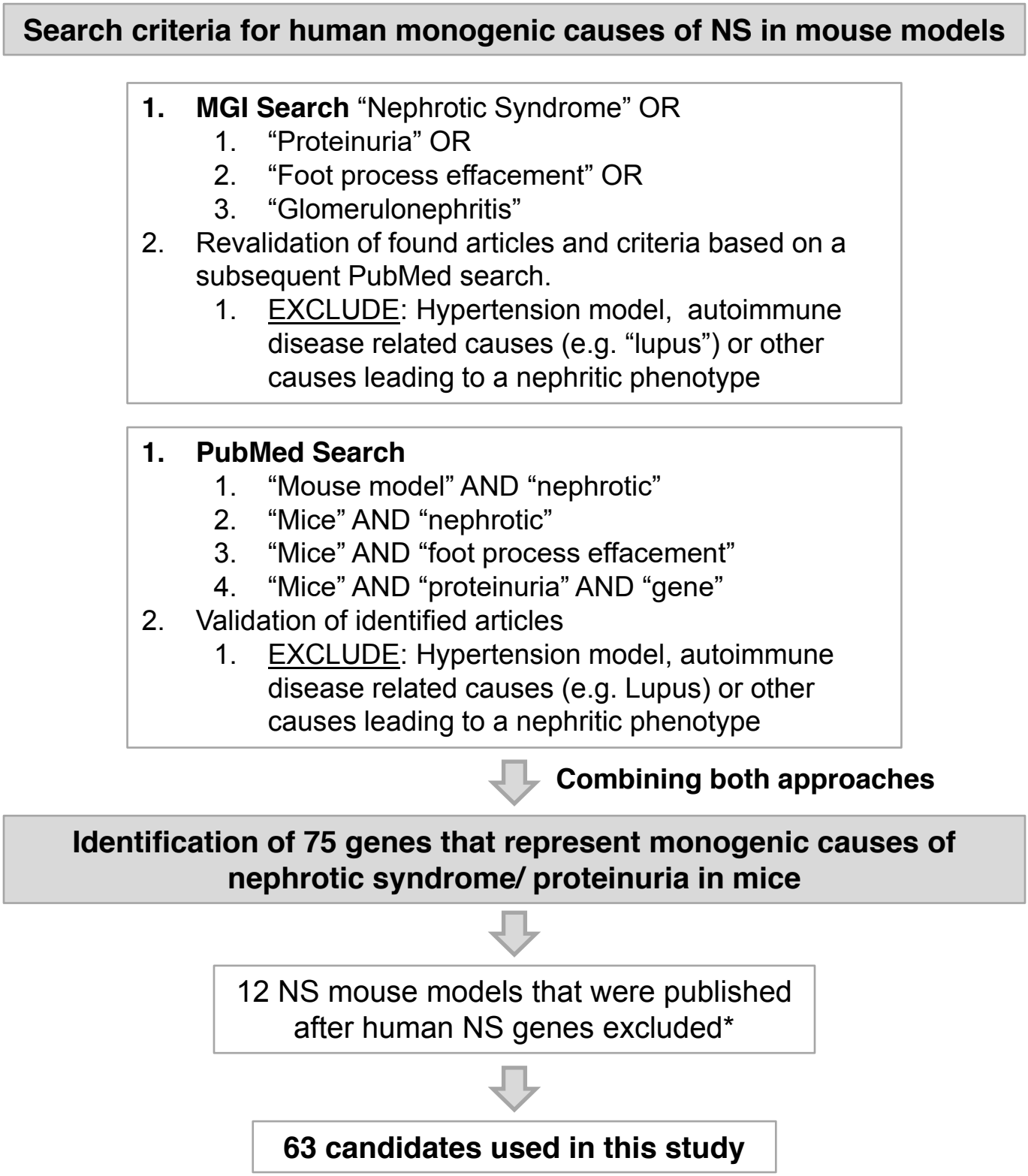
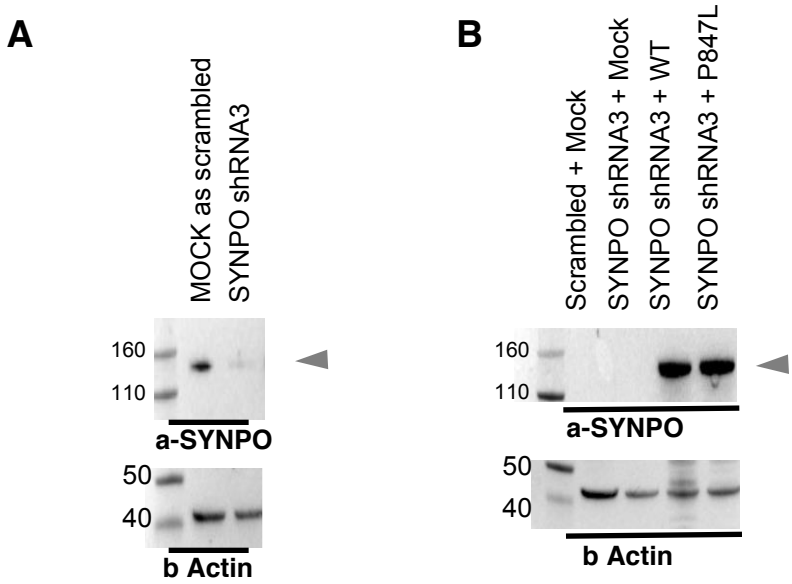


Suppl. Fig. 1. Workflow for searching for mouse candidate genes via MGI and PubMed. Two approaches were combined. A search in MGI was performed by filtering for "nephrotic syndrome", OR "proteinuria", OR "foot process effacement", OR "glomerulonephritis". Articles were read, and mouse models of hypertension, autoimmune disease related causes or nephritic syndrome were excluded. Results were combined with an additional PubMed search, in which the same exclusion criteria were used. 75 genes that represent monogenic causes of nephrotic syndrome in mice were identified. 12 out of these were excluded because the mouse phenotype was generated after the human equivalent was reported. * see **Suppl. Table 3**.

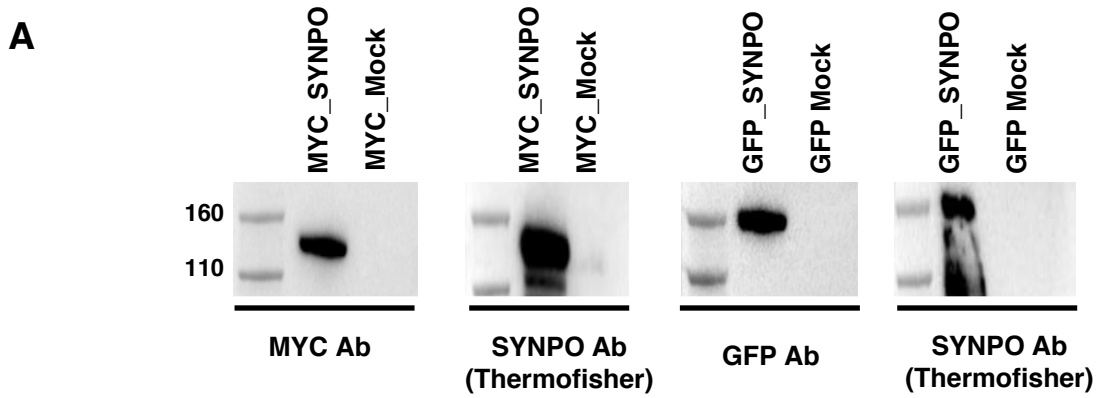


Suppl. Fig. 2 A. *SYNPO* knockdown in human podocytes.

Knockdown of *SYNPO* in podocytes was assessed by immuno blot, showing reduced protein expression in knockdown cells relative to scrambled control (grey arrow).

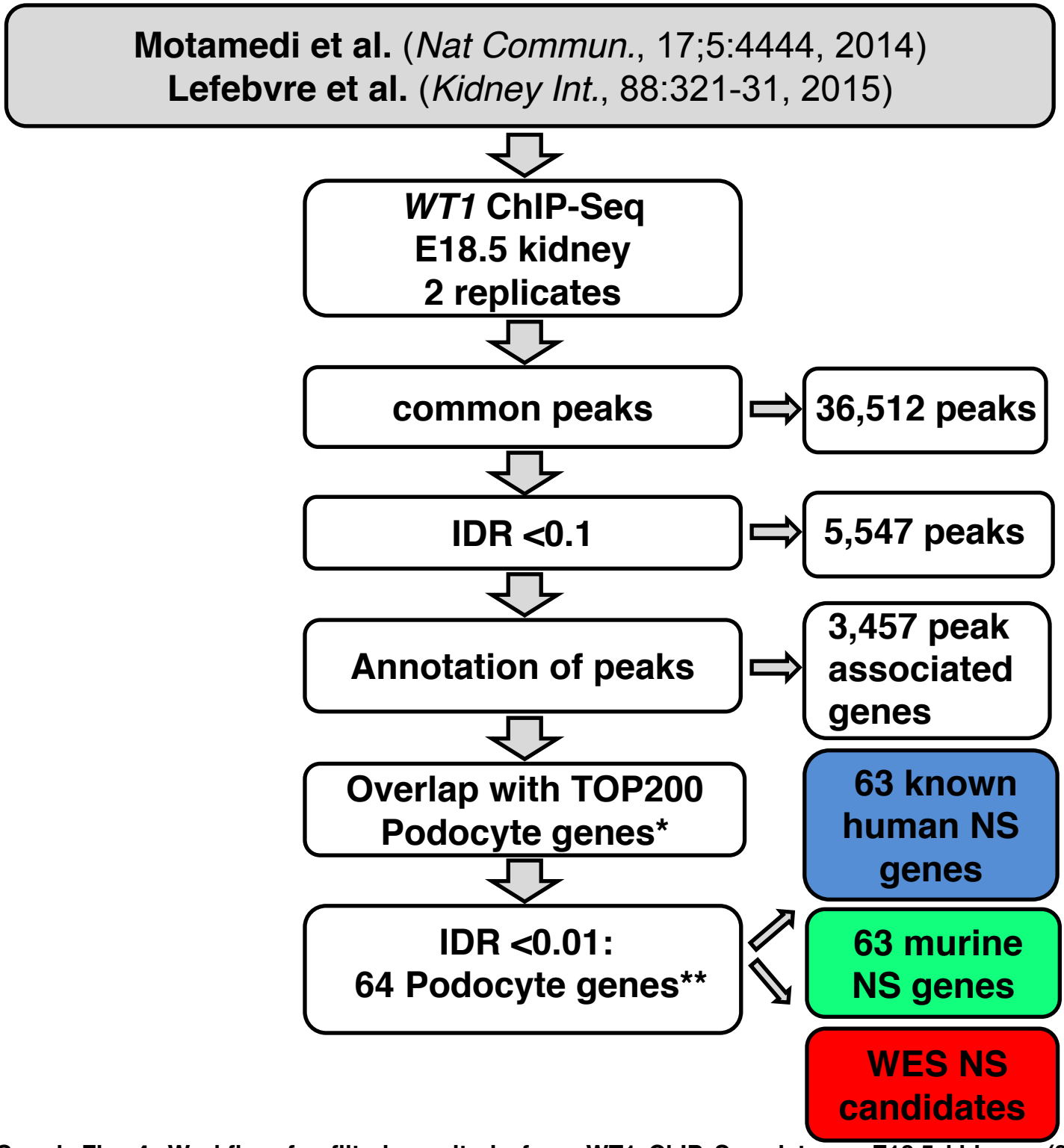
Suppl. Fig. 2 B. Immuno blot from lysates of stable scrambled shRNA negative control and *SYNPO*-shRNA3 expression in human immortalized podocytes co-transfected for rescue construct of WT vs. p.P847L *SYNPO* constructs.

Scrambled Mock and SYNPO shRNA3 + Mock confirm the strong reduction of SYNPO expression (lane 1 and 2). The mouse, wild type *Synpo* construct overexpression is shown in lane 3 to 4 (arrowhead).



Suppl. Fig. 3. SYNPO antibody and cDNA clone characterization.

Human podocytes were transfected with either MYC MOCK vs. WT MYC SYNPO cDNA or GFP MOCK vs. WT GFP SYNPO cDNA constructs. MYC, GFP or SYNPO (PA5-56997, rabbit thermo fisher) antibodies were used.



Suppl. Fig. 4. Workflow for filtering criteria from WT1 ChIP Seq data on E18.5 kidneys (2 replicates) published by Motamedi, (*Nat Commun*, 17;5:4444, 2014) and Lefebvre, (*Kidney Int*, 88:321-31, 2015).

Motamedi et al., performed in vivo WT1 ChIP-Seq analyses on E18.5 kidneys in two independent experiments. 36,512 peaks were identified. When using an IDR cutoff of ≤ 0.1 5,547 peaks were identified. After annotation of peaks, 3,457 peak associated genes were generated. Lefebvre et al., then overlapped this subset of genes, with the TOP200 podocytic genes and identified 64 podocytic potential WT1 downstream targets. MEME: multiple EM for motif elicitation; IDR, irreproducible discovery rate; *gudmap, (Brunski et al., *PloS one*, 2011;6:e24640), ** MEME analysis was performed and identified *WT1* motif.

A

WHITTLE DOWN for 63 known human monogenic NS downstream of WT1 candidates

	Nr. of Genes	Monogenic known human NS GENES	% of KNOWN GENES in cohort	Fold enrichment for known human NS gene
All genes in human genome	20,000	63	0.3	
All WT1 peak associated genes	3,457	19	0.55	1.8x
WT downstream candidate genes	64	5	7.8	14.2x 26x

B

WHITTLE DOWN for known mouse NS genes downstream of WT1 candidates

	Nr. of Genes	Monogenic known mouse NS GENES	% of KNOWN GENES in cohort	Fold enrichment for known murine NS gene
All genes in human genome	20,000	63	0.31	
All WT1 peak associated genes	3,457	32	0.925	2.2x
WT downstream candidate genes	64	10	15.6	16.8 x 50.3x

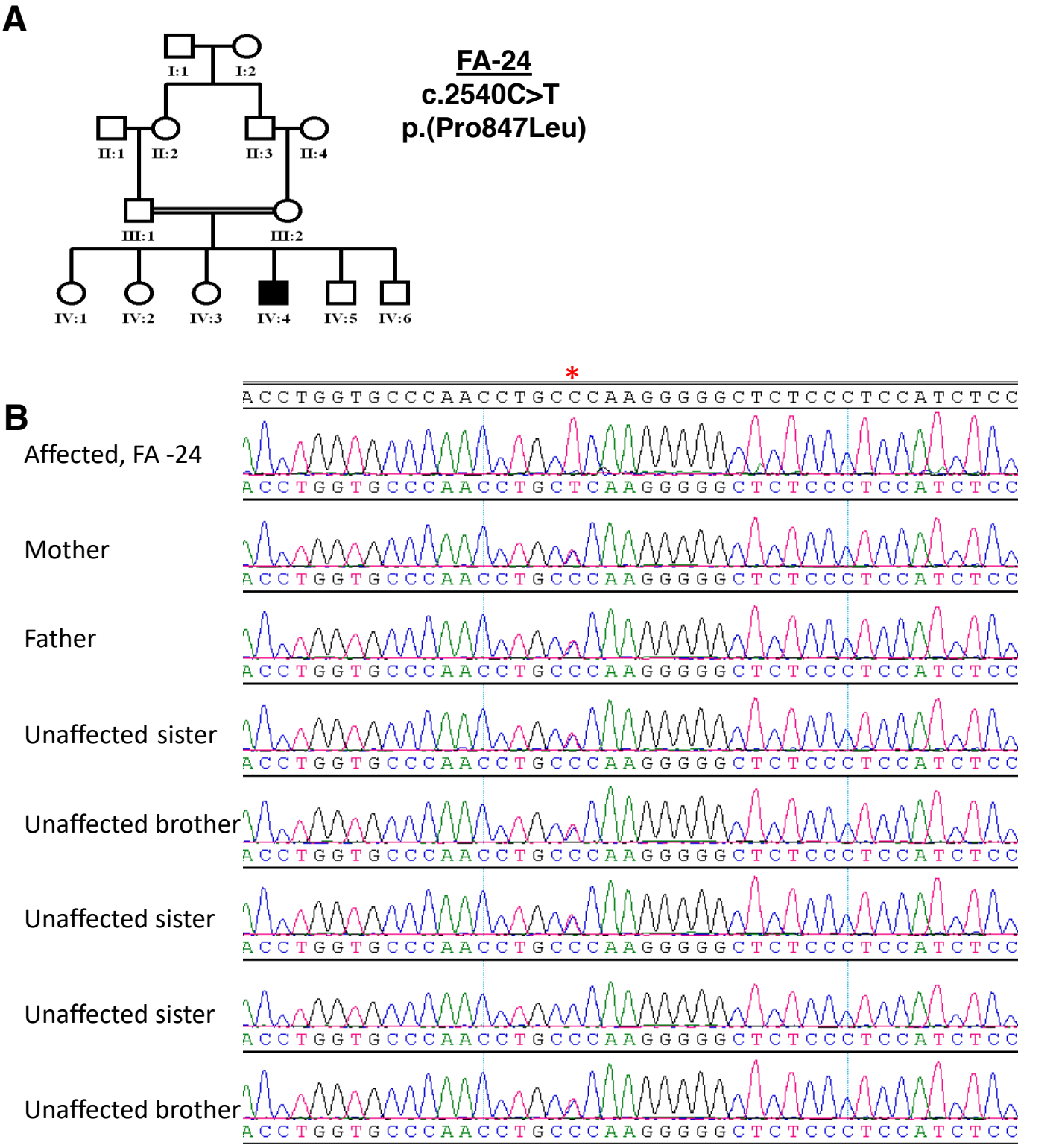
C

WHITTLE DOWN for human monogenic NS candidate genes resulting from our WES studies downstream of WT candidates

	Nr. of Genes	WES NS candidate genes	% of candidate GENES in cohort	Fold enrichment for WES candidate gene
All genes in human genome	20,000	120	0.6	
All WT1 peak associated genes	3,457	28	0.81	1.34x
WT downstream candidate genes	64	4	6.25	7.7x 10.4x

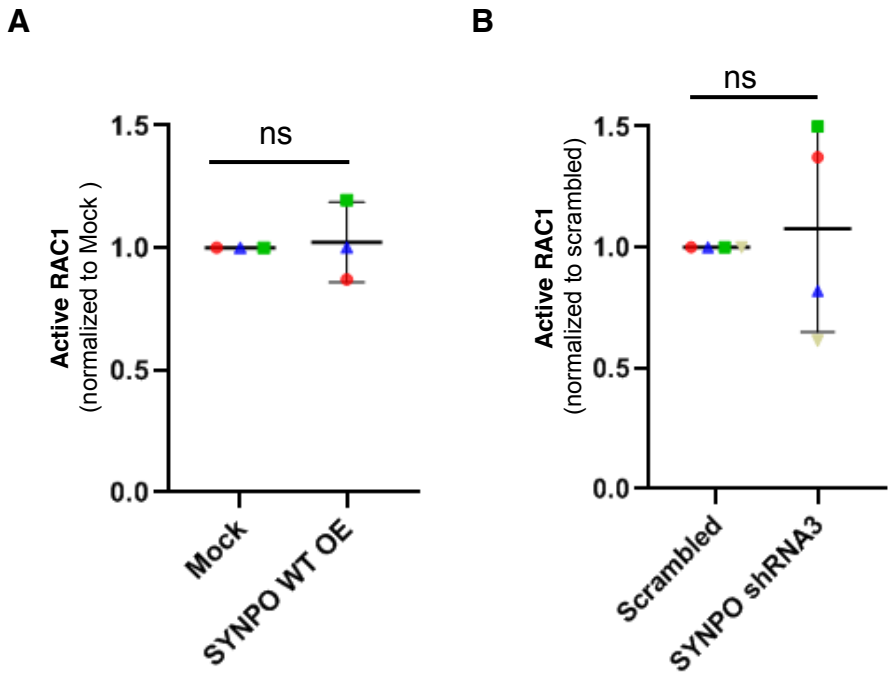
Suppl. Figure 5. Fold enrichment resulting from overlapping *WT1* downstream targets (Lefebvre, *Kidney Int*, 88:321-31, 2015) when being overlapped with human and murine NS genes as positive controls.

We compared the fold enrichment for either the **A)** human known monogenic NS genes, **B)** known monogenic mouse NS genes, **C)** human monogenic NS candidates resulting from WES within the cohort of all genes within the human genome (first row), all WT1 peak associated genes (middle row) and the 64 WT1 downstream candidates (lower row).



Suppl. Figure 6. Family pedigree and Sanger sequencing traces of *SYNPO* mutation.

A) Family pedigree structures is shown. **B)** Sanger sequencing traces of parents and sibling of FA-24 are indicated. Note that only the affected individual FA -21 has a homozygous mutation, while the patients parents and siblings are either unaffected heterozygous carrier or wild type for the mutation. *marks the mutation.



Suppl. Fig. 7 A-B. G-LISA for active RAC1 in human podocyte cell lines overexpression *SYNPO* cDNA constructs or in stable scrambled shRNA negative control vs. *SYNPO*-shRNA3 podocytes.

There is no significant difference of active RAC1 level in Mock vs. SYNPO WT expressing cells (**A**), or in scrambled vs. *SYNPO* knockdown cells (**B**).

Supplemental Table 1: List of 63 genes that lead to proteinuria/ nephrotic syndrome in mice in case of a global knockout. Genes that are underlined have a published human nephrotic syndrome phenotype.

Gene Symbol	PMID #	Protein-uria	FSGS	FPE	In-duction*	Human Disease (OMIN)	Ref
ADIPOQ	18431508	y	n	y	n	-	[1]
AKT2	24056770	y	y	y	n	Hypoinsulinemic, hypoglycemia with Hemihypertrophy (AD, 240900)	[2]
AMPD2	22212473	y	n	y	n	Pontocerebellar Hypoplasia, type 9 (AR, 615809)	[3]
ARHGDIA	10498891	y	y	y	n	NS (615244)	[4]
CCN1	16847066	y	y	y	y	-	[5]
CCR1	10587518	y	y	y	y	-	[6]
CD151	18787104	y	y	y	n	-	[7]
CD2AP	17713465	y	y	n	n	NS (607832)	[8]
CD38	21992601	y	y	y	n	-	[9]
CD55	12003997	y	n	y	y	Complement hyperactivation (AR, 226300)	[10]
CHD2	19142019	y	n	n	n	Epileptic encephalopathy (AD, 615369)	[11]
CLIC5	20664558	y	n	y	n	Deafness (AR, 616042)	[12]
COL17A1	22457199	y	n	y	n	Epidermolysis bullosa (AR, AD 226650/122400)	[13]
COL18A1	21193414	y	n	y	n	Knobloch syndrome (AR, 267750)	[14]
CRIM1	17460146	y	DMS	y	n	-	[15]
DDR1	15200417	y	n	y	n	-	[16]
EBF1	24172684	y	y	y	n	-	[17]
EDN1	9077548	y	y	n	n	Auricullocondylar syndrome (AR, 615706)	[18]
GNE	17549255	y	y	y	n	Nonaka myopathy (AR, 605820)	[19]
GOLM1	18830387	n/a	y	n	n	-	[20]
GRM1	21356376	y	y	y	n	Spinocerebellar ataxia (AR, AD,	[21]

						614831,617691)	
GSTK1	21826057	y	n	y	n	-	[22]
ITGA1	15277235	y	y	y	y	-	[23]
ITGA3	8951069	y	n	y	n	NS, Epidermolysis bullosa, interstitial lung disease (AR, 614748)	[24]
ITGB8	20826576	y	y	y	y	-	[25]
ITSN2	29773874	y	n	y	y	NS (AR, -)	[26]
KIRREL	11416156	y	n	y	n	NS (AR, -)	[27]
KL	27151926	y	n	n	n	-	[28]
KMO	27020856	y	n	y	n	-	[29]
LAMA5	20150535	y	y	y	n	NS (AR, -)	[30]
LAMB2	7670489	y	n	y	n	NS, Pierson syndrome (AR 609049)	[31]
LGALS3	11689472	y	y	n	y	-	[32]
LGMN	21292981	y	n	n	n	-	[33]
MAFB	16847325	n/a	n	y	n	Duane retraction syndrome (AD, 617041), multicentric carpotarsal osteolysis syndrome (AD, 166300)	[34]
MAGI2	25271328	y	y	y	n	NS (AR, 617609)	[35]
MAPKAPK2	29187369	y	y	n	y	-	[36]
MAPKAPK3	29187369	y	y	n	y	Macular dystrophy,(AD, 617111)	[36]
MPV17	10233845 ,1696177	y	y	y	n	CMT (AR 618400), Mitochondrial DNA depletion syndrome 6 (AR, 256810)	[37, 38]
MYO1E	19005011	y	y	y	n	NS (AR, 614131)	[39]
NOS1AP	unpublished	y	n	y	n	-	Majmundar, personal communication
PDGFB	12897053	y	y	n	n	Basal ganglia calcification (AD, 615493)	[40]
PIK3C2A	20974805	y	y	y	n	Oculoskeleto-dental syndrome (AR, 603601)	[41]

PNPLA2	28194887	y	n	y	n	Neutral lipid storage disease with myopathy (AR, 610717)	[42]
PODXL	11435469	n	y	y	n	-	[43]
PTGS2	8521477	n/a	y	y	n	-	[44]
PTPRO	11086029	n	y	y	n	NS (AR, 614196)	[45]
RHPN1	25071083	y	y	y	n	-	[46]
RRM2B	15723268	y	y	y	n	Mitochondrial DNA depletion syndrome (AR, 612075)	[47]
SCARB2	12620969	y	n	n	n	Epilepsy (AR, 254900)	[48]
SCGB1A1	9162006	y	y	n	n	-	[49]
SEMA3A	19906865	y	y	y	n	Hypogonadotropic hypogonadism (AD, 614897)	[50]
SEMA3G	27180624	y	n	y	y	-	[51]
SGK3	28935820	y	n	y	n	-	[52]
SH3GL1	23187129	y	n	y	n	Leukemia (AD, 601626)	[53]
SH3GL2	23187129	y	n	y	n	-	[53]
SH3GL3	23187129	y	n	y	n	-	[53]
SHROOM3	26940091	y	y	y	n	-	[54]
SYNJ1	23187129	y	n	y	n	Epileptic encephalopathy (AR, 617389), Parkinson (AR, 615530)	[53]
SYNPO	15841212	y	n	y	y	-	[55]
TAL1	1836514	n/a	y	y	n	Leukemia (613065)	[56]
TENC1/ TNS2	16688531	y	n	n	n	-	[57]
TK1	12559842	n/a	y	n	n	-	[58]
TNS1	9087448	n/a	y	n	n	-	[59]

FPE, foot process effacement; FSGS, focal segmental glomerulosclerosis; n, no; Ref, reference; y, yes. *Induction with substances as LPS or Adriamycin.

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Suppl. Table 2: Overview of 12 human nephrotic syndrome or phenocopy genes that had a nephrotic mouse with a global knockout published before the human equivalent was reported.

Human gene name (mouse gene name)	Transcript	Paper published for human phenotype	Paper published for mouse phenotype
ARHGDIA (Arhgdia)	NM_004309.6	[1, 2]	[3]
CD2AP (Cd2ap)	NM_012120.3	[4, 5]	[6]
ITGA3 (Itga3)	NM_002204.4	[7]	[8]
ITSN2 (Itsn2)	NM_006277.2	[9]	[9]
KIRREL1 (Kirrel)	NM_018240.7	[10]	[11]
LAMA5 (Lama5)	NM_005560.6	[12]	[13]
LAMB2 (Lamb2)	NM_002292.4	[14]	[15]
MAGI2 (Magi2)	NM_012301.4	[16]	[17]
MYO1E (Myo1e)	NM_004998.4	[18]	[19]
PTPRO (Ptpro)	NM_030667.3	[20]	[21]
SCARB2 (Scarb2)	NM_005506.4	[22]	[23]
TNS2 (Tns2)	NM_015319.2	[9]	[24]

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Suppl. Table 3: Overview of 12 global knockout mice that were excluded in this study as the equivalent human NS phenotype was published before the mouse model was reported.

Human gene name (mouse gene name)	Transcript	Paper published for human phenotype	Paper published for mouse phenotype
ADCK4 (Coq8b)	NM_024876.4	[1]	[2]
COL4A3 (Col4a3)	NM_000091.5	[3]	[4, 5]
COL4A4 (Col4a4)	NM_000092.5	[3]	[6]
COL4A5 (Col4a5)	NM_033380.1	[7]	[8]
CUBN (Cubn)	NM_001081.4	[9]	[10]
INF2 (Inf2)	NM_022489.4	[11]	[12]
LMX1B (Lmx1b)	NM_002316	[13]	[14]
NPHS1 (Nphs1)	NM_004646	[15]	[16]
NPHS2 (Nphs2)	NM_014625.4	[17]	[18, 19]
PDSS2 (Pdss2)	NM_020381.4	[20]	[21, 22]
SMARCAL1 (Smarcal1)	NM_014140.4	[23]	[24]
WT1 (Wt1)	NM_024426.5	[25]	[26 27]

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Suppl. Table 4. Recessive *SYNPO* mutation in 1 family (FA) with nephrotic syndrome.

Family	Nucleotide change	Amino acid change	Exon (Zyg)	PP2	SIFT	MT	Conser-vation	GnomAD (hom/het/ total)	Sex	Ethnic origin	PC	Age of on set	NS type (treatment)	Biopsy	Extra-renal
FA	c.2540C>T	p.P847L	5b (Hom)	0.998	Del	DC	*D. rerio*	0/0/ 250,754	M	Saudi	Y	4 yr	SDNS	ND	*LAMA2* Muscular dystrophy

Abbreviations: DC, disease causing; Del, deleterious; M, male; GnomAD, Genome Aggregation database (https://gnomad.broadinstitute.org/); Hom, homozygous; MT, mutation taster; ND, not done; PC, parental consanguinity; PP2, PolyPhen-2 prediction score; SIFT, “Sorting Tolerant from Intolerant” prediction score; yr, years; Zyg, zygosity.

Suppl. Table 5: Summary of families with 7 candidate genes

Gene symbol	Nr of families identified by unbiased WES	Renal Manifestation	Extrarenal Manifestation
SYNPO	1	SDNS	-
*DAAM2**	4	SRNS	1 patient: adrenal insufficiency
PIK3C2A	2	SRNS, CNS	-
*SEMA3G***	3	Proteinuria, SSNS	-
SEMA3A	1	SSNS	-
*NOS1AP****	2	SRNS	-
ITGB8	1	NS	-

Nr, Number; SDNS, steroid dependent nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome, WES, whole exome sequencing

* Schneider, submitted, July 2020, *AJHG*

** extensive functional work ongoing

*** Majmundar, submitted, July 2020, *Science Advances*