function was normal. Nephrocalcinosis was not observed. Patients 14 and 15 were diagnosed with steroid-resistant nephrotic syndrome in at least two different nephrology centers and treated with calcineurin inhibitors with no response before referral to our hospital on average 3 years after the onset of nephrotic syndrome. In all these patients whole exome sequencing showed a pathogenic variant in *CLCN5*. No other signs of tubular dysfunction (e.g. glycosuria, hypercalciuria) appeared over time in two patients, while the other one developed hypercalciuria later on, in agreement with a recent report showing that 50% of patients affected by Dent disease present with NS in absence of hypercalciuria (123).

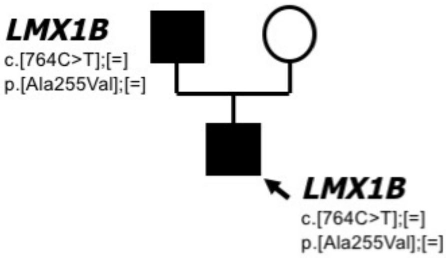


Case 16. This patient showed isolated nephrotic syndrome with a severe albuminuria and was diagnosed with steroid-resistant nephrotic syndrome in another nephrology center. Polyuria, hematuria, low-molecular weight proteinuria or other signs of tubular dysfunction were absent. Kidney ultrasounds and scintigraphy were normal. Kidney biopsy showed minimal change disease. He was referred to our center for a second opinion two years after the clinical onset. Whole exome sequencing showed two pathogenic variants in *CTNS* inherited from each of the parents. Upon reverse phenotyping, slit-lamp examination revealed symmetric corneal crystals. The half-cysteine levels in peripheral blood polymorphonuclear cells were elevated



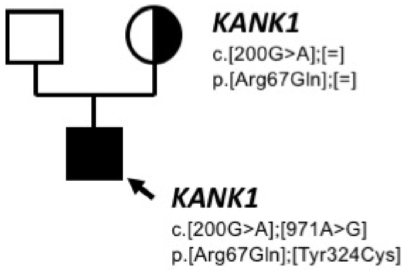
(2.0 nmol/mg of protein, normal values <0.3). Finally, biopsy re-evaluation showed several multinucleated podocytes on electron microscopy. Previous studies described how nephropathic cystinosis may clinically appear as a podocytopathy, with nephrotic syndrome (124-126), sometimes in absence of tubular dysfunction or extra-renal signs (127).

Case 17. This patient developed severe nephrotic syndrome resistant to steroids and calcineurin inhibitors. The biopsy showed focal segmental glomerulosclerosis. Although whole exome sequencing identified a pathogenic variant in *LMX1B* inherited from the apparently healthy father, no signs of Nail-Patella syndrome were evident apart from NS,



consistently with previous reports (128). Reverse phenotyping by X-rays showed a bilateral lack of the ossification nuclei of the radium, the only bone abnormality related to the syndrome. Upon re-evaluation we observed normal nails, but absence of the thumbs *lunulae*. Reverse phenotyping of the father showed microscopic hematuria and mild proteinuria (300-500 mg/day) (100).

Case 18. This patient showed isolated nephrotic syndrome with a severe albuminuria and was diagnosed with steroid-resistant nephrotic syndrome in another nephrology center. Genetic testing revealed compound heterozygous pathogenic variants in *KANK1*, one inherited by the mother and the other appeared *de novo*. Kidney biopsy showed a minimal change disease. The patient was also followed in the neurology department for an epilepsy that turned out to be multi-drug resistant that upon reverse phenotyping was also attributed to the KANK1 mutation (129).



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