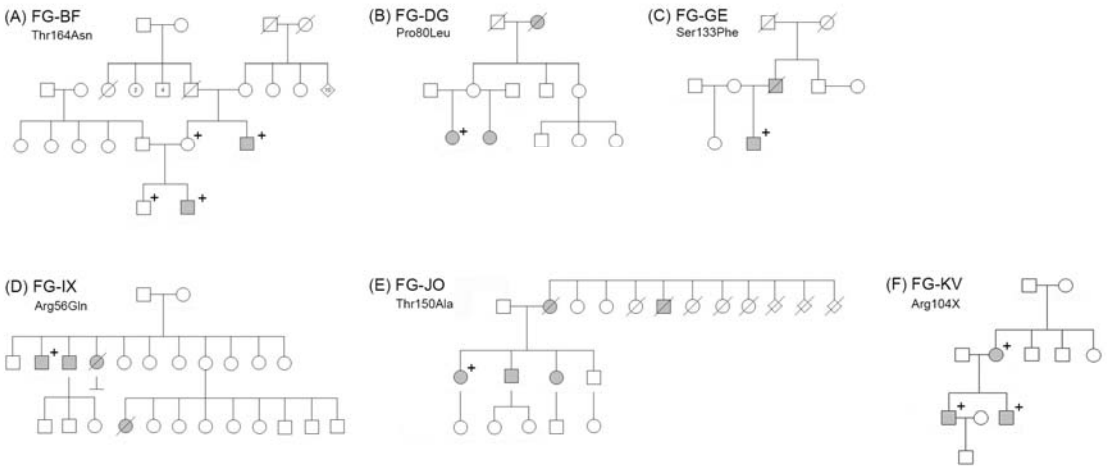
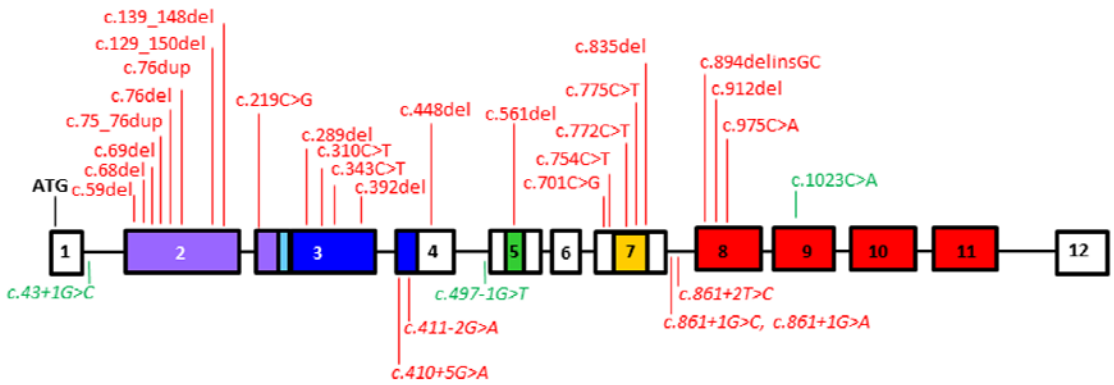
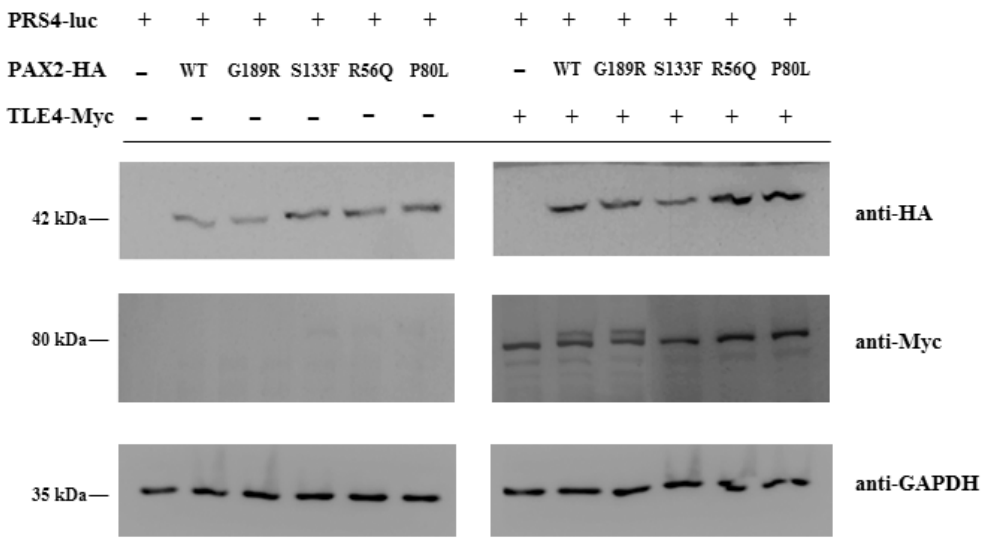


Supplementary Figure 1. Pedigrees of FSGS families with *PAX2* mutations. Affected individuals are indicated in gray. Individuals heterozygous for the *PAX2* mutation are denoted by "+" while individuals without the mutation are denoted by "-'. Individuals where no DNA was available have no notation. Numbers indicate number of individuals of that gender. Diamond represent individuals of unknown gender. Clinical re-evaluation of the affected members of family FG-KV heterozygous for the nonsense mutation revealed a more severe phenotype, compatible with undiagnosed PRS in one of the affected children. This same mutation, p.Arg104X, was previously described in PRS.



Supplementary Figure 2. Truncating PAX2 mutations reported in the *PAX2* variants database.



Supplementary Figure 3. Expression analysis of wild-type PAX2 and FSGS-associated mutants.

Gene	Chromosome	Position	Reference base	Nucleotide change	Amino Acid Change	Coverage
MACF1	1	39838241	ACAG	A	p.Ala2334del	22/40
FAM123C	2	131520076	A	G	p.Lys144Arg	5/8
FYCO1	3	46008554	G	A	p.Pro758Ser	4/9
MINA	3	97668751	CCTT	C	p.Lys331-	11/33
WWTR1	3	149374727	C	T	p.Glu123Lys	1/6
TNFSF10	3	172224420	T	G	p.Glu236Asp	19/57
IL1RAP	3	190321970	G	C	p.Asp40His	12/38
TMEM175	4	947002	C	T	p.His150Tyr	9/20
METTL14	4	119625153	A	G	p.Asn230Asp	17/29
NDUFS4	5	52942235	C	T	p.Thr113Met	13/34
MDN1	6	90428894	C	T	p.Met2006Ile	14/54
PDE1C	7	31867930	T	G	p.Thr421Pro	15/41
AASS	7	121721588	G	A	p.Pro749Leu	8/22
C8orf44	8	67590022	CG	C	-	13/23
PABPC1	8	101724941	C	T	p.Arg227Gln	12/24
C9orf93	9	15623341	T	C	p.Leu251Pro	21/52
KCNT1	9	138662242	G	A	p.Arg528His	7/19
PLAU	10	75673375	T	C	p.Ile144Thr	4/17
PAX2	10	102541071	G	A	p.Gly189Arg	12/19
VWCE	11	61032639	T	C	p.Thr136Ala	2/9
CAPRIN2	12	30872016	C	A	p.Gln431His	4/40
RBM19	12	114261045	T	G	p.Gln956Pro	7/10
TXNDC11	16	11781806	T	C	p.Tyr687Cys	0/10
ZNF585B	19	37676572	C	A	p.Val211Leu	0/8
BCOR	X	39923603	C	T	p.Arg1145Gln	9/10

Supplementary Table 1. List of variants after analysis of exome data from individuals FG-EQ III(8) and IV(8). Of the 25 variants found, 22 are nonsynonymous substitutions while 3 and indels. Chromosome coordinates are given by Hg19 reference. Coverage lists data for FG-EQ III(8)/FG-EQ IV(8).

Gene symbol	Overall score	Interaction	GO	HPO	MGD phenotypes	Expression correlation	Pfam	Interpro	Pathways
PAX2	12780	12739	14	4	16	7			
MACF1	49		7		10	8	6	18	
NDUFS4	43		2	4	22	10			5
PLAU	40		6	2	28	4			
BCOR	30		6		8	10	2	4	
WWTR1	29		9		16	4			
TNFSF10	23		8		12	3			
RBM19	19		7		6	6			
PABPC1	15		8			7			
FYCO1	14		4			10			
ZNF585B	13		5				2	6	
MINA	13		3			10			
IL1RAP	13		6		2	1		4	
AASS	12		2	3		2			5
MDN1	10		4			6			
PDE1C	10		5			0			5
CAPRIN2	8		5			3			
TXNDC11	3		3						
KCNT1	3		3						
VWCE	2		2						
TMEM175	2		2						
C8orf44	2					2			
METTL14	1		1						
C9orf93	0								
FAM123C	0								

Supplementary Table 2. Functional annotation of 25 candidate genes from several **data sources including Gene** Ontology (GO), Human Phenotype Ontology (HPO), Mouse Genome Database (MGD), Pfam, and Interpro. The Pfam database provides alignments and hidden Markov models for protein domains. Interpro is a database of protein families, domains and functional sites.

Gene	Protein function (from NCBI GENE, UniProtKB and specific references, where indicated)
MACF1	**Microtubule-actin crosslinking factor.** Cytoskeletal linker protein
FAM123C	**Family with sequence similarity 123C**. Also called AMER3 (APC membrane recruitment 3). Strongly expressed in the central as well as the peripheral nervous system, thus suggesting important roles of this gene during neurogenesis (Devel. Dyn., 2010, 239, 1867–1878; BMC Evolutionary Biology 2010, 10:280)
FYCO1	**FYVE and coiled-coil domain containing 1**. Plays a role in microtubule plus end-directed transport of autophagic vesicles
MINA	**MYC induced nuclear antigen.** Involved in cellular proliferation. May play an important role in cell growth and survival.
WWTR1	**WW domain-containing transcription regulator protein 1.** Highly expressed in kidney.
TNFSF10	**Tumor necrosis factor (ligand) superfamily, member 10.** Cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This protein preferentially induces apoptosis in transformed and tumor cells, but does not appear to kill normal cells although it is expressed at a significant level in most normal tissues.
IL1RAP	**Interleukin 1 receptor accessory protein**. Interleukin 1 induces synthesis of acute phase and proinflammatory proteins during infection, tissue damage, or stress, by forming a complex at the cell membrane with an interleukin 1 receptor and this accessory protein.
TMEM175	**Transmembrane protein 175**. Uncharacterized function.
METTL14	**Methyltransferase-like protein 14**. mRNA (2'-O-methyladenosine-N6-)-methyltransferase activity
NDUFS4	**NADH dehydrogenase (ubiquinone) Fe-S protein 4, 18kDa.** Accessory subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase (Complex I), or NADH:ubiquinone oxidoreductase, the first multi-subunit enzyme complex of the mitochondrial respiratory chain
MDN1	**MDN1, midasin homolog.** Nuclear chaperone required for maturation and nuclear export of pre-60S ribosome subunits (by similarity)
PDE1C	**Phosphodiesterase 1C, calmodulin-dependent 70kDa.** Cyclic nucleotide phosphodiesterases (PDEs) catalyze hydrolysis of the cyclic nucleotides cAMP and cGMP to the corresponding nucleoside 5-prime-monophosphates.
AASS	**Aminoadipate-semialdehyde synthase.** A bifunctional enzyme that catalyzes the first two steps in the mammalian

	lysine degradation pathway. The N-terminal and the C-terminal portions of this enzyme contain lysine-ketoglutarate reductase and saccharopine dehydrogenase activity, respectively, resulting in the conversion of lysine to alpha-aminoadipic semialdehyde.
C8orf44	**Chromosome 8 open reading frame 44.** Uncharacterized protein
PABPC1	**Poly(A) binding protein, cytoplasmic 1.** This protein shuttles between the nucleus and cytoplasm and binds to the 3' poly(A) tail of eukaryotic messenger RNAs via RNA-recognition motifs
C9orf93	**Chromosome 9 open reading frame 9.** Uncharacterized protein
KCNT1	**Potassium channel subfamily T member 1.** Outwardly rectifying potassium channel subunit Activated by high intracellular sodium or chloride levels and upon stimulation of G-protein coupled receptors,
PLAU	**Plasminogen activator, urokinase.** Serine protease involved in degradation of the extracellular matrix and possibly tumor cell migration and proliferation.
PAX2	**Paired box 2.** Transcription factor with a critical role in the development of the urogenital tract, the eyes, and the CNS.
VWCE	**von Willebrand factor C and EGF domains.** May be a regulatory element in the beta-catenin signaling pathway and a target for chemoprevention of hepatocellular carcinoma
CAPRIN2	**Caprin family member 2.** May regulate the transport and translation of mRNAs, modulating for instance the expression of proteins involved in synaptic plasticity in neurons. Involved in regulation of growth as erythroblasts shift from a highly proliferative state towards their terminal phase of differentiation. May be involved in apoptosis.
RBM19	**RNA binding motif protein 19.** Nucleolar protein that contains six RNA-binding motifs. May be involved in regulating ribosome biogenesis. Plays a role in embryo pre-implantation development (by similarity).
TXNDC11	**Thioredoxin domain containing 11.** May act as a redox regulator involved in DUOX proteins folding. The interaction with DUOX1 and DUOX2 suggest that it belongs to a multiprotein complex constituting the thyroid H_2O_2 generating system.
ZNF585B	**Zinc finger protein 585B.** May be involved in transcriptional regulation.
BCOR	**BCL6 corepressor.** Transcriptional corepressor. May specifically inhibit gene expression when recruited to promoter regions by sequence specific DNA-binding proteins such as BCL6 and MLLT3.

Supplementary Table 3. List of variants after analysis of exome data from individuals FG-EQ III(8) and IV(8). Chromosome coordinates are given using Hg19 reference.

	Number of alleles with rare coding NS variants	Number of alleles without rare coding NS variants	p-value
FSGS families	9	345	<0.0001
CAKUT	8	162	<0.0001
ESP (control)	57	12949	-

Supplementary Table 4. Burden of coding nonsynonymous and synonymous variants in FSGS and CAKUT groups compared to a control group. There is an enrichment of variants between the patient and control group, which is statistically significant when looking at the familial FSGS and CAKUT cohort. The abbreviations NS and ESP stand for non-synonymous and NHLBI Exome sequencing project, respectively.