Genetic Basis of Steroid Resistant Nephrotic Syndrome

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. 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.

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). SRNS is a genetically heterogeneous disease with over 70 SRNS- and/or FSGS-causing genes. A single causative genetic mutation in 20-30% of SRNS cohort patients was identified in recent studies. 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. 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.
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\(^{15}\).

\(\alpha\)-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 Fraser- 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\(^{20}\). 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-
| Gene          | Protein                                      | Mode of inheritance | Reference |
|--------------|----------------------------------------------|---------------------|-----------|
| 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)      |
| 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)      |
| ARHGGA24     | Rho GTPase-activating protein 24             | AD                  | (19)      |
| ARHGSDIA     | 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-RO              | AR                  | (48)      |
| EMP2         | Epithelial membrane protein 2               | AR                  | (49)      |
| APOL1        | Apolipoprotein L1 Biallelic                  | Biallelic           | (50)      |
| CLB1N        | Cublin                                       | AR                  | (51)      |
| PODXL        | Podosyndecan                                 | AD                  | (52)      |
| DLC1         | DLC1 Rho GTPase-activating protein           | AR                  | (53)      |
| ITSN 1/2     | Intersectin protein                          | AR                  | (53)      |
| TNS2         | Tensin-2                                     | AR                  | (53)      |
| WT1          | Wilms' tumor protein 1                       | AD, AR              | (22, 23)  |
| PAW2         | 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)       |
| XPOS         | Exportin 5                                   | AR                  | (29)      |
| E2F3         | E2F transcription factor                     | AD                  | (55)      |
| NXF5         | Nuclear RNA export Factor 5                  | XLR                 | (56)      |

**Table 1. 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)      |
| TRKKB        | KEOPS complex protein                        | AR                  | (60)      |
| LAGE3        | KEOPS complex protein                        | XL                  | (60)      |
| LAMN2        | Laminin subunit β2                          | AR                  | (31)      |
| ITG84        | Integrin B4                                 | AR                  | (61)      |
| ITG34        | Integrin a3                                 | AR                  | (62)      |
| COL4A 3/4/5  | Type IV collagen a3, a4, a5                  | AD, AR, XL          | (32)      |
| GPC5         | Glypican 5                                   | Risk gene           | (63)      |
| CD151        | CD151 antigen                                | AR                  | (64)      |
| COQ2         | Coenzyme Q2                                  | AR                  | (33)      |
| COQ6         | Coenzyme Q6                                  | AR                  | (34)      |
| PDS52        | Prenyl-diphosphate synthase subunit 2        | AR                  | (35)      |
| COQ8B/ADCK4  | Coenzyme Q8B                                 | AR                  | (36)      |
| MTTL1        | Mitochondrial RNA 1                          | Mt                  | (37)      |
| SCARB2       | Scavenger receptor class B, membre 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)      |
| TCC21B       | 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)      |
| ANKRY1       | Ankyrin repeat and FYVE domain containing 1  | AR                  | (72)      |
| TBC1D88      | TBC1 domain family member 88                | 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\textsuperscript{25}. LIM homeobox transcription factor 1β (encoded by \textit{LMX1B}) protein regulates the development of podocyte foot process and SD. \textit{LMX1B} mutations were found to exhibit clinical manifestations ranging from isolated proteinuria to Nail-Patella syndrome\textsuperscript{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 (\textit{NUP85}, \textit{NUP93}, \textit{NUP107}, \textit{NUP133}, \textit{NUP160}, \textit{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\textsuperscript{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\textsuperscript{30}.

Laminin is a heterotrimer of α, β, and γ glycoprotein chains. Mutations in \textit{LAMB2} (encoding laminin β2) were found to cause isolated congenital and childhood-onset SRNS or typically Pierson syndrome, depending on the genotype\textsuperscript{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 \textit{COL4A3}, \textit{COL4A4}, and \textit{COL4A5}) were found to cause Alport syndrome, which is characterized by familial nephropathy with sensorineural deafness and ocular abnormalities\textsuperscript{32}.

**Mitochondrial genes**

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

Mutations in four genes (\textit{COQ2}, \textit{COQ6}, \textit{COQ8B/ADCK4}, \textit{PDS2}) hitherto associated with coenzyme Q\textsubscript{10} biosynthesis have been identified to cause SRNS. The mutations in \textit{COQ6} and \textit{COQ8B/ADCK4} were found to be associated with early-onset SRNS and sensorineural deafness, and childhood-onset SRNS with nephrocalcinosis, respectively\textsuperscript{33-36}. In some rare cases, the A3243G mutation in the \textit{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\textsuperscript{37}.

**Lysosomal, metabolic, and cytosolic protein-encoding genes**

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

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