Review article

Child Kidney Dis 2019;23:86-92
DOI: https://doi.org/10.3339/jkspn.2019.23.2.86

ISSN 2384-0242 (print)
ISSN 2384-0250 (online)

Genetic Basis of Steroid Resistant Nephrotic Syndrome

Eujin Park, M.D

Department of Pediatrics, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea

Corresponding author: Eujin Park, M.D
1, Singil-ro, Yeongdeungpo-gu, Seoul, 07441, Republic of Korea
Tel: +82-2-829-1314
Fax: +82-2-871-4912
E-mail: eujinpark@hallym.or.kr

Received: 8 September 2019
Revised: 18 September 2019
Accepted: 24 September 2019

Steroid-resistant nephrotic syndrome (SRNS) has long been a challenge for clinicians due to its poor responsiveness to immunosuppressants, and rapid progression to end-stage renal disease. Identifying a monogenic cause for SRNS may lead to a better understanding of podocyte structure and function in the glomerular filtration barrier. This review focuses on genes associated with slit diaphragm, actin cytoskeleton, transcription factors, nucleus, glomerular basement membrane, mitochondria, and other proteins that affect podocyte biology.

Key words: Nephrotic syndrome, Proteinuria, Podocyte, Gene

Introduction

Nephrotic syndrome (NS) in children refers to a glomerular filtration barrier (GFB) failure disease. NS manifests itself with severe proteinuria, and later on leads to hypoalbuminemia, hypercholesterolemia, and generalized edema[1]. NS has long been considered an immunological derangement since most patients respond well to immune suppression and some patients recur even after renal transplantation. However, the non-responsiveness of 15–20% of NS patients to conventional immunosuppressants remained unexplained[2].

Steroid-resistant nephrotic syndrome (SRNS) is defined as failure to achieve remission after eight weeks of daily corticosteroid therapy. SRNS is the second most frequent cause of end-stage renal disease (ESRD) in childhood, and mostly associated with focal segmental glomerulosclerosis (FSGS)[3]. SRNS is a genetically heterogeneous disease with over 70 SRNS- and/or FSGS-causing genes[3,4]. A single causative genetic mutation in 20-30% of SRNS cohort patients was identified in recent studies[5-7]. Identification of a genetic cause of SRNS implied podocyte as a central player in proteinuria pathogenesis, and advanced our understanding of the podocyte pathobiology.

Podocytes are a major GFB component, and are considered to be highly specialized and terminally-differentiated with limited regenerative capacity. Podocyte injury leads to foot process effacement, and is associated with urinary protein leakage, renal function deterioration, and progression to ESRD[8]. Protein-coding genes that affect podocyte structural stability and function can be categorized as, (1) slit diaphragm (SD)-associated, (2) actin cytoskeleton and membrane protein-encoding, (3) transcription factor and nuclear protein-encoding, (4) glomerular basement membrane (GBM), (5) mitochondrial, and (6) lysosomal, metabolic, and cytosolic protein-encoding genes

(Table 1).

Herein, several SRNS-associated genes are reviewed with respect to their roles in podocyte pathobiology.

Slit diaphragm-associated genes

The SD is a unique intercellular junction that connects neighboring podocyte foot processes, regulates filtration selectivity and mediates a variety of signaling pathways related to the plasticity of foot processes[9]. The genetic basis of SRNS was first established by findings on SD proteins nephrin and podocin, which are encoded by *NPHS1* and *NPHS2*, respectively.

Nephrin is a large transmembrane protein within the zipper-like SD structure. Podocin is an integral membrane protein, and acts as a binder between nephrin and podocyte actin cytoskeleton. Mutations in genes encoding these proteins were found to be associated with autosomal recessive (AR) nephrotic syndrome presenting early in life[10,11]. At least 250 and 170 mutations in *NPHS1* and *NPHS2* were found to cause early-onset nephrotic syndrome, respectively. Phospholipase C epsilon 1 (encoded by *PLCE1*) is expressed in the developing kidney, and affects cell adhesion by interacting with podocyte cell junction proteins. Mutations in *PLCE1* were found to cause early-onset SRNS via AR inheritance[12]. Transient receptor potential channel 6 (encoded by *TRPC6*) binds to podocin, and regulates the calcium influx into the podocytes. *TRPC6* mutations were found to cause dysregulation of the actin cytoskeleton, and result in podocyte injury, with an autosomal dominant (AD) inheritance and usually onset later in childhood[13]. CD2AP is an adaptor protein linking nephrin and podocin to the podocyte actin cytoskeleton. The CD2AP protein is involved in actin remodeling via synaptopodin binding. Mutations in the gene encoding CD2AP were found to cause AD and AR nephrotic syndrome[14].

Actin cytoskeleton and membrane protein-encoding genes

After the breakthrough discovery of SD genes, additional genes related to proteins of foot process actin cytoskeleton were revealed. Podocyte foot process is a highly dynamic architecture including parallel actin filament bundles, connecting adjacent foot processes to each other, and forming the SD. Mutations in podocyte cytoskeleton-associated genes were found to alter podocyte actin dynamics, and cause changes in podocyte morphology and function[12].

α-actinin 4 (encoded by *ATCN4*) is an F-actin-binding protein that regulates the binding affinity of actin and adhesion to the GBM. *ATCN4* mutations were found to be associated with AD late-onset SRNS[16]. Non-muscle myosin heavy chain 9 (encoded by *MYH9*) is a myosin IIA subunit that is involved in actin cytoskeleton translocation in the podocytes. *MYH9* mutations were found to cause the syndromic form of SRNS called *MYH9*-related disease, with symptoms of AD FSGS, macrothrombocytopenia, and sensorineural deafness[17]. Inverted formin-2 (encoded by *INF2*) also regulates actin-binding to the podocytes. *INF2* mutations were found to be associated with adolescent-onset AD FSGS and Charcot-Marie-Tooth disease[18].

Rho GTPase (also known as RHoA, Rac, or Cdc42) maintains the integrity of podocyte structure by regulating the actin bundle and actin network formation. Mutations in *ARHGAP24* (encoding Rho GTPase activating protein 24) were demonstrated to increase the Rho GTPase activity in podocytes, thereby leading to AD-FSGS[19]. *ARHGDIA* and *KANK1/KANK2/KANK4* mutations were also found to increase Rho GTPase activity in podocytes, and were associated with AR-FSGS[20,21].

Transcription factor and nuclear protein-encoding genes

Wilms' tumor protein 1 (encoded by *WT1*) is a transcription factor with a critical role in renal development and podocyte stabilization. *WT1* gene mutations encompass a wide range of sequence variations, and exhibit a variety of phenotypes from isolated proteinuria to Fraiser- and Denys-Drash syndromes[22,23]. Along with *NPHS1, NPHS2*, and *LAMB2, WT1* is one of the most common genes found in congenital and infantile nephrotic syndrome[24]. Paired box protein 2 (encoded by *PAX2*) is also an important transcription factor during nephrogenesis. *PAX2* variants were detected within a wide phenotypic spectrum, from con-

Table1. Genes Associated with Steroid-resistant Nephrotic Syndrome

Gene	Protein	Mode of inheritance	Reference
Slit diaphragm-associated genes			
NPHS1	Nephrin	AR	(10)
NPHS2	Podocin	AR	(11)
PLCE1	Phospholipase C epsilon 1	AR	(12)
TRPC6	Transient receptor potential channel C6	AD	(13)
CD2AP	CD2-associated protein	AD, AR	(14)
CRB2	Crumbs family member2	AR	(41)
FAT1	FAT atypical cadherin 1	AR	(42)
KIRREL1	Kin of IRRE-like protein 1	AR	(43)
Actin cytoskeleton and membrane encoding genes			
ACTN4	α-actinin 4	AD	(16)
MYH9	Myosin heavy chain 9, non-muscle	AD	(17)
INF2	Inverted formin 2	AD	(18)
MYO1E	Myosin 1E	AR	(44)
MAGI2	Membrane Associated Guanylate Kinase, inverted 2	AR	(45)
ANLN	Anillin actin binding protein	AD	(46)
ARHGA24	Rho GTPase-activating protein 24	AD	(19)
ARHGDIA	Rho GDP dissociation inhibitor α	AR	(20)
KANK 1/2/4	Kidney ankyrin repeat-containing protein	AR	(21)
SYNPO	Synaptopodin	AD	(47)
PTPRO	Protein-tyrosine phosphatase-R O	AR	(48)
EMP2	Epithelial membrane protein 2	AR	(49)
APOL1	Apolipoprotein L1	Biallelic	(50)
CUBN	Cubilin	AR	(51)
PODXL	Podocalyxin	AD	(52)
DLC1	DLC1 Rho GTPase-activating protein	AR	(53)
ITSN 1/2	Intersectin protein	AR	(53)
TNS2	Tensin-2	AR	(53)
Transcription factor and nucleus encoding genes			
WT1	Wilms' tumor protein 1	AD, AR	(22, 23)
PAX2	Paired box protein 2	AD	(25)
LMX1B	LIM homeobox transcription factor 1β	AD	(26)
SMARCAL1	SMARCA-like protein	AR	(54)
NUP 85/93/107/133/160/205	Nuclear pore complex protein	AR	(27-29)
XPO5	Exportin 5	AR	(29)
E2F3	E2F transcription factor	AD	(55)
NXF5	Nuclear RNA export Factor 5	XLR	(56)

Table1. Genes Associated with Steroid-resistant Nephrotic Syndrome (Continue)

Gene	Protein	Mode of inheritance	Reference
MAFB	MAF bZIP transcription factor B	AD	(57)
LMNA	Lamin A and C	AD	(58)
WDR73	WD repeat domain 73	AR	(59)
OSGEP	KEOPS complex protein	AR	(60)
TP53RK	KEOPS complex protein	AR	(60)
TPRKB	KEOPS complex protein	AR	(60)
LAGE3	KEOPS complex protein	XL	(60)
Glomerular basement membrane genes			
LAMB2	Laminin subunit β2	AR	(31)
ITGB4	Integrin β4	AR	(61)
ITGA3	Integrin α3	AR	(62)
COL4A 3/4/5	Type IV collagen α3, α4, α5	AD, AR, XL	(32)
GPC5	Glypican 5	Risk gene	(63)
CD151	CD151 antigen	AR	(64)
Mitochondrial genes			
COQ2	Coenzyme Q2	AR	(33)
COQ6	Coenzyme Q6	AR	(34)
PDSS2	Prenyl-diphosphate synthase subunit 2	AR	(35)
COQ8B/ADCK4	Coenzyme Q8B	AR	(36)
MTTL1	Mitochondrial tRNA 1	Mt	(37)
Lysosomal, metabolic, and cytosolic protein encoding genes			
SCARB2	Scavenger receptor class B, member 2	AR	(38)
OCRL1	Oculocerebrorenal syndrome of Lowe	XLR	(65)
ZMPSTE24	Zinc metallopeptidase STE24	AR	(66)
PMM2	Phosphomannomutase 2	AR	(67)
ALG1	Asparagine-linked glycosylation 1	AR	(68)
TTC21B	Tetratricopeptide repeat protein 21B	AR	(39)
CFH	Complement factor H	AR	(69)
DGKE	Diacylglycerol kinase ε	AR	(40)
CDK20	Cyclin-dependent kinase	AR	(53)
MEFV	Pyrin	AR	(70)
NEIL1	Nei endonuclease VIII-like 1	AR	(71)
GAPVD1	GTPase activating protein and VPS9 domains 1	AR	(72)
ANKFY1	Ankyrin repeat and FYVE domain containing 1	AR	(72)
TBC1D8B	TBC1 domain family member 8B	XL	(73)

AD, Autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; XL, X-linked; Mt, Mitochondrial

genital anomaly of kidney and urinary tract to late-onset FSGS[25]. LIM homeobox transcription factor 1β (encoded by *LMX1B*) protein regulates the development of podocyte foot process and SD. *LMX1B* mutations were found to exhibit clinical manifestations ranging from isolated proteinuria to Nail-Patella syndrome[26].

Nuclear pore complex proteins are involved in another pathway implicated in SRNS pathogenesis. This was determined through the identification of mutations in six genes (*NUP85, NUP93, NUP107, NUP133, NUP160, NUP205*). Mutations in these nuclear pore complex protein genes lead to abnormal nucleoprotein assembly, thereby inhibiting podocyte proliferation, promoting podocyte apoptosis, and disrupting the structural integrity of the GFB. Mutations in these genes were mostly found to underlie childhood-onset AR-FSGS[27-29].

Glomerular basement membrane genes

The GBM is composed of a network of laminin, type IV collagen, nidogen, and heparan sulfate proteoglycans. GBM is a GFB component located between podocytes and endothelial cells. Changes in GBM composition or morphology are known to affect the integrity of glomerular filtration [30].

Laminin is a heterotrimer of α, β, and γ glycoprotein chains. Mutations in *LAMB2* (encoding laminin β2) were found to cause isolated congenital and childhood-onset SRNS or typically Pierson syndrome, depending on the genotype[31]. The α3, α4, and α5 collagen IV heterotrimers are essential for maintaining the GBM. Defects in these proteins impair podocyte adherence to GBM, and accelerate podocyte detachment. Mutations in type IV collagen α3, α4, and α5 chains (encoded by *COL4A3, CLO4A4*, and *COL4A5*) were found to cause Alport syndrome, which is characterized by familial nephropathy with sensorineural deafness and ocular abnormalities[32].

Mitochondrial genes

The discovery of mitochondrial gene mutations raised awareness regarding the importance of mitochondrial podocytopathy in SRNS. Coenzyme Q_{10}, also known as ubiquinone, is essential for transporting electrons in the mitochondrial respiratory chain to produce energy. Genetic defects in coenzyme Q_{10} biosynthesis lead to mitochondrial dysfunction, thereby resulting in podocyte injury and apoptosis.

Mutations in four genes (*COQ2, COQ6, COQ8B/ADCK4, PDSS2*) hitherto associated with coenzyme Q_{10} biosynthesis have been identified to cause SRNS. The mutations in *COQ6* and *COQ8B/ADCK4* were found to be associated with early-onset SRNS and sensorineural deafness, and childhood-onset SRNS with nephrocalcinosis, respectively [33-36]. In some rare cases, the A3243G mutation in the *MTTL1* gene (encoding leucine tRNA) caused a respiratory chain defect, and was associated with FSGS and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome[37].

Lysosomal, metabolic, and cytosolic protein-encoding genes

Various pathways related to lysosomes, endosomes, and metabolism are associated with SRNS development. Mutations in *SCARB2* (encoding a lysosomal integral membrane protein) were found to cause podocyte damage via impaired autophagy regulation, thereby resulting in myoclonus renal failure syndrome[38]. A mutation in *TTC21B* (encoding an intraflagellar transport-A component of primary cilium) was found to be associated with AR FSGS and nephronophthisis[39]. Diacylglycerol kinase ε (encoded by *DGKE*) is an intracellular lipid kinase. Diacyclglycerol kinase ε regulates the phosphatidylinositol cycle by controlling the concentration of diacylglycerol. A *DGKE* mutation was found to be associated with AR NS and atypical hemolytic uremic syndrome[40].

Other SRNS-associated genes not mentioned above are presented in Table 1.

Conclusions

The identification of genetic mutations in SRNS expanded our knowledge of the molecular basis of proteinuria, and took us a step closer towards finding a cure. However, cli-

nical heterogeneity is observed in patients carrying identical mutation, and these genes are only responsible for a small part of the SRNS pathogenesis; a large portion remains unknown. Further research is needed to identify other pathogenic mutations and to clarify currently unknown mechanisms of SRNS pathogenesis in order to provide a personalized therapeutic approach, including avoidance of unnecessary immunosuppressive therapy, screening for associated extra-renal malformations, prediction of post-transplant outcome, and genetic counselling.

Conflict of interest

The author declares no competing interests.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet 2018;392:61-74.
2. Kang HG, Cheong HI. Nephrotic syndrome: what's new, what's hot? Korean J Pediatr 2015;58:275-82.
3. Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. Nat Rev Nephrol. 2016;12:133-46.
4. Preston R, Stuart HM, Lenon R. Genetic testing in steroid-resistant nephrotic syndrome: why, who, when and how? Pediatr Nephrol 2019;34:195-210.
5. Trautmann A. Bodria M, Ozaltin F, Gheisari A, Nelk A, Azocar M, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. Clin J Am Soc Nephrol 2015;10:592-600.
6. Sadowski CE, Lovric S, Ashraf S, Pabst WL, Gee HY, Kohl S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol 2015;26:1279-89.
7. Warejko JK, Tan W, Daga A, Schapiro D, Lawson JA, Shril S, et al. Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol 2018;13:53-62.
8. Marshall CB, Shankland SJ. Cell cycle regulatory proteins in podocyte health and disease. Nephron Exp Nephrol 2007;106:e51-9.
9. Grahammer F, Schell C, Huber TB. The podocyte slit diaphragm-from a thin grey line to a complex signalling hub. Nat Rev Nephrol 2013;9:587-98.
10. Kestilä M, Lenkkeri U, Männikkö M, Lamerdin J, McCready P, Putaala H, et al. Positionally cloned gene for a novel glomerular protein--nephrin--is mutated in congenital nephrotic syndrome. Mol Cell 1998;1:575-82.
11. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber, A et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. Nat Genet 2000;24:349-54.
12. Hinkes B, Wiggins RC, Gbadegesin R, Vlangos CN, Seelow D, Nurnberg G, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nat Genet 2006;38:1397-405.
13. Winn MP, Conlon PJ, Lynn KL, Farrington MK, Creazzo T, Hawkins AF, et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science 2005;308:1801-4.
14. Lowik MM, Groenen PJ, Pronk I, Lilien MR, Goldschmeding R, Dijkman HB, et al. Focal segmental glomerulosclerosis in a patient homozygous for a CD2AP mutation. Kidney Int 2007;72:1198-203.
15. Faul C, Asanuma K, Yanagida-Asanuma E, Kim K, Mundel P, et al. Actin up: regulation of podocyte structure and function by components of the actin cytoskeleton. Trend Cell Biol. 2007;17:428-37.
16. Kaplan JM, Kim SH, North KN, Rennke H, Correia LA, Tong HQ, et al. Mutations in ACTN4, encoding alphaactinin-4, cause familial focal segmental glomerulosclerosis. Nat Genet 2000;24:251-6.
17. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet 2008;40:1175-84.
18. Boyer O, Benoit G, Gribouval O, Nevo F, Tete MJ, Dantal J, et al. Mutations inINF2 are a major cause of autosomal dominant focal segmental glomerulosclerosis. J Am Soc Nephrol 2011;22239-45.
19. Akilesh S, Suleiman H, Yu H, Stander MC, Lavin P, Gbadegesin R, et al. Arhgap24 inactivates Rac1 in mouse podocytes, and a mutant form is associated with familial focal segmental glomerulosclerosis. J Clin Invest 2011;121:4127-37.
20. Gee HY, Saisawat P, Ashraf S, Hurd TW, Vega-Warner V, Fang H, et al. ARHGDIA mutations cause nephrotic syndrome via defective RHO GTPase signaling. J Clin Invest 2013;123:3243-53.
21. Gee HY, Zhang F, Ashraf S, Kohl S, Sadowski CE, Vega-Warner V, et al. KANK deficiency leads to podocyte dysfunction and nephrotic syndrome. J Clin Invest 2015;125:2375-84.
22. Barbaux S, Niaudet P, Gubler MC, Grunfeld JP, Jaubert F, Kuttenn F, et al. Donor splice-site mutations in WT1 are responsible for Frasier syndrome. Nat Genet 1997;17:467-70.
23. Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JE, et al. Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell 1991;67:437-47.
24. Lee JH, Han KH, Lee H, Kang HG, Moon KC, Shin JI, et al. Genetic basis of congenital and infantile nephrotic syndromes. Am J Kidney Dis 2011;58:1042-3.
25. Kerti A, Csohany R, Wagner L, Javorszky E, Maka E, Tory K. NPHS2 homozygous p.R229Q variant: potential modifier instead of causal effect in focal segmental glomerulosclerosis. Pediatr Nephrol 2013;28:2061-4.

26. Dreyer SD, Zhou G, Baldini A, Winterpacht A, Zabel B, Cole W, et al. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in Nail Patella syndrome. Nat Genet 1998;19:47-50.
27. Miyake N, Tsukaguchi H, Koshimizu E, Shono A, Matsunaga S, Shiina M, et al. Biallelic Mutations in Nuclear Pore Complex Subunit NUP107 Cause Early-Childhood-Onset Steroid-Resistant Nephrotic Syndrome. Am J Hum Genet 2015;97:555-66.
28. Braun DA, Sadowski CE, Kohl S, Lovric S, Astrinidis SA, Pabst WL, et al. Mutations in nuclear pore genes NUP93, NUP205 and XPO5 cause steroid-resistant nephrotic syndrome. Nat Genet 2016;48:457-65.
29. Zhao F, Zhu JY, Richman A, Fu Y, Huang W, Chen Y, et al. Mutations in NUP160 Are Implicated in Steroid-Resistant Nephrotic Syndrome. J Am Soc Nephrol 2019;30:840-53.
30. Jeffrey HM. The glomerular basement membrane. Exp Cell Res 2012;318:973-8.
31. Zenker M, Aigner T, Wendler O, Tralau T, Müntefering H, Fenski R, et al. Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. Hum Mol Genet 2004;13:2625-32.
32. Voskarides K, Damianou L, Neocleous V, Zouvani I, Christodoulidou S, Hadjiconstantinou V, et al. COL4A3/COL4A4 mutations producing focal segmental glomerulosclerosis and renal failure in thin basement membrane nephropathy. J Am Soc Nephrol 2007;18:3004-16.
33. Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, Laverda AM, et al. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology 2005;65:606-8.
34. Heeringa SF, Chernin G, Chaki M, Zhou W, Sloan AJ, Ji Z, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest 2011;121:2013-243 .
35. Lopez LC, Schuelke M, Quinzii CM, Kanki T, Rodenburg RJ, Naini A, Dimauro S, et al. Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations. Am J Hum Genet 2006;79:1125-9.
36. Ashraf S, Gee HY, Woerner S, Xie LX, Vega-Warner V, Lovric S, et al. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. J Clin Invest 2013;123:5179-89.
37. 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 2000;275:4251-7.
38. Berkovic SF, Dibbens LM, Oshlack A, Silver JD, Katerelos M, Vears DF, et al. Array-based gene discovery with three unrelated subjects shows SCARB2/LIMP-2 deficiency causes myoclonus epilepsy and glomerulosclerosis. Am J Hum Genet 2008;82:673-84.
39. Huynh Cong E, Bizet AA, Boyer O, Woerner S, Gribouval O, Filhol E, Arrondel C, et al. A homozygous missense mutation in the ciliary geneTTC21B causes familial FSGS. J Am Soc Nephrol 2014;25:2435-43.
40. Ozaltin F, Li B, Rauhauser A, An SW, Soylemezoglu O, Gonul II, et al. DGKE variants cause a glomerular microangiopathy that mimics membranoproliferative GN. J Am Soc Nephrol 2013;24:377-84.
41. Ebarasi L, Ashraf S, Bierzynska A, Gee HY, McCarthy HJ, Lovric S, et al. Defects of CRB2 cause steroid-resistant nephrotic syndrome. Am J Hum Genet 2015;96:153-61.
42. Gee HY, Sadowski CE, Aggarwal PK, Porath JD, Yakulov TA, Schueler M, et al. FAT1 mutations cause a glomerulotubular nephropathy. Nat Commun 2016;7.
43. Solanki AK, Widmeier E, Arif E, Sharma S, Daga A, Srivastava P, et al. Mutations in KIRREL1, a slit diaphragm component, cause steroid-resistant nephrotic syndrome. Kidney Int 2019;10.
44. Mele C, Iatropoulos P, Donadelli R, Calabria A, Maranta R, Cassis P, et al. MYO1E mutations and childhood familial focal segmental glomerulosclerosis. N Engl J Med. 2011;365:295-306.
45. Bierzynska A, Soderquest K, Dean P, Colby E, Rollason R, Jones, et al. MAGI2 mutations cause congenital nephrotic syndrome. J Am Soc Nephrol 2017;28:1614-21.
46. Gbadegesin RA, Hall G, Adeyemo A, Hanke N, Tossidou I, Burchette J, et al. Mutations in the gene that encodes the F-actin binding protein anillin cause FSGS. J Am Soc Nephrol 2014;25:1991-2002.
47. Dai S, Wang Z, Pan X, Wang W, Chen X, Ren H, et al. Functional analysis of promoter mutations in the ACTN4 and SYNPO genes in focal segmental glomerulosclerosis. Nephrol Dial Transplant 2010;25:824-35.
48. Ozaltin F, Ibsirlioglu T, Taskiran EZ, Baydar DE, Kaymaz F, Buyukcelik M, et al. Disruption of PTPRO causes childhood onset nephrotic syndrome. Am J Hum Genet 2011;89:139-47.
49. Gee HY, Ashraf S, Wan X, Vega-Warner V, Esteve-Rudd J, Lovric S, Fang H, et al. Mutations in EMP2 cause childhood-onset nephrotic syndrome. Am J Hum Genet 2014;94:884-90.
50. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. ApoL1 variants with kidney disease in African Americans. Science 2010;329:841-5.
51. Ovunc B, Otto EA, Vega-Warner V, Saisawat P, Ashraf S, Ramaswami G, et al. Exome sequencing reveals cubilin mutation as a single-gene cause of proteinuria. J Am Soc Nephrol 2011;22:1815-20.
52. Barua M, Shieh E, Schlondorff J, Genovese G, Kaplan BS, Pollak MR. Exome sequencing and in vitro studies identified podocalyxin as a candidate gene for focal and segmental glomerulosclerosis. Kidney Int 2014;85:124-33.
53. Ashraf S, Kudo H, Rao J, Kikuchi A, Widmeier E, Lawson JA, et al. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. Nat Commun 2018;9:1960.
54. Boerkoel CF, Takashima H, John J, Yan J, Stankiewicz P, Rosenbarker L, et al. Mutant chromatin remodeling protein SMARCAL1 causes Schimke immuno-osseous dysplasia. Nat Genet 2002;30:215-20.

55. Izu A, Yanagida H, Sugimoto K, Fujita S, Sakata N, Wada N, et al. Pathogenesis of focal segmental glomerular sclerosis in a girl with the partial deletion of chromosome 6p. Tohoku J Exp Med 2011; 223:187-92.
56. EspositoT, Lea RA, Maher BH, Moses D, Cox HC, Magliocca S, et al. Unique X-linked familial FSGS with co-segregating heart block disorder is associated with a mutation in the NXF5 gene. Hum Mol Genet 2013;22:3654-66.
57. Sato Y, Tsukaguchi H, Morita H, Higasa K, Tran MTN, Hamada MA, et al. mutation in transcription factor MAFB causes Focal Segmental Glomerulosclerosis with Duane Retraction Syndrome. Kidney Int 2018;94:396-407.
58. Thong KM, Xu Y, Cook J, Takou A, Wagner B, Kawar B, et al. Cosegregation of focal segmental glomerulosclerosis in a family with familial partial lipodystrophy due to a mutation in LMNA. Nephron Clin Pract 2013;124:31-7.
59. Colin E, Huynh Cong E, Mollet G, Guichet A, Gribouval O, Arrondel C, et al. Loss-of-function mutations in WDR73 are responsible for microcephaly and steroid-resistant nephrotic syndrome: Galloway-Mowat syndrome. Am J Hum Genet 2014;95:637-48.
60. Braun DA, Rao J, Mollet G, Schapiro D, Daugeron MC, Tan W, et al. Mutations in KEOPS-complex genes cause nephrotic syndrome with primary microcephaly. Nat Genet 2017;49:1529-38.
61. Kambham N, Tanji N, Seigle RL, Markowitz GS, Pulkkinen L, Uitto J, et al. Congenital focal segmental glomerulosclerosis associated with beta4 integrin mutation and epidermolysis bullosa. Am J Kidney Dis 2000;36:190-6.
62. Has C, Sparta G, Kiritsi D, Weibel L, Moeller A, Vega-Warner V, et al. Integrin alpha3 mutations with kidney, lung, and skin disease. N Engl J Med 2012;366:1508-14.
63. 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 2011;43:459-63.
64. Karamatic Crew V, Burton N, Kagan A, Green CA, Levene C, Flinter F, et al. CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin. Blood 2004;104:2217-23.
65. Kaneko K, Hasui M, Hata A, Hata D, Nozu K Focal segmental glomerulosclerosis in a boy with Dent-2 disease. Pediatr Nephrol 2010;25:781-2.
66. Agarwal AK1, Zhou XJ, Hall RK, Nicholls K, Bankier A, Van Esch H, et al. Focal segmental glomerulosclerosis in patients with mandibuloacral dysplasia owing to ZMPSTE24 deficiency. J Investig Med 2006;54:208-13.
67. van der Knaap MS, Wevers RA, Monnens L, Jakobs C, Jaeken J, van Wijk JA. Congenital nephrotic syndrome: a novel phenotype of type I carbohydrate-deficient glycoprotein syndrome. J Inherit Metab Dis 1996;19:787-91.
68. Kranz C, Denecke J, Lehle L, Sohlbach K, Jeske S, Meinhardt F, et al. Congenital disorder of glycosylationtype Ik(CDG-Ik): A Defect of Mannosyltransferase I. Am J Hum Genet 2004;74:545-51.
69. Sethi S, Fervenza FC, ZhangY, Smith RJ. Secondary focal and segmental glomerulosclerosis associated with single-nucleotide polymorphisms in the genes encoding complement factor H and C3. Am J Kidney Dis 2012;60:316-21.
70. Fisher PW, Ho LT, Goldschmidt R, Semerdjian RJ, Rutecki GW. Familial Mediterranean fever, inflammation and nephrotic syndrome: fibrillary glomerulopathy and the M680I missense mutation. BMC Nephrol 2003;4:6.
71. Sanna-Cherchi S, Burgess KE, Nees SN, Caridi G, Weng PL, Dagnino M, et al. Exome sequencing identified MYO1E and NEIL1 as candidate genes for human autosomal recessive steroid-resistant nephrotic syndrome. Kidney Int 2011;80:389-96.
72. Hermle T, Schneider R, Schapiro D, Braun DA, van der Ven AT, Warejko JK, et al. GAPVD1 and ANKFY1 Mutations Implicate RAB5 Regulation in Nephrotic Syndrome. J Am Soc Nephrol 2018;29: 2123-38.
73. Dorval G, Kuzmuk V, Gribouval O, Welsh GI, Bierzynska A, Schmitt A, et al. TBC1D8B Loss-of-Function Mutations Lead to X-Linked Nephrotic Syndrome via Defective Trafficking Pathways. Am J Hum Genet 2019;104:348-55.