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Inclusion criteria	Exclusion criteria
Age <25 years at nephrotic syndrome onset -AND-	Patients with non-nephrotic range proteinuria or hematuria only
Clinical diagnosis of nephrotic syndrome (e.g. proteinuria, hypoalbuminemia, edema) -AND/OR-	SSNS, SDNS, acute GN (e.g. hypocomplementemia, gross hematuria), acute kidney injury.
Renal histology of FSGS or DMS	Patient age >25 year at nephrotic syndrome onset

Supplementary Table 1: Inclusion and exclusion criteria for enrollment in study.

DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; SDNS, steroid dependent nephrotic syndrome; SSNS, steroid sensitive.

Supplementary Table 2: Thirty-three genes known to cause monogenic steroid-resistant nephrotic syndrome and mode of inheritance. Underlined genes were discovered and published by the laboratory of F.H. during performance of the whole exome sequencing study. References for original publications are given on the right. Blue background indicates known steroid-resistant nephrotic syndrome gene and orange background a phenocopy gene for steroid-resistant nephrotic syndrome. Citations for these references are provided on page 20-23 of the supplementary information.

Gene	Mode of inheritance	OMIM ID	Reference
ACTN4	AD	#604638	Kaplan, JM (2000) (1)
ADCK4	AR	#615567	Ashraf, SA (2013) (2)
ARHGDIA	AR	#601925	Gee, HY (2013) (3)
CD2AP	AR/AD	#604241	Kim, JM (2003) (4)
COQ2	AR	#609825	Diomedi-Camassei, F (2007) (5)
COQ6	AR	#614647	Heeringa, SF (2011) (6)
CRB2	AR	#609720	Ebarasi, L (2015) (7)
CUBN	AR	#602997	Sadowski, CA (2014) (8)
DGKE	AR	#601440	Sadowski, CA (2014) (8)
FAT1	AR	#600976	Gee, HY (2016) (9)
INF2	AD	#610982	Brown, EJ (2010) (10)
ITGA3	AR	#605025	Has, C (2012) (11)
KANK1	AR	#607704	Gee, HY (2015) (12)
KANK2	AR	#614610	Gee, HY (2015) (12)
KANK4	AR	#614612	Gee, HY (2015) (12)
LAMB2	AR	#150325	Zenker, M (2004) (13)
LMX1B	AD	#602575	Boyer, O (2013) (14)
MYO1E	AR	#601479	Mele, C (2011) (15)
NPHS1	AR	#602716	Kestila, M (1998) (16)
NPHS2	AR	#604766	Boute, N (2000) (17)
NUP205	AR	#614352	Braun, DA (2016) (18)
NUP93	AR	#614351	Braun, DA (2016) (18)
PAX2	AD	#167409	Barua, M (2014) (19)
PDSS2	AR	#610564	Lopez, LC (2006) (20)
PLCE1	AR	#608414	Hinkes, B (2006) (21)
PODXL	AD	#602632	Barua, M (2014) (22)
SGPL1	AR	#603729	Lovric, S (2017) (23)
SMARCAL1	AR	#606622	Boerkoel, CF (2002) (24)
TRPC6	AD	#603652	Winn, MP (2005) (25)
TTC21B	AR	#612014	Huynh Cong, E (2014) (26)
WDR73	AR	#616144	Colin, E (2014) (27)
WT1	AD	#607102	Mendelsohn, HB (1982) (28)
XPO5	AR	#607845	Braun, DA (2016) (18)
AGXT	AR	#604285	Nishiyama, K (1991) (29)
COL4A3	AR	#120070	Lemmink, HH (1994) (30)
COL4A4	AR	#120131	Mochizuki, T. (1994) (31)
COL4A5	X-LINKED	#303630	Barker, DF (1990) (32)
CLCN5	X-LINKED	#300008	Lloyd, SE (1996) (33)
CTNS	AR	#606272	Town, M (1998) (34)
FN1	AD	#135600	Castelletti, F (2008) (35)
GLA	X-LINKED	#300644	Bernstein, HS (1989) (36)
LRP2	AR	#600073	Kantarci, S (2007) (37)
MEVF	AD/AR	#608107	International FMF Consortium (1997) (38)
OCRL	X-LINKED	# 300535	Attree, O (1992) (39)

AR, autosomal recessive; AD, autosomal dominant.

Supplementary Table 3: Variant calling as disease causing for autosomal recessive and dominant disease in genes known to cause steroid-resistant nephrotic syndrome.

Autosomal recessive variant calling in known genes	
Include allele as disease causing if:	**Truncating mutation (stop, abrogation of start or stop, obligatory splice, frameshift).** **Missense mutation:** **- Continuously conserved at least among vertebrates** **-or-** **-Previously reported as disease causing** **-or-** **- Loss of function in human allele is supported by functional data.** **-or-** **- Phenotype correlates with the published phenotype for the gene.** **- or-** **- Predicted deleterious for the protein function (at least in two among three prediction programs (Polyphen (>0.5), SIFT (Del), Mutation taster (DC)).**
Consider excluding allele as disease causing if:	**Allele Frequency** **- Heterozygous allele frequency >0.1% (in ExAC)** **- Homozygous allele frequency (> 2 individuals in ExAC)** **- Non-segregation in the case of compound heterozygotes**
Autosomal dominant variant calling in known genes	
Include allele as disease causing if:	**Truncating mutation (Stop, abrogation of start or stop, obligatory splice, frameshift).** **Missense mutation:** **- Continuously conserved at least among vertebrates** **-or-** **-Previously reported as disease causing** **-or-** **- Loss of function in human allele is supported by functional data.** **-or-** **- Phenotype correlates with the published phenotype for the gene.** **- or-** **- Predicted deleterious for the protein function (at least in two among three prediction programs (Polyphen (>0.5), SIFT (Del), Mutation taster (DC)).**
Consider excluding allele as disease causing if:	**Allele Frequency** **- Heterozygous allele frequency (>3 individuals in ExAC)** **- If the variant is present homozygously in any individual in ExAC** **- Non-segregation (note that variable expressivity and incomplete penetrance must be taken into consideration when evaluating dominant genes).**

Supplementary Table 4: Number of families evaluated by panel sequencing in Sadowski (8) and by whole exome sequencing in this study. 94 families were evaluated by whole exome sequencing and panel sequencing. In 20/94 families, a causative mutation was detected in one of 26 genes known to cause steroid resistant nephrotic syndrome gene by both whole exome sequencing and panel sequencing. In nine families of the 94 no causative mutation was detected by panel sequencing but a causative mutation was detected by whole exome sequencing. Phenotypes and genotypes of families with a causative mutation detected are given in **Supplementary Table 9.**

Total families evaluated by panel sequencing and WES	**94/300 (31%)**
Total families evaluated by WES only	**206/300 (69%)**
Total families with a causative mutation detected by panel sequencing and WES	**20/74 (27% of solved cases)**
Total families with a causative mutation detected by WES and not by panel sequencing	**9/74 (12%)**
Total families evaluated by WES only with a causative mutation detected	**45/74 (61%)**

WES (whole exome sequencing).

Supplementary Table 5: Selection of novel candidate genes for 11 families with steroid resistant nephrotic syndrome in whom a causative mutation in a known nephrosis or phenocopy gene was excluded. Each candidate gene represents the most deleterious mutation within a homozygous peak region of the respective families.

Family ID	*Gene*	Zygosity	Accession #	c. position	p. position	Continuously conserved to	MT/SFT/PPi	ExAC	Clinical diagnosis.)
A1756	*DDX53*	Hemi	NM_182699.3	c.24G>A	p.Trp8*	Truncating	-	NR	SRNS
A4684	*MXRA5*	Hemi	NM_015419.3	c.204_205insT	p.Ala69Cysfs*22	Frameshift	-	NR	SRNS
B51	*DHTKD1*	Hom	NM_018706.6	c.886G>A	p.Val296Met	*Dm*	DC/Del/1	0/3/121366	De-identified
B52	*DHTKD1*	Hom	NM_018706.6	c.886G>A	p.Val296Met	*Dm*	DC/Del/1	0/3/121366	De-identified
A5013	*CDK20*	Hom	NM_001039803.2	c.610T>C	p.Phe204Leu	*Dm*	DC/Del/1	NR	SRNS
B50	*OSGEP*	Hom	NM_017807.3	c.40A>T	p.Ile14Phe	*Dr*	DC/Del/0.023	NR	SRNS
B57	*OSGEP*	Hom	NM_017807.3	c.40A>T	p.Ile14Phe	*Dr*	DC/Del/0.023	NR	De-identified
B123	TPRKB	Hom	NM_016058.2	c.407T>C	p.Leu136Pro	*Xt*	DC/Del/1	NR	SRNS
B377	*OSGEP*	Hom	NM_017807.3	c. 740G>A	p.Arg247Gln	*Dm*	DC/Tol/0.998	0/8/121400	CNS
B787	*SLC35F1*	Hom	NM_001029858.3	c.878T>G	p.Met293Arg	*Ce*	DC/Del/0.999	NR	SRNS
B1356	*COG1*	Hom	NM_018714.2	c.1070+5G>A	Splice	Splice	-	NR	SRNS

Bx, biopsy; *Ce*, *Caenorhabditis elegans*; CNS, congenital nephrotic syndrome; DC, disease causing; Del, deleterious; *Dm*, *Drosophila melanogaster*; *Dr*, *Danio rerio*; Hom, homozygous; Hemi, Hemizygous; *Mm*, *Mus musculcus*; MT, MutationTaster; NR, not reported; PPi, Polyphene score; Sc, *Saccharomyces cerevisiae*; SFT, SIFT; SRNS, steroid-resistant nephrotic syndrome; Tol, tolerated; *Xt*, *Xenopus tropicalis*.

Supplementary Table 6: Age, sex, and ethnic characteristics of the steroid-resistant nephrotic syndrome cohort and of the families in whom a causative monogenic mutation was detected in either a steroid-resistant nephrotic syndrome gene or a phenocopy gene. Age and sex demographics are given for a subset of 81 individuals from 74 families in whom a causative mutation was detected in a steroid-resistant nephrotic syndrome gene or 15 individuals from 11 families in whom a causative mutation was detected in a phenocopy gene are shown. Additionally, ethnic and racial data are given for all the families in the cohort, with a subset of 74 families in which a mutation was detected in a steroid-resistant nephrotic syndrome gene and in 11 families with a mutation detected in a phenocopy gene. Age and sex is represented graphically in **Figure 3A**, race and ethnicity are represented graphically in **Supplementary Figure 1**. Families from Egypt identified as being African and Arabic and families from Saudi Arabia identified as being Arabic and Asian. Percents >10% are rounded to the nearest whole number.

	Clinical Characteristics of Total Cohort	Clinical Characteristics of Individuals with Causative Mutation Detected	
	Number of individuals (%)	Number of individuals with SRNS mutation detected (%)	Number of individuals with mutation detected - phenocopy gene (%)
Gender			
Male	163/335 (49%)	41/81 (51%)	9/15 (60%)
Female	138/335 (41%)	35/81 (43%)	5/15 (33%)
Unknown	34/335 (10%)	5/81 (6%)	1/15 (6.7%)
Total	335/335 (100%)	81/81 (100%)	15/15 (100%)
Median age (range) at diagnosis (in years)	4 (0-24)	1.7 (0-21)	4 (0.3-16)
Infants ≤ 90 days	31/335 (9.3%)	16/81 (20%)	0/15 (0%)
Infants >3 mo and ≤ 12 mo	62/335 (19%)	19/81 (24%)	4/15 (27%)
Children > 1 yr and ≤ 6 yr	94/335 (28%)	19/81 (24%)	4/15 (27%)
Children > 6 and ≤ 12yr	54/335 (16%)	11/81 (14%)	1/15 (6.7%)
Children > 12 yr or <18 yr	34/335 (10%)	5/81 (6%)	2/15 (13%)
Young adults ≥ 18 yr or <25 yr	8/335 (2.4%)	2/81 (2.5%)	0/15 (0%)
Not reported	52/335 (16%)	9/81 (11%)	4/15 (27%)
Total	335/335 (100%)	81/81 (100%)	15/15 (100%)
Race/Ethnicity			
	Number of families (%)	Number of families (%)	Number of families (%)
Arabic	77/300 (26%)	29/74 (39%)	3/11 (27%)
European/Caucasian	59/300 (20%)	8/74 (11%)	3/11 (27%)
Turkish	29/300 (10%)	12/74 (16%)	2/11 (18%)
Hispanic/Latino	22/300 (7.3%)	2/74 (2.7%)	1/11 (9.1%)
Asian	21/300 (7%)	7/74 (9.5%)	0/11 (0%)
African and Arabic	15/300 (5%)	4/74 (5.4%)	0/11 (0%)
African/African American	8/300 (2.7%)	2/74 (2.7%)	0/11 (0%)
Arabic and Asian	9/300 (3%)	0/74 (0%)	0/11 (0%)
Other/multiple races indicated	6/300 (2%)	1/74 (1.4%)	1/11 (9.1%)
Ashkenazi Jewish	1/300 (0.3%)	0/74 (0%)	0/11 (0%)
Roma	1/300 (0.3%)	1/74 (1.4%)	0/11 (0%)
Unknown/not indicated	52/300 (17%)	8/74 (11%)	1/11 (9.1%)

Total	**300/300 (100%)**	**74/74 (100%)**	**11/11 (100%)**

SRNS, steroid-resistant nephrotic syndrome.

Supplementary Table 7: Presence of consanguinity, homozygosity, or multiple affected statuses in 300 families with steroid-resistant nephrotic syndrome. A subset of 74 families in whom a causative mutation was detected in a steroid-resistant nephrotic syndrome gene or 11 families in whom a causative mutation was detected in a phenocopy gene are shown. In addition, the presence of extra-renal manifestations in 335 individuals from 300 families with steroid-resistant nephrotic syndrome compared to a subset of 81 individuals from 74 families in whom a causative mutation was detected in a steroid-resistant nephrotic syndrome gene or 15 individuals from 11 families in whom a causative mutation was detected in a phenocopy gene. Pedigree characteristics are represented graphically in **Figure 4**. Extra-renal manifestations are represented graphically in **Supplementary Figure 2**. Percents >10% are rounded to the nearest whole number.

	Clinical Characteristics of Total Cohort	Clinical Characteristics of Individuals/Families with Causative Mutation Detected	
	Number of families (%)	Number of families with SRNS mutation detected (%)	Number of families with mutation detected - phenocopy gene (%)
Pedigree			
Consanguineous	**146/300 (49%)**	**56/74 (76%)**	**6/11 (55%)**
Non-consanguineous	**135/300 (45%)**	**17/74 (23%)**	**4/11 (36%)**
Unknown consanguinity	**19/300 (6.3%)**	**1/74 (1.4%)**	**1/11 (9.1%)**
Homozygosity on mapping >100Mbp	**147/300 (49%)**	**56/74 (76%)**	**5/11 (45%)**
Homozygosity on mapping <100Mbp	**153/300 (51%)**	**18/74 (24%)**	**6/11 (55%)**
Families with one affected individual	**174/300 (58%)**	**41/74 (55%)**	**2/11 (18%)**
Families with 2 affected individuals	**65/300 (22%)**	**21/74 (28%)**	**5/11 (46%)**
Families with 3 or greater affected individuals	**28/300 (9.3%)**	**7/74 (9.5%)**	**3/11 (27%)**
Unknown/de-identified sample	**33/300 (11%)**	**5/74 (6.8%)**	**1/11 (9.1%)**
Total families	**300/300 (100%)**	**74/74 (100%)**	**11/11 (100%)**
Extra-renal manifestations			
	Number of individuals (%)	**Number of individuals (%)**	**Number of individuals (%)**
Yes	**91/335 (27%)**	**22/81 (27%)**	**6/15 (40%)**
No	**219/335 (65%)**	**58/81 (72%)**	**7/15 (47%)**
Unknown/de-identified sample	**25/335 (7.5%)**	**1/81 (1.2%)**	**2/15 (13%)**
Total individuals	**335/335 (100%)**	**81/81 (100%)**	**15/15 (100%)**

SRNS, steroid-resistant nephrotic syndrome.

Supplementary Table 8: Clinical and histologic diagnosis of 335 individuals from 300 families with steroid-resistant nephrotic syndrome. A subset of 85 individuals from 78 families in whom a causative mutation was detected in a steroid-resistant nephrotic syndrome gene and 15 individuals from 11 families in whom a phenocopy gene was detected are shown. Clinical diagnosis is represented graphically in **Supplementary Figure 3**; histologic diagnoses are represented graphically in **Supplementary Figure 4**. Percents >10% are rounded to the nearest whole number.

	Clinical Characteristics of Total Cohort	Clinical Characteristics of Individuals/Families with Causative Mutation Detected	
	Number of families (%)	Number of families with SRNS mutation detected (%)	Number of families with mutation detected - phenocopy gene (%)
Clinical diagnosis			
SRNS	205/300 (68%)	48/74 (65%)	9/11 (82%)
CNS	32/300 (11%)	17/74 (23%)	0/11 (0%)
Infantile nephrotic syndrome	9/300 (3%)	1/74 (1.4%)	0/11 (0%)
Nephrotic syndrome with ESRD on presentation	1/300 (0.3%)	1/74 (1.4%)	0/11 (0%)
ESRD on presentation, FSGS or DMS on biopsy	4/300 (1.3%)	1/74 (1.4%)	0/11 (0%)
Nephrotic syndrome with FSGS or DMS on biopsy	6/300 (2%)	0/74 (0%)	0/11 (0%)
Nephrotic range proteinuria with FSGS or DMS of biopsy	7/300 (2.3%)	1/74 (1.4%)	0/11 (0%)
De-identified sample	36/300 (12%)	5/74 (6.8%)	2/11 (18%)
Total families enrolled	300/300 (100%)	74/74 (100%)	11/11 (100%)
	Number of individuals (%)	Number of individuals (%)	Number of individuals (%)
Diagnosis on biopsy	Diagnosis on biopsy (n=223)	Diagnosis on biopsy (n=50)	Diagnosis on biopsy (n=9)
FSGS	153/223 (69%)	37/50 (74%)	3/9 (33%)
DMS	14/223 (6.3%)	2/50 (4%)	1/9 (11%)
MCNS	20/223 (9%)	4/50 (8%)	0/9 (0%)
MPGN	10/223 (4.5%)	2/50 (4%)	1/9 (11%)
CNS/Finnish type	5/223 (2.2%)	1/50 (2%)	0/9 (0%)
Membranous GN	1/223 (0.4%)	0/50 (0%)	0/9 (0%)
Other	20/223 (9%)	4/50 (8%)	4/9 (44%)
No bx data available	112/335 (33%)	31/81 (38%)	6/15 (40%)

CNS, congenital nephrotic syndrome; DMS, diffuse mesangial sclerosis; ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; SRNS, steroid resistant nephrotic syndrome.

Supplementary Table 9: Summary of causative mutations detected in one of 20steroid-resistant nephrotic syndrome causing genes and 8 phenocopy genes in 90 of 300 families with steroid-resistant nephrotic syndrome by family and clinical phenotype.

Gene	Family ID and indiv. #	c. change	p. change	Zygo-sity	Cons.	SFT	MT	PPi	ExAC (home/het/ total alleles)	Age (years)	Sex (M/F)	Race/ Ethnicity	Consang. (Y/N)	# affected per family	Synd. (Y/N)	Clin. Dx	Kidney biopsy results
COQ2	B1425_21	c.176_177insT	p.F59fs	Comp het	FS	-	-	-	NR	2	M	C/E	N	1	N	SRNS	FSGS
		c.683A>G	p.N228S	Comp het	*Dm*	Tol	DC	0.918	0/20/120566								
DGKE	A4431_21	c.610del	p.T204Qfs*6	Hom	FS	-	-	-	NR	17	F	C/E	Y	3	N	SRNS	FSGS
	A4431_22	c.610del	p.T204Qfs*6	Hom	FS	-	-	-	NR	8	F	C/E	Y		N	SRNS	MPGN
INF2	B788_21	c.532T>G	p.F178V	Het	*Dr*	Tol	DC	0.996	NR	21	M	C/E	N	7	N	SRNS	FSGS
ITGA3	A1605_21	c.2593del	p.D865Tfs*38	Hom	FS	-	-	-	NR	<1	M	Turkish	Y	1	N	SRNS	FSGS
	A3113_21	c.1883G>C	p. R628P	Hom	*Dm*	Del	DC	0.3	0/3/118974	4 mo	F	Asian	Y	1	N	CNS	No bx
KANK4	B324_21	c.2401T>C	p.Y801H	Hom	*Dm*	Del	DC	1	0/121/120924	2 mo	F	Roma	N	4	Y	CNS	MCNS
LAMB2	A1757_21	c.143A>C	p.Y48S	Hom	*Dr*	Del	DC	1	0/70/117226	13	M	Hispanic	N	2	N	SRNS	FSGS
	A1757_22	c.143A>C	p.Y48S	Hom	*Dr*	Del	DC	1	0/70/117226	13	F	Hispanic	N		N	SRNS	FSGS
	B819_21	c.395C>T	p.A132V	Hom	*Xt*	T	P	0.002	0/2/121366	0	F	Turkish	Y	2	N	CNS	No bx
	A2356_23	c.736C>T	p. R246W	Hom	*Dm*	Del	DC	1	0/1/119680	3mo	M	Arabic	Y	2	Y	CNS	CNS
	A5284_12	c.1731+1G>A	Splice	Hom	Splice	-	-	-	0/1/118980	1 mo	F	Asian	Y	1	Y	CNS	No bx
	A2263_23	c.4537C>T	p.Q1513*	Hom	Trunc.	-	-	-	NR	2 mo	M	Arabic	Y	1	Y	SRNS	No bx
	B1219_21	c.4573C>T	p.Q1525*	Hom	Trunc.	-	-	-	0/1/121384	0.2	F	Arabic	Y	1	Y	CNS	No bx

LMX1B	A200_21	c.737G>A	p.R246Q	Het	*Dm*	Del	DC	0.998	NR	8	F	Turkish	Y	2	N	SRNS	FSGS
	A4642	c.737G>A	p.R246Q	Hom	*Dm*	Del	DC	0.998	NR	unk	unk	unk	unk	unk	unk	De-identified	unk
MYO1E	A146_21	c.1228G>A	p.E410K	Hom	*Sc*	Del	DC	0.98	NR	18	M	unk	Y	1	N	ESRD at presentation	Other - chronic renal failure
	A3656_21	c.1978C>T	p.Q660*	Hom	Trunc.	-	-	-	NR	45 do	M	Asian	Y	1	N	CNS	MCD
NPHS1	A5151_21	c.139del	p.A47Pfs81*	Hom	FS	-	-	-	0/2/114206	4 mo	M	Arabic	Y	1	N	SRNS	No bx
	A4472_22	c.515_517del	p.T172del	Hom	In-frame del	-	-	-	NR	60 do	F	Arabic	Y	2	N	SRNS	No bx
	B1122_21	c.1048T>C	p.S350P	Comp het	*Dm*	Del	P	0.76	0/2/121174	unk	F	C/E	Y	1	N	CNS	unk
		c.2506+5G>T	Splice	Comp het	Splice	-	-	-	0/1/120468								
	B1238	c.1379G>A	p.R460Q	Hom	*Ce*	Tol	Pol	0.48	0/1/119280	0.25	M	Arabic	Y	4	N	CNS	No bx
	B55	c.1760T>G	p.L587R	Hom	*Dr*	Del	DC	0.99	NR	unk	unk	unk	Y	unk	Y	De-identified	No bx
	A5275_21	c.2014G>A	p.A672T	Comp het	*Dr*	Del	DC	0.99	0/1/82174	5 mo	M	Turkish	N	1	Y	Infantile NS	FSGS
		c. 3250dupG	p.V1084Gfs*	Comp het	FS	-	-	-	0/1/82174								
	A3432_24	c.2020C>A	p.P674T	Hom	*Dr*	Del	DC	0.3	0/3/118974	1 mo	M	Arabic	Y	4	N	CNS	No bx
	A1500_21	c.2728T>C	p.S910P	Hom	*Dr*	Del	DC	0.959	NR	1	M	A/AA	N	1	N	SRNS	MCNS
	A3509_21	c.3478C>T	p.R1160*	Hom	Trunc.	-	-	-	0/8/121256	0	F	Asian	Y	1	N	CNS	No bx
	A3594_21	c.3478C>T	p.R1160*	Hom	Trunc.	-	-	-	0/8/121256	0	F	Arabic	Y	1	N	CNS	No bx
	A3708_21	c.3478C>T	p.R1160*	Hom	Trunc.	-	-	-	0/8/121256	2 mo	M	A/AA	Y	1	N	CNS	FSGS
	A4427_23	c.3478C>T	p.R1160*	Hom	Trunc.	-	-	-	0/8/121256	0	F	Other/multiple races	N	1	N	CNS	No bx

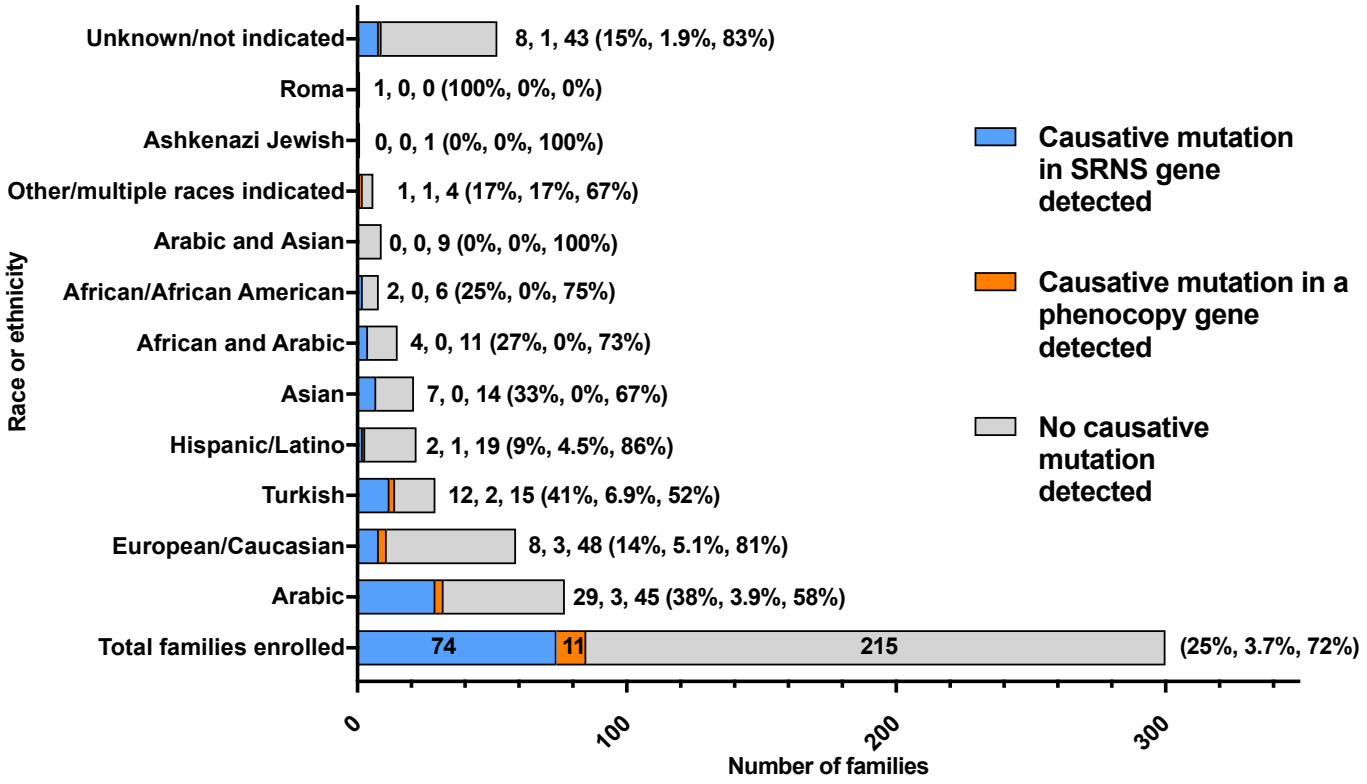
	B1357_21	c.3478C>T	p.R1160*	Hom	Trunc.	-	-	-	0/8/121256	0.1	F	African/ Arabic	Y	1	N	CNS	No bx
NPHS2	A4681_21	c.1A>T	p.M1?	Hom	Start loss	-	-	-	NR	7	F	Arabic	Y	1	N	SRNS	FSGS
	A679_21	c.397del	p.R133Efs*2	Comp het	FS	-	-	-	NR	unk	M	C/E	N	2	N	SRNS	No bx
		c.413G>A	p.R138Q	Comp het	*Dm*	Del	DC	0.999	0/82/121298								
	A679_22	c. 397del	p.R133Efs*2	Comp het	FS	-	-	-	NR	unk	M	C/E	N		N	SRNS	No bx
		c.413G>A	p.R138Q	Comp het	*Dm*	Del	DC	0.999	0/82/121298								
	A3133_21	c.419del	p.G140Dfs*41	Hom	FS	-	-	-	0/1/121308	5.8	F	Arabic	Y	2	N	SRNS	FSGS
	A3133_43	c.419del	p.G140Dfs*41	Hom	FS	-	-	-	0/1/121308	2	F	Arabic	Y		N	SRNS	FSGS
	B963_21	c.538G>A	p.V180M	Hom	*Dr*	Del	DC	0.58	0/3/120452	9 mo	F	Arabic	Y	1	N	SRNS	No bx
	A667_21	c.686G>A	p.R229Q	Comp het	*Xt*	Tol	P	0.313	69/3526/119108	14	F	C/E	N	2	N	SRNS	FSGS
		c.916A>T	p.R306W	Comp het	*Dr*	Del	DC	0.98	NR								
	A667_22	c.686G>A	p.R229Q	Comp het	*Xt*	Tol	P	0.313	69/3526/119108	9	M	C/E	N		N	SRNS	No bx
		c.916A>T	p.R306W	Comp het	*Dr*	Del	DC	0.98	NR								
	A4309_21	c.705_713del9	p.L236del	Hom	In-frame del	-	-	-	NR	3 mo	M	Asian	Y	1	Y	CNS	Other - diffuse mesangial hypercellularity
	B1090	c.800A>T	p.D267V	Hom	*Ce*	Del	DC	1	NR	8	M	African/ Arabic	Y	1	N	SRNS	FSGS
	B188	c.855_856del	p.R286Tfs*17	Hom	FS	-	-	-	0/8/115938	3	F	Hispanic	Y	2	N	SRNS	MCNS
NUP205	B140_21	c.3095G>A	p.C1032Y	Hom	*Dm*	Tol	DC	1	NR	3	M	Arabic	Y	1	Y	SRNS	FSGS
	A1733_21	c.5984T>C	p.F1995S	Hom	*Dm*	Tol	DC	0.99	NR	3.5	F	Turkish	N	2	N	SRNS	FSGS

	A1733_22	c.5984T>C	p.F1995S	Hom	*Dm*	Tol	DC	0.99	NR	3	M	Turkish	N		N	SRNS	No bx
NUP93	A1626_21	c.1772G>T	p.G591V	Hom	*Sc*	Del	DC	1	0/14/121252	2.5	M	Turkish	Y	1	N	SRNS	FSGS
	A1671_21	c.1886A>G	p.Y629C	Hom	*Sc*	Del	DC	0.997	0/1/120978	1.3	M	Turkish	N	1	N	SRNS	IgA
	A2241_22	c.1886A>G	p.Y629C	Hom	*Sc*	Del	DC	0.997	0/1/120978	11 mo	M	Turkish	Y	2	N	SRNS	No bx
	B1311_21	c.2017C>T	p.R673W	Hom	*Dr*	Tol	DC	1	NR	1	F	Arabic	Y	2	N	CNS	FSGS
PDSS2	A3853_22	c.1145C>T	p.Ser382Leu	Hom	*Dr*	Del	DC	1	0/4/121372	1	M	Arabic	Y	2	Y	SRNS	No bx
PLCE1	B913_21	c.1709del	p.S570Tfs*29	Hom	FS	-	-	-	NR	9 mo	M	Turkish	Y	1	Y	SRNS	FSGS
	A1678_21	c.2576_2577insT	p.Q859Hfs*31	Hom	FS	-	-	-	NR	7.9	M	Turkish	Y	1	N	SRNS	DMS
	A3617_25	c.3379_3380del	p.N1127*	Hom	Trunc.	-	-	-	NR	9 mo	F	Arabic	Y	3	N	SRNS	FSGS
	A3921_22	c.4506+2T>C	Splice	Hom	Splice	-	-	-	NR	6 mo	F	Arabic	Y	2	N	SRNS	FSGS
	A59_21	c.4887del	p.A1630Qfs*40	Hom	FS	-	-	-	NR	7 mo	F	Turkish	N	1	N	SRNS	FSGS
	B354_22	c.4978_4981CAGA	p.Q1660Lfs*9	Hom	FS	-	-	-	NR	1	M	Arabic	Y	2	N	SRNS	DMS
	A4654_21	c.5521A>G	p.K1841E	Hom	*Sc*	Del	DC	1	NR	4	F	Arabic	Y	2	N	SRNS	FSGS
	A4654_22	c.5521A>G	p.K1841E	Hom	*Sc*	Del	DC	1	NR	2.4	F	Arabic	Y		N	SRNS	FSGS
	A3869_24	c.5521A>G	p.K1841E	Hom	*Dm*	Del	DC	1	NR	7 mo	M	Arabic	Y	1	N	SRNS	FSGS
	B1432_24	c.5950_5952delAAC	p.N1984del	Hom	In-frame del.	-	-	-		0.5	M	Arabic	Y	1	N	SRNS	FSGS
	A4043_21	c.5951-5953delACA	p.N1984del	Hom	In-frame del.	-	-	-	NR	6 mo	M	Arabic	Y	1	N	SRNS	FSGS
	A5171_21	c.5951_5953del	p.N1984del	Hom	In-frame del.	-	-	-	NR	5	Male	Arabic	Y	2	N	SRNS	FSGS
SGPL1	A280_21	c.665G>A	p.R222Q	Hom	*Dm*	Del	DC	1	0/2/120744	2.5	M	Asian	Y	3	Y	SRNS	FSGS
	B46	c.1037G>T	p.S346I	Hom	*Sc*	Del	DC	1	NR	unk	unk	unk	Y	unk	Y	De-identified	No bx
	B56	c.1037G>T	p.S346I	Hom	*Sc*	Del	DC	1	NR	unk	unk	unk	Y	unk	Y	De-identified	No bx

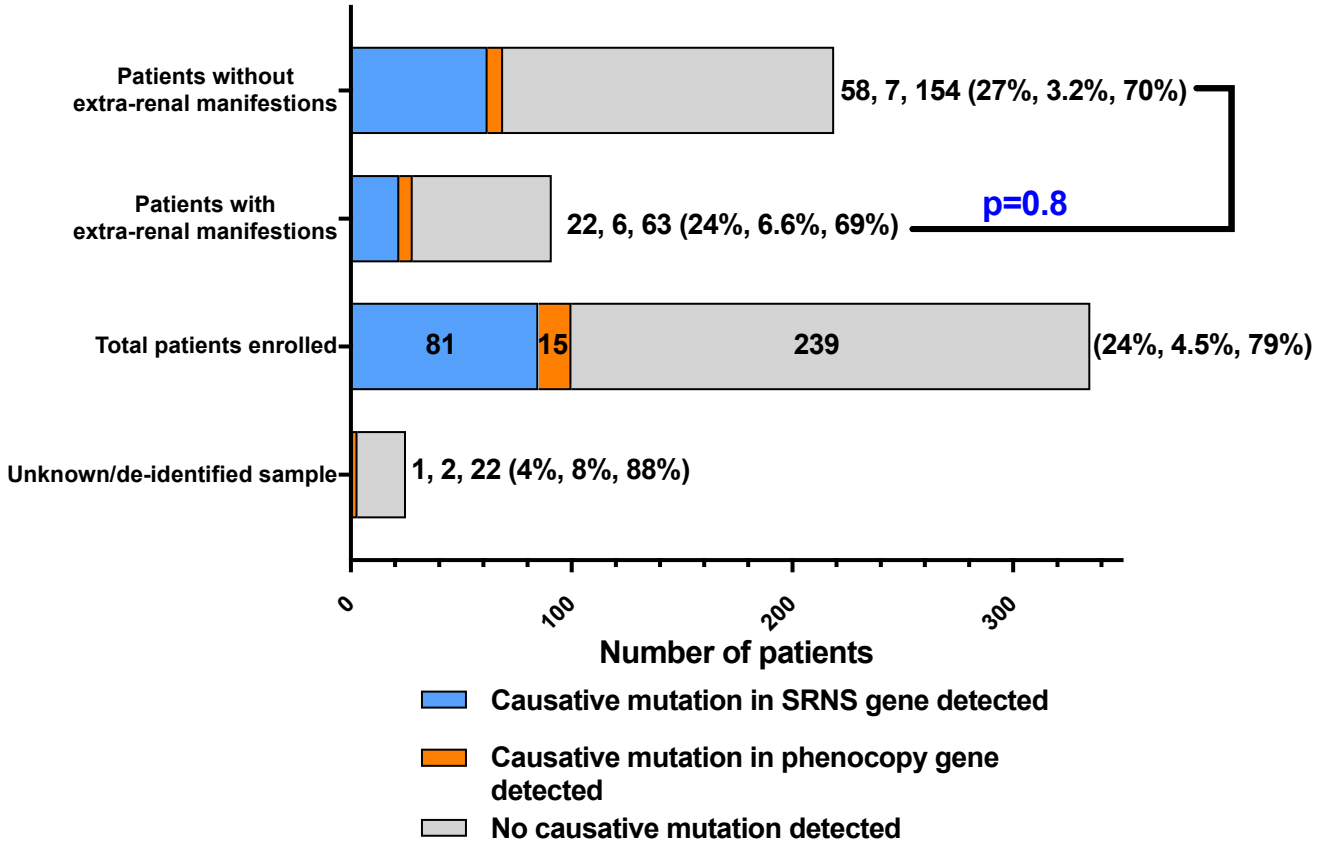
SMARCAL1	A925_21	c.1736C>A	p.S579*	Hom	Trunc.	-	-	-	NR	2.9	M	Arabic	Y	1	Y	SRNS	FSGS
	A1683_21	c.1756C>T	p.R586W	Hom	*Dm*	Del	DC	1	0/1/121386	7.6	M	Turkish	Y	1	Y	SRNS	FSGS
	F1367_21	c.1756C>T	p.R586W	Hom	*Dm*	Del	DC	1	0/1/121386	4	F	unk	Y	1	N	ESRD, FSGS on bx	FSGS
	B1067	c.1822T>C	p.F608L	Hom	*Dm*	Del	DC	1	NR	14	M	Arabic	Y	1	Y	SRNS	FSGS
	B672_21	c.1940A>C	p.K647T	Hom	*Dm*	Del	DC	1	NR	6	F	Arabic	Y	2	N	SRNS	No bx
	B142_22	c.2290C>T	p.R764W	Hom	*Dm*	Del	DC	1	NR	8	M	Arabic	Y		N	SRNS	FSGS
	B1319_21	c.2290C>T	p.R764W	Hom	*Dm*	Del	DC	1	NR	unk	F	African/ Arabic	Y	1	Y	SRNS	MPGN
	B1134_21	c.2542G>T	p.E848*	Hom	Trunc.	-	-	-	0/14/121298	11	M	C/E	N	1	Y	Nephrotic range proteinuria, FSGS on bx	FSGS
TRPC6	A4685_21	c.523C>T	p.R175W	Het	*Dr*	Del	DC	1	NR	7	F	Arabic	N	1	N	SRNS	FSGS
TTC21B	A5262_21	c.626C>T	p.P209L	Hom	*Dr*	Tol	DC	1	0/8/121264	8	F	African/ Arabic	Y	1	N	SRNS	FSGS
	A5002_21	c.2569G>A	p.Ala857Thr	Hom	*Ce*	Del	DC	0.983	NR	5 mo	M	Asian	Y	1	N	SRNS	No bx
WDR73	B49	c.287G>A	p.R96K	Hom	*Dr*	Tol	DC	1	NR	<1y	M	unk	Y	2	Y	SRNS	No bx
	B129_21	c.703C>T	p.Q235*	Hom	Trunc.	-	-	-	NR	3	M	Arabic	N	2	Y	SRNS	No bx
	B41	c.940C>T	p.Q315*	Hom	Trunc.	-	-	-	NR	unk	unk	unk	Y	unk	Y	De-identified	No bx
WT1	B1018_21	c.1432+5G>A	Splice	Het	Splice	-	-	-	NR	3	F	Arabic	N	1	N	SRNS	Other-focal mesangial proliferation
	B1244_21	c.1432+5G>A	Splice	Het	Splice	-	-	-	NR	5	F	C/E	N	1	N	SRNS	No bx
AGXT	A63_21	c.33dup	p.K12Qfs*156	Hom	FS	-	-	-	NR	4 mo	M	Turkish	Y	1	Y	SRNS	No bx

	B465_23	c.863G>A	p. W288*	Hom	Trunc.	-	-	-	NR	4 mo	M	Arabic	Y	3	unk	De-identified	No bx
CLCN5	A3094_22	c.933G>C	p.E311D	Hemi	*Sc*	Del	DC	1	NR	12	M	C/E	Y	2	Y	SRNS	FSGS
COL4A3	A1221_21	c.4825C>T	p.Arg1609*	Het	Trunc.	-	-	-	0/3/121000	5	F	C/E	N	2	Y	SRNS	FSGS
	A1221_22	c.4825C>T	p.Arg1609*	Het	Trunc.	-	-	-	0/3/121000	5	M	C/E	N		Y	SRNS	Other - Alport's
COL4A5	A4644_21	c.3088G>A	p.G1030S	Hemi	*Dm*	Del	DC	0.999	NR	unk	unk	unk	unk	unk	unk	De-identified	No bx
	A2058_21	c.3722G>A	p.G1241D	Hemi	*Dr*	Del	DC	1	NR	16	M	Hispanic	N	>3	N	SRNS	FSGS
	A169_21	c.3722G>A	p.G1241D	Hemi	*Dr*	Del	DC	1	NR	11 mo	M	Turkish	Y	2	N	SRNS	MPGN
	A169_22	c.3722G>A	p.G1241D	Hemi	*Dr*	Del	DC	1	NR	unkn	M	Turkish	Y		N	SRNS	Other - Cresentric GN
CTNS	B249_21	c.809_811del	p.S270del	Hom	In-frame del.	-	-	-	0/1/120874	4	F	Arabic	Y	4	N	SRNS	No bx
	B249_22	c.809_811del	p.S270del	Hom	In-frame del.	-	-	-	0/1/120874	4	F	Arabic	Y		N	SRNS	No bx
	B249_31	c.809_811del	p.S270del	Hom	In-frame del.	-	-	-	0/1/120874	unk	F	Arabic	Y		N	SRNS	No bx
FN1	A4936_21	c.6836T>C	p.V2279A	Het	*Dr*	Del	DC	0.696	NR	1	F	C/E	N	2	N	SRNS	Other - IgM nephropathy
GLA	B912_21	c.504A>C	p. K168N	Hemi	*Dr*	Del	DC	1	NR	14	M	Arabic	Y	1	Y	SRNS	Other - Fabry's disease
WDR19	B1119_21	c.3533G>A	p.R1178Q	Hom	Ce	T	DC	0.948	0/9/69008	1	M	Other/multiple races	N	2	Y	SRNS	DMS

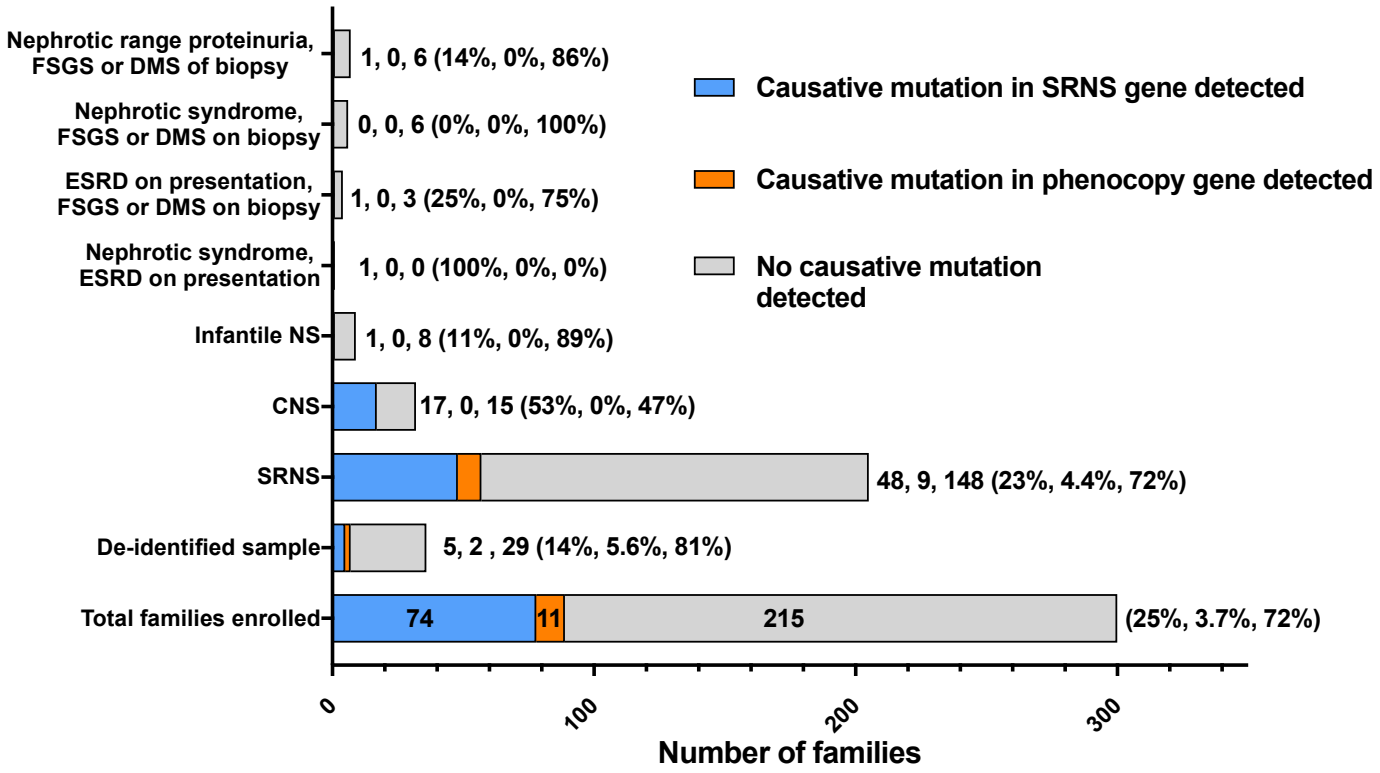
Ce, Caenorhabditis elegans; *Cs, Ciona savignyi*; DC, disease causing; Del, deleterious; *Dm, Drosophila melanogaster*; DMS, diffuse mesangial sclerosis; do, days old; *Dr, Danio rerio*; F, female; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; Hom, homozygous; Het, heterozygous; Hemi, Hemizygous; indiv., individual; M, male; *Mm, Mus musculus*; mo, months old; MPGN, membranoproliferative glomerulonephritis; MT, MutationTaster; NR, not reported; PPi, Polyphene score. *Sc, Saccharomyces cerevisiae*; SFT, SIFT; SRNS, steroid-resistant nephrotic syndrome; Tol, tolerated; *Xt, Xenopus tropicalis.* Orange shading indicates a gene that is a phenocopy for steroid-resistant nephrotic syndrome.



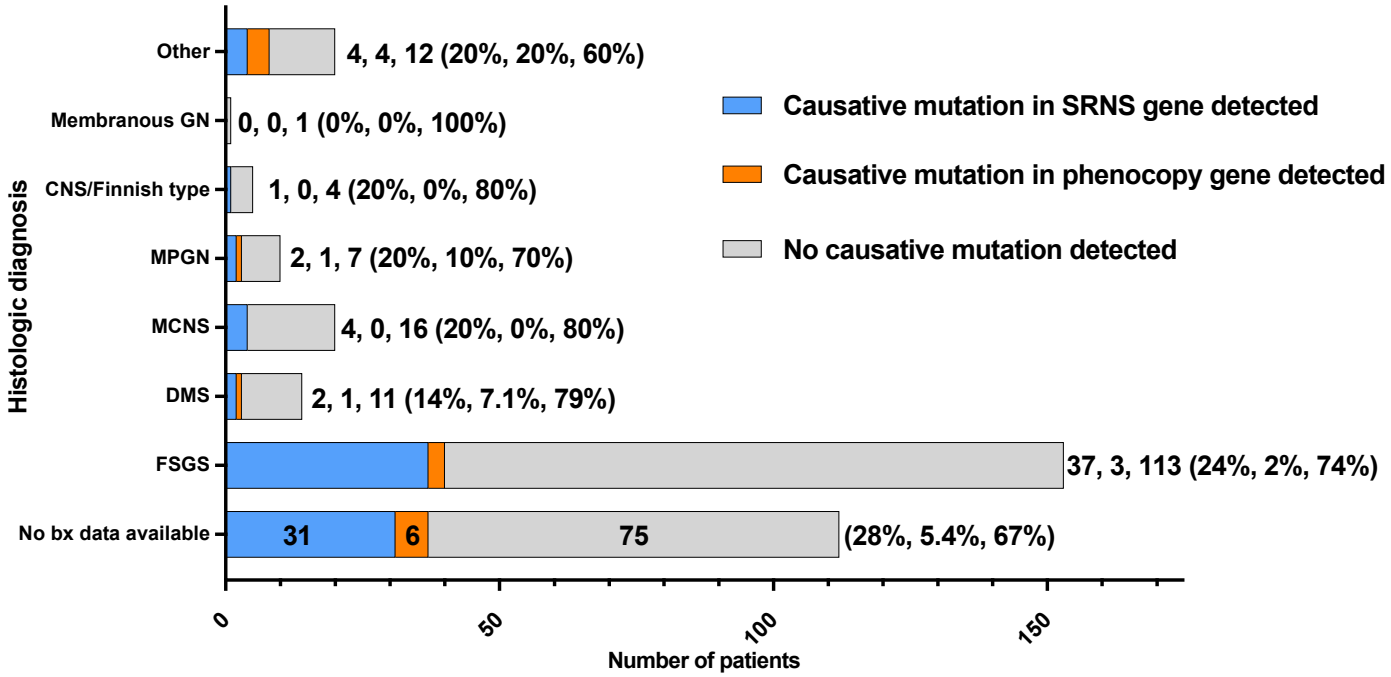
Supplementary Figure 1: Distribution of families regarding gene identification status (steroid-resistant nephrotic syndrome (SRNS) gene, phenocopy gene, no mutation detected for race or ethnicity in 335 individuals with SRNS from 300 families. Families in whom a causative mutation in a known steroid-resistant nephrotic syndrome gene (blue) or a phenocopy gene (orange) was detected as compared to those families in whom no causative mutation was detected (gray). Bars and numbers represent number of affected individuals in each race or ethnic category, divided into those with a causative mutation detected in an steroid-resistant nephrotic syndrome gene (blue), those with a causative mutation detected in a phenocopy gene (orange) and those without a causative mutation detected (gray). Percent at end of each bar reflect the same three categories. Percents >10% are rounded to the nearest whole number. Percent of each race or ethnicity per total cohort population or per total population with a mutation detected in an steroid-resistant nephrotic syndrome or phenocopy gene is shown in **Supplementary Table 6**. Families from Saudi Arabia were identified as Arabic and Asian, and a portion of families from Egypt identified as Arabic and African.



Supplementary Figure 2: Distribution of affected individuals regarding gene identification status (steroid-resistant nephrotic syndrome (SRNS) gene, phenocopy gene, or no mutation detected) for extra-renal (additional systemic) manifestations in 335 individuals with steroid-resistant nephrotic syndrome **from 300 families.** Families in whom a causative mutation in a known steroid-resistant nephrotic syndrome gene (blue) or a phenocopy gene (orange) was detected are compared with those families in whom no causative mutation was detected (gray). Bars and numbers represent number of affected individuals in each category, divided into those with a causative mutation detected in an steroid-resistant nephrotic syndrome gene (blue), those with a causative mutation detected in a phenocopy gene (orange) and those without a causative mutation detected (gray). Percent at end of each bar reflect the same three categories. Percents >10% are rounded to the nearest whole number. Percent of each category per total cohort population or per total population with a mutation detected is shown in **Supplementary Table 7**. Rate of mutation identification in an steroid-resistant nephrotic syndrome gene in patients with extra-renal manifestations was not statistically different than those who did not have syndromic features by two-sided chi squared test (p=0.8).



Supplementary Figure 3: Distribution of families regarding gene identification status (steroid-resistant nephrotic syndrome (SRNS) gene, phenocopy gene, or no mutation detected) for clinical diagnosis in 300 families with steroid-resistant nephrotic syndrome**.** Families in whom a causative mutation in a known steroid-resistant nephrotic syndrome gene (blue) or a phenocopy gene (orange) was detected are compared with those families where no causative mutation was detected (gray). Bars and numbers represent number of families in each category, divided into those families with a causative mutation detected (blue), those families with a causative mutation detected in a phenocopy gene (orange) and those families without a causative mutation detected (gray). Percent at end of each bar reflect the same three categories. Percents >10% are rounded to the nearest whole number. Percent of each category per total cohort population or per total population with a mutation detected in an steroid-resistant nephrotic syndrome gene or phenocopy gene is shown in **Supplementary Table 8**. CNS, congenital nephrotic syndrome; DMS, diffuse mesangial sclerosis: ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; NS, nephrotic syndrome.



Supplementary Figure 4: Distribution regarding gene identification status (steroid-resistant nephrotic syndrome (SRNS) gene, phenocopy gene, or no mutation detected) for histologic diagnosis in 335 affected individuals with steroid-resistant nephrotic syndrome **from 300 families.** Individuals in whom a causative mutation in a known steroid-resistant nephrotic syndrome gene (blue) or a phenocopy gene (orange) was detected are compared with those families where no causative mutation was detected (gray). Bars and numbers at end of bars represent total number of affected individuals in each race or ethnic category, divided into those with a causative mutation detected in an steroid-resistant nephrotic syndrome gene (blue), those with a causative mutation detected in a phenocopy gene (orange) and those without a causative mutation detected (gray). Percent at end of each reflect the same three categories. Percents >10% are rounded to the nearest whole number. Percent of each category per total cohort population or per total population with a mutation detected is shown in **Supplementary Table 8**. CNS, congenital nephrotic syndrome; DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis.

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