Supplemental Table 1. Clinical features of three patients in a non-consanguineous Chinese family with steroid-resistant nephrotic syndrome

Family-Individual	Gender	Age of onset (yrs)	Urinary protein (g/24h)	Extrarenal manifestations	Biopsy	Renal phenotype and therapy (ESRD at yrs)	Transplantation (yrs)/ Death (yrs)
II2	F	N/A	3+ (N/A)	No	N/A	SRNS, ESRD (N/A)	Death (17)[1]
II3	M	14	3+ (6.20)	No	N/A	SRNS, ESRD (16)	Death (17)[2]
II6	F	7	3+ (8.34)	No	FSGS	SRNS, ESRD (15)	Transplantation (16.4)[3]

ESRD, end-stage renal disease; F, female; FSGS, focal segmental glomerulosclerosis; M, male; N/A, no applicable; SRNS, steroid-resistant nephrotic syndrome; yrs, years. 1- Patient II2 died in 1993; 2 - Patient II3 died in 1998. 3 - Patient II6 keeps a normal renal function after transplantation performed in 2005.

Supplemental Table 2. A list of known genes associated with steroid-resistant nephrotic syndrome

Gene	Inheritance	Disease	Histology
ACTN4	AD	SRNS (late onset)	FSGS
ADCK4	AR	CoQ10 biosynthesis disruption, SRNS	FSGS
ALG1	AR	Congenital defect of glycosylation	FSGS
ANLN	AD	SRNS (adult-onset)	FSGS
APOL1	Biallelic (G1, G2 risk alleles)	Increased susceptibility to FSGS and ESRD in African Americans, Hispanic Americans and in individuals of African descent	FSGS
ARHGAP24	AD	FSGS (adult-onset)	FSGS
ARHGDIA	AR	SRNS (CNS), seizures, cortical blindness	FSGS
AVIL	AR	SRNS	DMS
CD151	AR	ESRD, pretibial bullous skin lesions, sensorineural deafness, bilateral lacrimal duct stenosis, nail dystrophy, and β-thalassemia minor	FSGS
CD2AP	AD, AR	SRNS	FSGS
CFH	AR	MPGN type II + NS	FSGS
COL4A3	AD, AR	Alport syndrome	FSGS
COL4A4	AD, AR	Alport syndrome	FSGS
COL4A5	XLD	Alport syndrome	FSGS
COQ2	AR	CoQ10 deficiency, SRNS +/−encephalopathy	CG
COQ6	AR	CoQ10 deficiency, SRNS and deafness	FSGS, DMS
CRB2	AR	SRNS	FSGS
CUBN	AR	Intermittent nephrotic range proteinuria +/- with epilepsia	FSGS
DGKE	AR	Hemolytic-Uremic Syndrome + SRNS	FSGS
E2F3	AD	FSGS, mental retardation (gene deletion)	FSGS
EMP2	AR	SRNS and SSNS (childhood-onset)	FSGS
FAT1	AR	SRNS, tubulopathy, neurological involvement	glomerulotubular nephropathy (variable)
GPC5	Risk gene	NS (adult-onset)	Variable
INF2	AD	SRNS, FSGS-associated Charcot-Marie-Tooth neuropathy	FSGS
ITGA3	AR	Congenital interstitial lung disease, SRNS, and mild epidermolysis bullosa	FSGS

ITGB4	AR	Epidermolysis bullosa and pyloric atresia , FSGS	FSGS
KANK1	AR	SSNS	MCD
KANK2	AR	SSNS/SDNS +/- hematuria	MCD
KANK4	AR	SRNS + haematuria	FSGS
LAMA5	AR	Partially treatment-responsive NS (childhood-onset) with homozygous variants of unknown significance	FSGS
LAMB2	AR	Pierson syndrome	DMS, FSGS
LMNA	AD	Familial partial lipodystrophy, FSGS	FSGS
LMX1B	AD	Nail-patella syndrome; isolated SRNS	FSGS
MAGI2	AR	CNS, SRNS	MCD
MTTL1	Mitochondria	MELAS, diabetes, deafness, SRNS	FSGS
MYH9	AD	MYH9-related disease, Epstein and Fechtner syndromes, SRNS	FSGS
MYO1E	AR	Familial SRNS	FSGS
NUP85	AR	SRNS, microscopic hematuria, +/- short stature, intellectual disability, partial growth hormone deficiency	FSGS
NUP93	AR	Childhood SRNS	FSGS, DMS
NUP107	AR	Childhood SRNS, +/- microscopic hematuria, dilated cardiomyopathy, arterial hypertension, microcephaly, developmental delay, intellectual disability, short stature, facial dysmorphism, cleft lip, cleft palate	FSGS, DMS, Glomerulosclerosis
NUP133	AR	Childhood SRNS	FSGS
NUP205	AR	Childhood SRNS	FSGS
NPHS1	AR	Congenital nephrotic syndrome/SRNS	PTRD, PMS, FSGS, MCD
NPHS2	AR	CNS, SRNS	FSGS, MCD
NXF5	XLR	FSGS with co-segregating heart block disorder	FSGS
OCRL1	XLR	Dent disease, Lowe syndrome, +/- FSGS, +/- nephrotic range proteinuria	FSGS
PAX2	AD	FSGS (adult-onset) without extrarenal manifestations	FSGS
PDSS2	AR	CoQ10 deficiency, SRNS, Leigh syndrome	FSGS
PLCE1	AR	CNS, SRNS (early onset)	DMS, FSGS
PMM2	AR	Congenital disorder of glycosylation	CG
PODXL	AD	FSGS	FSGS

PTPRO	AR	SRNS (childhood-onset)	FSGS, MCD
SCARB2	AR	Action myoclonus renal failure syndrome +/- hearing loss	FSGS
SGPL1	AR	nephrosis (SRNS) with ichthyosis and adrenal insufficiency	FSGS
SMARCAL1	AR	Schimke immuno-osseous dysplasia	FSGS
SYNPO	AD	Sporadic FSGS (promoter mutations)	FSGS
TRPC6	AD	SRNS (late onset)	FSGS
TTC21B	AR	FSGS with tubulointerstitial involvment	FSGS
WDR73	AR	Galloway-Mowat syndrome (microcephaly and SRNS)	FSGS, DMS
WT1	AD, Smu	Denys-Drash, Frasier syndrome, isolated SRNS +/- abnormal genitalia	FSGS, DMS
XPO5	AR	Childhood SRNS	MCD
ZMPSTE24	AR	Mandibuloacral dysplasia with FSGS	FSGS

AD, Autosomal dominant; SRNS, steroid-resistant nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; AR, autosomal recessive; ESRD, end-stage renal disease; CNS, congenital nephrotic syndrome; DMS, diffuse mesangial sclerosis; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; XLD, X-linked dominant; CG, collapsing glomerulopathy; SSNS, steroid-sensitive nephrotic syndrome; MCD, minimal change disease; SDNS, steroid-dependent nephrotic syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; PMS, progressive mesangial sclerosis; PTRD, proximal tubule radial dilatation; XLR, X-linked recessive; Smu, Somatic mutation.

References:

1. Preston R, Stuart HM, Lennon R. Genetic testing in steroid-resistant nephrotic syndrome: why, who, when and how? *Pediatr Nephrol*. 2017 Nov 27. doi:10.1007/s00467-017-3838-6.

2. Bierzynska A, Soderquest K, Dean P, Colby E, Rollason R, Jones C, et al. MAGI2 Mutations Cause Congenital Nephrotic Syndrome. *J Am Soc Nephrol* 28: 1614-1621, 2017.

3. Rao J, Ashraf S, Tan W, van der Ven AT, Gee HY, et al. Advillin acts upstream of phospholipase C ϵ1 in steroid-resistant nephrotic syndrome. *J Clin Invest* 127: 4257-4269, 2017.

4. Gee HY, Sadowski CE, Aggarwal PK, Porath JD, Yakulov TA, Schueler M, et al. FAT1 mutations cause a glomerulotubular nephropathy. *Nat Commun* 7: 10822, 2016.

5. Braun DA, Warejko JK, Ashraf S, Tan W, Daga A, Schneider R, et al. Genetic variants in the LAMA5 gene in pediatric nephrotic syndrome. *Nephrol Dial Transplant*. 2018 Mar 9. doi:10.1093/ndt/gfy028.

6. Okamoto K, Tokunaga K, Doi K, Fujita T, Suzuki H, Katoh T, et al. Common variation in GPC5 is associated with acquired nephrotic syndrome. *Nat Genet* 43: 459-463, 2011.

7. Yasukawa T, Suzuki T, Ueda T, Ohta S, Watanabe K. Modification defect at anticodon wobble nucleotide of mitochondrial tRNAs(Leu)(UUR) with pathogenic mutations of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *J Biol Chem* 275: 4251-4257, 2000.

8. Lovric S, Goncalves S, Gee HY, Oskouian B, Srinivas H, Choi WI, et al. Mutations in sphingosine-1-phosphate lyase cause nephrosis with ichthyosis and adrenal insufficiency. *J Clin Invest* 127: 912-928, 2017.

9. Prasad R, Hadjidemetriou I, Maharaj A, Meimaridou E, Buonocore F, Saleem M, et al. Sphingosine-1-phosphate lyase mutations cause primary adrenal insufficiency and steroid-resistant nephrotic syndrome. *J Clin Invest* 127: 942-953, 2017.

10. Braun DA, Lovric S, Schapiro D, Schneider R, Marquez J, Asif M, et al. Mutations in multiple components of the nuclear pore complex cause nephrotic syndrome. *J Clin Invest* 128: 4313-4328, 2018.

Supplemental Table 3. Mapping statistics of whole exome sequencing

	Patient (II6)	Sister (II5)	Father (I1)	Mother (I2)	Mean	Std. Error
Reads on target region (%)	84.10	83.52	84.99	84.76	84.34	0.33
Reads mapped to target ± 150bp (%)	84.66	84.09	85.55	85.31	84.90	0.33
Reads mapped to target ± 500bp (%)	85.41	84.87	86.28	86.03	85.65	0.32
Mean depth in target region	125.38	99.04	109.73	115.08	112.31	5.49
Covered target regions (%)	99.83	99.82	99.97	99.82	99.86	0.04
Target base covered at least 1 × (%)	99.84	99.82	99.96	99.83	99.86	0.03
Target base covered at least 5 × (%)	99.60	99.52	99.74	99.56	99.61	0.05
Target base covered at least 10 × (%)	99.20	98.94	99.31	99.10	99.14	0.08
Target base covered at least 30 × (%)	95.53	92.73	94.57	94.66	94.37	0.59
Target base covered at least 50 × (%)	87.02	79.01	83.55	84.49	83.52	1.67

In Figure 1 C, I1 is Father, I2 is Mother, II5 is Sister, II6 is Patient.

Supplemental Table 4. Rare variants found in the patient (II6)

gene and variant	dbSNP151	DP_ Sample	Nref_ Sample	Nalt_ Sample	Genotype Quality	Phred scaled variant quality	ExAC				Additional significant information[1]
							Allele count	Allele Number	Number of homozygotes	Allele freq	
TTC12: NM_017868:exon22:c.G2071A:p.Gly691Ser (H)	rs138333675	250	0	250	99	18393	213	1E+05	5	0.0018	Polyphen: probably_damaging; SIFT: deleterious; PROVEAN: Deleterious; MutationTaster: disease causing. Father, Mother and Sister are heterozygous. The *TTC12* gene encodes TTC12 protein which is predicted to be localized to the nucleoplasm. TTC12 protein contains a tetratricopeptide repeat domain and 3 armadillo repeat domains. Expression of the *TTC12* gene in human cells in both glomeruli and tubules is low. Haplotypic variants in *TTC12* are associated with tobacco addiction (PMID: 17085484), comorbid alcohol and drug dependence (PMID: 18828801, PMID: 17761687), but 5 homozygous individuals with p.Gly691Ser in *TTC12* present no kidney phenotype.
DCANP1 (*C5orf20*): NM_130848:exon1:c.G587A:p.Arg196His (H)	rs59567190	112	1	112	99	10111	615	1E+05	23	0.0051	Polyphen: benign; SIFT: tolerated_low_confidence; PROVEAN: Deleterious; MutationTaster: polymorphism. Father, Mother and Sister are heterozygous.The intronless gene of *DCANP1* encodes DCANP1 protein which is predicted to be localized mainly in the perinucleus. DCANP1 protein is specifically expressed in dendritic cells (DCs). Expression of DCANP1 protein is not detected in neither cells in glomeruli nor cells in tubules. One of the alleles (A/T) of this gene, that causes premature translation termination at aa 117, has been associated with an increased prevalence of major depression in humans (PMID:16189510). But 23 homozygous individuals with p.Arg196His in *DCANP1* present no kidney phenotype.
KIAA1549: NM_020910:exon16:c.G5186A:p.Arg1729Lys (H)	rs607973111	26	0	26	66	2071.8	836	1E+05	45	0.007	Polyphen: benign; SIFT: deleterious; PROVEAN: Deleterious; MutationTaster: polymorphism. Father and Mother are heterozygous, and Sister is normal. The *KIAA1549* gene encodes KIAA1549 protein which is predicted to be mainly localized to the nuclear membrane and the intermediate filaments. KIAA1549 protein belongs to the UPF0606 family. Expression of the *KIAA1549* gene in human cells in both glomeruli and tubules is medium. This gene has been found to be fused to the *BRAF* oncogene in many cases of pilocytic astrocytoma (PMID: 18974108, PMID: 27608415). The fusion results from 2Mb tandem duplications at 7q34. Alternative splicing results in multiple transcript variants. But 45 homozygous individuals with p.Arg1729Lys in *KIAA1549* present no kidney phenotype.

DNAH5: NM_001369:exon76:c.G13286A:p.Arg4429Gln (h)	rs61744047	161	80	85	99	21546	586	1E+05	15	0.0048	Polyphen: possibly_damaging; SIFT: N/A; PROVEAN: Deleterious; MutationTaster: disease causing (p.Arg4429Gln). Polyphen: benign; SIFT: N/A; PROVEAN: Deleterious; MutationTaster: disease causing (p.His4123Tyr). Father, Mother and Sister are heterozygous. The *DNAH5* gene encodes a dynein protein, which is part of a protein complexes composed of several heavy, light, and intermediate chains. The dynein heavy chains (DHCs) function as a force-generating protein with ATPase activity and contain a highly conserved catalytic domain with 4 P-loop consensus motifs involved in nucleotide binding. As a microtubule-associated motor protein, dynein expression is not detected in human cells of glomeruli and tubules. Mutations in the *DNAH5* gene cause primary ciliary dyskinesia type 3 (PMID: 23261302), as well as Kartagener syndrome (PMID: 11788826), which are both diseases due to ciliary defects.
DNAH5: NM_001369:exon72:c.C12367T:p.His4123Tyr (h)	rs151145750	243	128	121	99	5984.3	85	1E+05	0	0.0007	
HYDIN: NM_001270974:exon56:c.G9319C:p.Gly3107Arg (h)	rs200794485	154	117	45	99	1534	255	1E+05	0	0.0021	Polyphen: probably_damaging; SIFT: N/A; PROVEAN: Deleterious; MutationTaster: disease causing (p.Gly3107Arg). Polyphen: probably_damaging; SIFT: N/A; PROVEAN: Deleterious; MutationTaster: disease causing (p.Gly489Asp). Polyphen: probably_damaging; SIFT: N/A; PROVEAN: Neutral; MutationTaster: polymorphism (p.Val3899Met). p.Gly489Asp is from Father. Both p.Gly489Asp and p.Val3899Met are from Mother. Mother and Sitster carry the same genotype. The *HYDIN* gene encodes HYDIN protein which is predicted to be localized to the plasma membrane and cytosol. Database and sequence analyses revealed HYDIN transcripts that had been isolated from lung, testis, NT2 neuronal precursor cells, and Jurkat leukemic T cells. But expression of HYDIN protein is not detected in human cells of glomeruli and tubules. HYDIN protein is involved in cilia motility. Mice homozygote with a mutation in *HYDIN* develops hydrocephaly after birth. Mutations in *HYDIN* cause of autosomal recessive primary ciliary dyskinesia-5 (PMID: 23022101), a disorder characterized by the accumulation of cerebrospinal fluid within the ventricles of the brain.
HYDIN: NM_001270974:exon12:c.G1466A:p.Gly489Asp (h)	rs62040318	104	87	22	99	15057	-	-	-	-	
HYDIN: NM_001270974:exon69:c.G11695A:p.Val3899Met (h)	rs1626593	117	92	31	99	2872	-	-	-	-	
NUP160: NM_015231:exon19:c.G2407A:p.Glu803Lys (h)	rs775637217	165	82	87	99	5613.4	2	1E+05	0	######	Polyphen: benign; SIFT: TOLERATED; PROVEAN: Neutral; MutationTaster: disease causing (p.Glu803Lys). Polyphen: N/A; SIFT: N/A; PROVEAN: Deleterious; MutationTaster: disease causing (p.Arg1173X).This compound heterozygote is in trans. Substitution is inherited from Father and nonsense SNV from Mother. Substitution is present only as a heterozygote in Sister. The *NUP160* gene encodes Nup160 protein localized to the basket side of the nuclear pore, facing the nucleoplasm. Nup160 forms part of the Nup160-Nup107 subcomplex in the nuclear pore which is composed of Nup133, Nup96, Nup85, Nup43,

NUP160: NM_015231:exon30: c.C3517T:p.Arg1173 X (h)	-	72	37	36	99	1762.3	-	-	-	-	Nup37, Sec13, and Seh1. This complex plays a role in RNA export and in tethering Nup98 and Nup153 to the nucleus. Nup160 contains a histidine acid phosphatase motif. The N-terminal beta-propeller regions of Nup160 and Nup155 interact individually with an N-terminal domain of the nuclear pore membrane protein POM121, which lies close to the nuclear membrane. The *NUP160* gene is expressed in both human and mouse kidney cells. [2] Knockdown of *NUP160* impairs mouse podocytes in cell culture (PMID: 29704630). Two compound-heterozygous mutations (p.Glu803Lys and p.Arg910X) in *NUP160* were discovered in two siblings, older brother with steroid-resistant nephrotic syndrome and younger sister with proteinuria, from a non-consanguineous Chinese family (PMID: 30179222).

dbSNP151 (https://www.ncbi.nlm.nih.gov/SNP/); DP, read depth in target region; Nref, read depth for reference allele; Nalt, read depth for alternative allele; ExAC - The Exome Aggregation Consortium (http://exac.broadinstitute.org/); H, homozygous; h, heterozygous. 1 - Additional information obtained from GeneCards (http://www.genecards.org/), Mouse GenomeInformatics (http://www.informatics.jax.org/) and The Human Protein Atlas (http://www.proteinatlas.org/); Polyphen (http://genetics.bwh.harvard.edu/pph2/); SIFT (http://sift.jcvi.org/www/SIFT_enst_submit.html); PROVEAN (http://provean.jcvi.org/seq_submit.php); MutationTaster (http://www.mutationtaster.org/); N/A, no applicable. All variants were found through exome analysis. Compound heterozygous mutations (p.Glu803Lys and p.Arg1173X) in *NUP160* were checked with Sanger sequencing. 2 - https://proteomescout.wustl.edu/proteins/57894/expression.

Supplemental Figure 1