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REVIEW

Genetic causes of proteinuria and nephrotic syndrome: Impact on podocyte pathobiology

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Abstract In the past 20 years, multiple genetic mutations have been identified in patients with congenital nephrotic syndrome (CNS) and both familial and sporadic focal segmental glomerulosclerosis (FSGS). Characterization of the genetic basis of CNS and FSGS has led to the recognition of the importance of podocyte injury to the development of glomerulosclerosis. Genetic mutations induce injury due to effects on the podocyte's structure, actin cytoskeleton, calcium signaling, and lysosomal and mitochondrial function. Transgenic animal studies have contributed to our understanding of podocyte pathobiology. Podocyte endoplasmic reticulum stress response, cell polarity, and autophagy play a role in maintenance of podocyte health. Further investigations related to the effects of genetic mutations on podocytes may identify new pathways for targeting therapeutics for nephrotic syndrome.

Keywords Focal segmental glomerulosclerosis · Nephrotic syndrome · Steroid resistant nephrotic syndrome · Genetic mutation · Podocyte signaling

Introduction

Podocytes are highly differentiated and specialized pericyte-like cells with a complex cyto-architecture that form a major component of the glomerular filtration barrier. The podocyte consists of a cell body that extends major (primary) processes. These processes ramify and terminate in specialized structures called foot processes that wrap around the glomerular capillaries. Neighboring foot processes interdigitate and link to each other by specialized cell–cell junctions spanning distances of 40 nm, known as slit diaphragms. The podocyte foot processes with slit diaphragms act as molecular sieves that help establish the permselectivity of the glomerular filter. The three-dimensional structure of the podocyte is supported by its complex cytoskeleton. The podocyte foot processes contain a central actin bundle surrounded by a network of cortical actin fibers [1]. The extensive actin cytoskeleton allows for dynamic contraction of podocyte foot processes in response to different stimuli, such as changes in glomerular capillary hydrostatic pressure (about 60 mmHg), which is much greater than pressures typical of other capillary beds [2].

Podocyte injury and loss are thought to be the initiating factor leading to glomerulosclerosis. Why is podocyte loss so critical? The predominant view is that podocytes are terminally differentiated cells that cannot repopulate after podocyte loss. Recent studies have demonstrated a subpopulation of parietal epithelial cells that may contribute to podocyte regeneration; however, the capacity for regeneration appears to be limited [3–6]. Thus, podocyte loss beyond this regenerative capacity leads to glomerular hyperfiltration and hypertrophy of the remaining podocytes [7], which results in additional podocyte stress, injury, loss, and ultimately scar formation [7].

The identification of genetic mutations in familial nephrotic syndrome and focal segmental glomerulosclerosis (FSGS) over the past few decades (Table 1) has advanced our understanding of podocyte biology. These genetic mutations affect proteins that are expressed in a variety of locations within the podocyte, including the cell membrane, nucleus, cytoskeleton, lysosomes and mitochondria (Fig. 1). Here we review some of the mechanisms by which these genetic mutations lead to podocyte injury.

Mutations in genes encoding slit diaphragm components

Some of the earliest identified genetic defects leading to nephrotic syndrome were those in genes encoding the slit

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Table 1 Genetic causes of proteinuria

Gene	Protein*	Mode of inheritance	Phenotype	Selected references
Slit diaphragm and cell signaling proteins				
NPHS1	nephrin	AR	CNS, SRNS	[8, 18, 118]
NPHS2	podocin	AR	CNS, SRNS	[9, 119]
PLCE1	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase epsilon-1	AR	DMS, SRNS	[72, 120]
TRPC6	short transient receptor potential channel 6	AD	SRNS	[66]
CD2AP	CD2-associated protein	AD/AR	SRNS	[35, 43, 44]
Cytoskeleton components				
ACTN4	α-actinin-4	AD	Late onset SRNS	[33]
INF2	inverted formin-2	AD	SRNS, Charcot-Marie-Tooth disease with glomerulopathy	[34, 64]
MYH9	myosin-9	AD	Macrothrombocytopenia with sensorineural deafness, Epstein syndrome, Sebastian syndrome, Fechtner syndrome	[112, 121, 122]
MYO1E	unconventional myosin-Ie	AR	SRNS	[53]
ARHGDIA	rho GDP-dissociation inhibitorα 1	AR	SRNS; seizures, cortical blindness	[65]
Nuclear proteins				
WT1	Wilms tumor protein	AD/AR	SRNS, Denys-Drash syndrome, Frasier syndrome	[99, 123]
LMX1B	LIM homeobox transcription factor 1-β	AD	Nail-patella syndrome/irregular GBM thickening with patchy lucent ("moa-eaten") areas	[124, 125]
SMARCAL1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A-like protein 1	AR	Schimke immuno-osseous dysplasia	[126, 127]
GBM proteins				
LAMB2	laminin subunit β–2	AR	Pierson syndrome	[103, 128]
Mitochondrial proteins				
COQ2	4-hydroxybenzoate polyprenyltransferase, mitochondrial	AR	Early-onset SRNS, CoQ10 deficiency	[79]
COQ6	ubiquinone biosynthesis monooxygenase COQ6	AR	NS with sensorineural deafness	[81]
PDSS2	decaprenyl-diphosphate synthase subunit 2	AR	Leigh syndrome / CoQ10 deficiency	[80]
*MT-TL1***	N/A	Maternal	Maternally-inherited diabetes or hearing loss presenting with FSGS / MELAS syndrome	[78, 129-131]
Lysosomal proteins				
SCARB2	lysosome membrane protein 2 (LIMP II)	AR	Action myoclonus-renal failure syndrome	[82]
Other proteins				
APOL1	apolipoprotein L1	n/a	Sporadic FSGS in African-American patients	[110]
PTPRO	receptor-type tyrosine-protein phosphatase O (aka glomerular epithelial protein 1/GLEPP1)	AR	SRNS	[91, 132]

Red: mutations causing non-syndromal renal disease

Blue: mutations causing syndromal renal disease

*For simplicity in the text, protein products are indicated by non-italicized gene symbols ** this encodes a tRNA; no protein is encoded by this gene

Official full names: *ACTN4* actinin, alpha 4; *APOL1* apolipoprotein L, 1; *CD2AP* CD2-associated protein; *COQ2* coenzyme Q2 4-hydroxybenzoate polyprenyltransferase; *COQ6* coenzyme Q6 monooxygenase; *INF2* inverted formin, FH2 and WH2 domain containing; *LAMB2* laminin, beta 2 (laminin S); *LIMP2* lysosome membrane protein 2; *LMX1B* LIM homeobox transcription factor 1 beta; *MT-TL1* mitochondrially encoded tRNA leucine 1 (UUA/G); *MYH9* myosin, heavy chain 9, non-muscle; *MYO1E* myosin IE; *NPHS1* nephrosis 1, congenital, Finnish type (nephrin); *NPHS2* nephrosis 2, idiopathic, steroid-resistant (podocin); *PDSS2* prenyl (solanesyl) diphosphate synthase, subunit 2; *PLCE1* phospholipase C, epsilon 1; *PTPRO* protein tyrosine phosphatase receptor type O; *SCARB2* scavenger receptor class B, member 2; *SMARCAL1* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1; *TRPC6* transient receptor potential cation channel, subfamily C, member 6; *WT1* Wilms tumor 1
MELAS syndrome: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

diaphragm protein nephrin (NPHS1) and podocin (NPHS2), an integral membrane protein that associates with NPHS1 [8, 9]. The slit diaphragm protein NPHS1 is a transmembrane protein of the immunoglobulin family of cell-adhesion molecules. The large extracellular portion of NPHS1 has eight immunoglobulin G-like domains and a single fibronectin

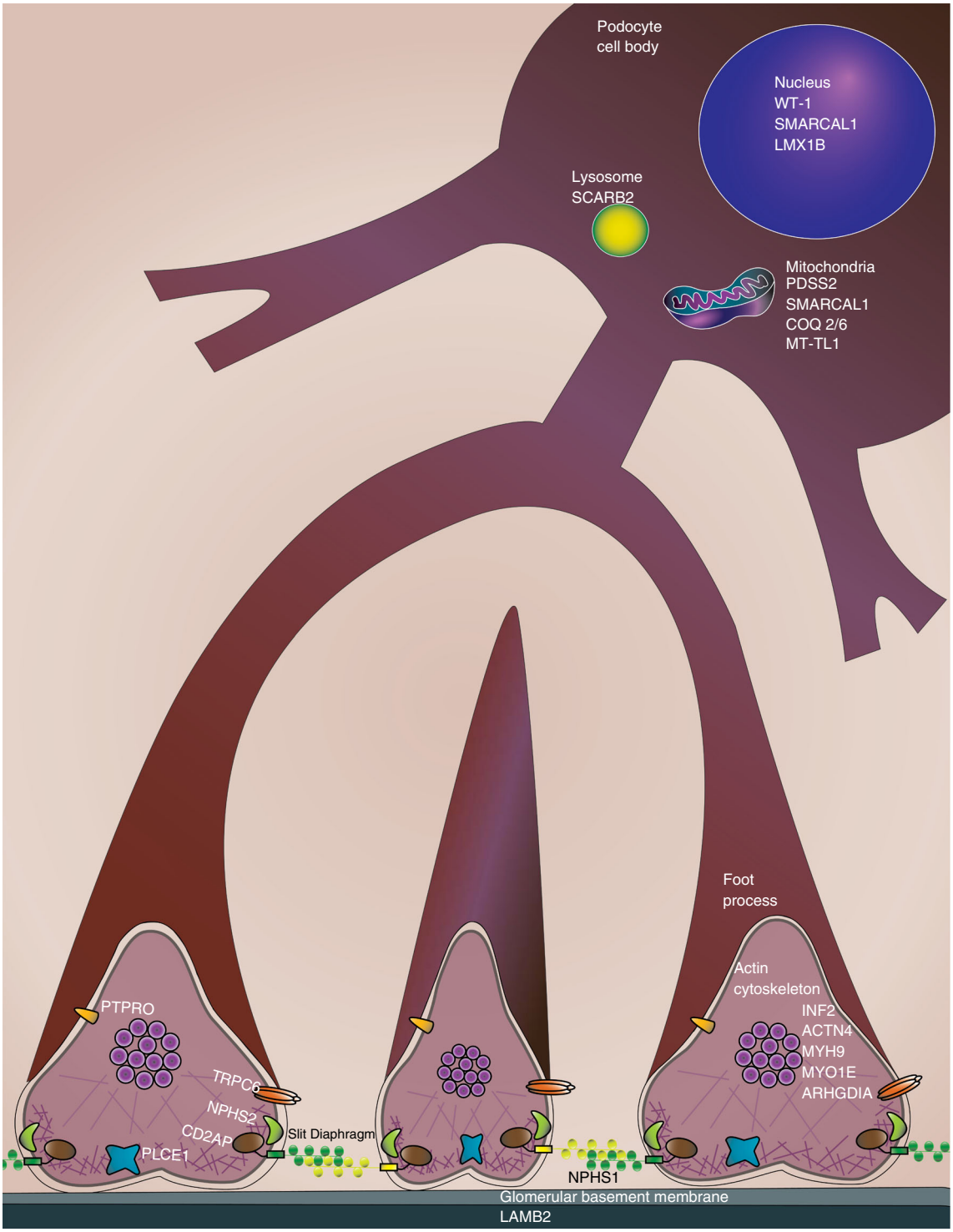

Fig. 1 Genetic mutations associated with nephrotic syndrome induce injury due to effects on the podocyte's structure, actin cytoskeleton, calcium signaling, and lysosomal and mitochondrial function

type-3 motif. It forms homo- and hetero-dimers with proteins such as NEPH1, 2, and 3 that are expressed on adjacent podocyte foot processes to generate the zipper-like multi-protein complexes of the slit diaphragm.

In addition to forming a key structural barrier to loss of protein in the urine, a complex of NPHS1 and NEPH1 mediates "outside–in" cell signaling to regulate the podocyte actin cytoskeleton [10]. Once thought to be fairly static, the foot

processes are perhaps better viewed as dynamic structures that are able to remodel due to active regulation of the actin cytoskeleton. The cytoplasmic tail of NPHS1 is characterized by multiple SH2 domains which allow Src tyrosine kinases Fyn and Yes to bind and phosphorylate NPHS1. Adapter proteins NCK1/2 are recruited to these phosphorylated NPHS1 domains, leading to actin polymerization [11–13]. Podocyte-specific deletion of *NCK1/2* in mice leads to FSGS lesions, suggesting that dysregulation of NPHS1 signaling induces podocyte injury [12].

Phosphorylated NPHS1 also binds to the p85 subunit of phosphatidylinositide 3-kinase (PI3K), leading to activation of AKT signaling [13, 14]. Classically, PI3K/AKT is an anti-apoptotic and cell survival pathway, but the PI3K/AKT pathways also regulate the podocyte actin cytoskeleton via effects on cofilin (CFL1) [14]. CFL1 is an enzyme that allows for actin filament severing, facilitating actin elongation and remodeling [13]. Loss of CFL1 in cultured podocytes leads to the accumulation of polymerized actin and impaired migration [13, 15], and in mice, it results in an inability for podocytes to regain their structure after injury [13].

Hence, NPHS1 plays critical roles in maintaining podocyte health via its effects on cell–cell adhesion, cell survival, cell signaling, and regulation of the actin cytoskeleton. Homozygous *NPHS1* loss-of-function mutations result in the severe phenotype of congenital nephrotic syndrome (CNS). More than 140 different *NPHS1* mutations have been identified, such as nonsense, missense, frameshift insertion/deletion, and splice-site mutations, including the classic Fin_{major} and Fin_{minor} mutations that are responsible for 94 % of the CNS cases in the Finnish population [16]. The Fin_{major} mutation is a 2-bp deletion (c.121delCT; p.L41fs) in the second exon of *NPHS1* that leads to truncation of the NPHS1 polypeptide chain from 1,241 to 90 amino acids [8, 16]. Similarly, the less common Fin_{minor} mutation is a nonsense mutation which results in a truncated NPHS1 1,109-amino acid protein that lacks the 82 C-terminal amino acids that interact with NPHS2. NPHS1 missense mutant proteins are retained in the endoplasmic reticulum (ER), likely causing a null allele phenotype [17]. Recently, some less severe missense *NPHS1* mutations have been identified in children and adults with FSGS [18].

NPHS2 mutations induce injury in part via effects on the NPHS1 and the actin cytoskeleton. NPHS2 is a member of the stomatin family and localizes to lipid rafts where it forms homo-oligomers [19]. Lipid rafts are microdomains in the plasma membrane that are enriched with sphingolipids and cholesterol. The lipid composition is less fluid and more rigid, and facilitates the concentration of signaling receptors to these microdomains. NPHS2 binds cell–cell junction proteins and serves as a scaffold anchoring the actin cytoskeleton to cell–cell contacts [20]. NPHS2 also recruits NPHS1 and other signaling proteins, such as TRPC6, to lipid rafts, potentially forming a mechano-sensory signaling platform to regulate the podocyte actin cytoskeleton [21–24].

More than 100 pathogenic *NPHS2* mutations have been reported that involve nonsense and frameshift mutations in exons. Recessive NPHS2 mutations are the most common mutations identified in Central European patients with early-onset steroid-resistant nephrotic syndrome (SRNS) [9, 25, 26]; in contrast, NPHS2 mutations are relatively rare in African American children [27]. Complete loss of function may alter glomerular development and cause CNS [28, 29]. Mutations in the C-terminus, such as R138Q (common in European populations), cause retention of NPHS2 within the ER and away from the plasma membrane [30]. Mis-localization of NPHS2 can also result in mis-localization of its binding partners NPHS1, CD2AP, and TRPC6 [30–32]. Other *NPHS2* mutations do not affect NPHS2 localization but induce podocyte apoptosis [30].

Mutations in genes encoding proteins involved in the podocyte actin cytoskeleton

Following the discovery of the role of NPHS1 and NPHS2, mutations in actin cytoskeleton-associated genes (*CD2AP*, *ACTN4*, *MYO1E*, *INF2*, *ARHGDIA*) were identified in patients with nephrotic syndrome [33–35]. How do defects in actin cytoskeleton regulation lead to podocyte injury? One possibility is they may impair the ability of podocyte foot processes to respond to the dynamic changes in the pressure and shape of the capillary walls. In vivo fluorescent imaging of podocytes suggests that podocytes are motile and migrate in the presence of injury [6]. Altered podocyte motility and decreased adhesion could induce detachment from the glomerular basement membrane (GBM) and eventually podocyte loss [36].

CD2AP is an 80-kDa cytoplasmic adaptor protein originally identified as a ligand interacting with the T-cell-adhesion protein CD2 [37]. In podocytes, CD2AP serves as a linker that anchors NPHS1 and NPHS2 to the actin cytoskeleton [19, 38]. In addition, CD2AP binds other regulators of the actin cytoskeleton. Cell motility requires the formation of projections of the actin cytoskeleton, known as lamellipodia. CD2AP recruits actin capping proteins to cortactin in the cortical actin cytoskeleton, promoting lamellipodia formation [39]. CD2AP also binds synaptopodin (SYNPO), an alpha-actin binding protein that promotes the formation of unbranched actin filaments and is required for actin remodeling [40, 41]. In addition to its effects on the actin cytoskeleton, CD2AP deletion induces podocyte injury and apoptosis

through the upregulation of transforming growth factor beta [42]. *CD2AP*$^{-/-}$ mice develop early onset, severe nephrotic syndrome, while *CD2AP*$^{+/-}$ (heterozygous) mice develop FSGS-like lesions at 9 months [43, 44]. *CD2AP* mutations may be rare in humans; to date, only a few heterozygous *CD2AP* mutations linked to FSGS [35, 44, 45] and one case of homozygous *CD2AP* mutations in infantile form of nephrotic syndrome have been reported [46].

Alpha-4-actinin (ACTN4) is a 100-kDa actin-binding protein that belongs to the spectrin gene superfamily. ACTN4 forms cross-links between actin filaments and binds adhesion molecules alpha-1-integrin and vinculin. Missense mutations in *ACTN4* are associated with incompletely penetrant and late-onset autosomal dominant (AD) FSGS [33]. Mutations in *ACTN4* are relatively rare, accounting for only approximately 4 % of familial FSGS [47]. The identified mutations result in non-conservative amino acid substitutions affecting the ACTN4 binding domain. Mutant ACTN4 exhibits increased binding to filamentous actin in vitro compared with wild-type protein, and the mutant protein formed aggregates within the podocyte, impairing podocyte migration in vitro [48, 49].

In addition to effects on the actin cytoskeleton, mutant *ACTN4* may have other deleterious effects on the podocyte. Transgenic "knock–in" mice that express K255E mutant *ACTN4* develop FSGS lesions and demonstrate activation of the ER stress response [50, 51]. The ER is a network of membrane-enclosed tubes (cisternae). Proteins are synthesized on ribosomes attached to the ER, and the ER is enriched in chaperones that help the nascent proteins fold. These chaperones, such as GRP78/BIP, have dual roles, as they also regulate the cell's response to stress (reviewed in [52]). In the absence of stress, members of the unfolded protein response (UPR) signaling cascade [including inositol-requiring kinase 1 (IRE1a), PRKR-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6)] are bound and inhibited by GRP78/BIP [52]. Accumulation of unfolded proteins in the ER sequesters GRP78/BIP and releases this inhibition. Mis-folded proteins are also targeted for degradation by the ubiquitin–proteasome system. Back-up (or "choking") of the ubiquitin–proteosome system with misfolded proteins further activates the UPR. Early on, activation of UPR elements leads to the global suppression of mRNA transcription and cell cycle arrest. This is likely to be an adaptive response to enable the cell to recover. However, continued UPR activation leads to p38 MAPK phosphorylation and increased expression of C/EBP homologous protein (CHOP) and BIM [52]. These proteins are pro-apoptotic and can induce cell death. The K255E mutant *ACTN4* causes "choking" of the ubiquitin–protesome system and activation of the UPR signaling pathways [51]. Thus, mutant *ACTN4* may also induce podocyte injury via ER stress.

Two mutations (A159P and Y695X) in *MYO1E*, the gene encoding non-muscle class I myosin, myosin 1E, have been associated with childhood-onset autosomal-recessive FSGS [53]. MYO1E is a member of the actin-dependent motor proteins. Myosins are bound to actin and generate force by hydrolysis of ATP to ADP, leading to a conformational change that stimulates movement of the actin filaments. Like other myosins, the N-terminus of MYO1E has an actin-binding domain and ATPase [54]. In addition to binding actin, MYO1E localizes to the slit diaphragm via interactions with ZO1, a cell–cell junction protein that can form a complex with slit diaphragm components [54]. MYO1E is required for the organization of podocyte actin filaments along cell–cell contacts. In one study, cultured podocytes expressing mutant A159P *MYO1E* failed to organize actin filaments at cell–cell junctions [54], and in another study, knockdown of *MYO1E* led to impaired podocyte adhesion and podocyte detachment in vitro [55]. In sum, *MYO1E* mutations impact both the assembly of the actin cytoskeleton and cell–cell adhesion, likely leading to podocyte injury and loss.

INF2 encodes inverted formin 2 (INF2), a member of the diaphanous formin subfamily of actin-regulating proteins (mDias). mDias are effectors for RHOA signaling. RHOA, CDC42, and RAC belong to the RHO family of GTPases that regulate the actin cytoskeleton and modulate cell shape, motility, adhesion, polarity, cell cycle, and transcription. A delicate balance of RHOA, RAC, and CDC42 signaling is required in podocytes, and excess RHOA activation induces podocyte injury and FSGS lesions in mice [56, 57]. When RHOA is bound by GTP, and it can bind and active mDias to stimulate actin polymerization. The mDias have formin homology domains that are the sites of actin nucleation and polymerization. They also have two regulatory domains: the diaphanous inhibitory domain (DID) and the diaphanous autoregulatory domain (DAD). In the absence of RHOA–GTP binding, the DID/DAD domains interact to inhibit actin polymerization. INF2 is homologous to mDias, and its DID domain can inhibit mDias and actin polymerization [58]. Thus, INF2 acts to fine-tune RHOA signaling. Loss of function disrupts the cortical actin network in cultured podocytes [58].

Most of the described mutations in *INF2* are heterozygous missense variants clustered in exons 2–4, which code for the N-terminal DID of the protein [59–61]. *INF2* mutations lead to loss of its inhibitory function and tip the balance towards mDia activation [58]. *INF2* mutations account for up to 9–17 % of familial cases of AD FSGS but are rarely associated with the sporadic cases of FSGS [34, 59, 62, 63]. *INF2* mutations have been also identified in individuals with FSGS and Charcot–Marie–Tooth disease [64].

Mutations in *ARHGDIA* have recently been identified in an infant with CNS and in two siblings with early onset SRNS [65]. ARHGDIA regulates GDP/GTP binding to RHO GTPases. It can act as a regulatory switch by determining the proportion of RHO GTPases bound to GDP (inactive)

versus GTP (active). In cultured podocytes, wild-type ARHGDIA binds RHOA, RAC, and CDC42 and inhibits cell migration [65]. Expression of the mutant *ARHGDIA* leads to increased RAC1 and CDC42 activity in vitro [65]. Taken together, data on the mutations in *INF2* and *ARHGDIA* indicate the need for tight regulation of the actin cytoskeleton to maintain podocyte health.

Mutations associated with calcium signaling in podocytes

The identification of calcium transporter TRPC6 mutations as a cause of familial FSGS brought to the forefront the concept that calcium signaling contributes to the maintenance of podocyte health [66]. Analyses suggested that an activating *TRPC6* mutation led to the AD inheritance pattern [66–68]. Congruent with these findings, podocyte overexpression of TRPC6 was found to induce FSGS in mice [69]. However, the mechanisms by which excess calcium entry into podocytes results in injury remain unclear. One possibility is that podocyte TRPC6-mediated calcium influx participates in mechanosensation. In vitro studies support this hypothesis, as NPHS2 binds TPRC6 and can block stretch-induced calcium influx into TRPC6 channels [70]. Increased calcium influx into the podocyte activates RHOA, leading to perturbations of the actin cytoskeleton [71]. It can also lead to downregulation of NPHS1 and loss of podocytes, either through apoptosis or detachment [71]. Interestingly, these studies reveal a possible mechanism by which NPHS2 loss-of-function mutations may lead to podocyte injury via excess calcium influx.

Phospholipase C epsilon 1 (*PLCE1*) mutations were initially described in children who develop early onset nephrotic syndrome [72]. In this study, children with truncating mutations had characteristic histologic lesions of diffuse mesangial sclerosis (DMS), whereas those with missense mutations had FSGS [72]. PLCE1 is a member of the phospho-inositide-specific phospholipase C (PLC) family. PLCs catalyze the hydrolysis of membrane phospholipids to generate the second messengers inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). IP_3 diffuses through the cytoplasm to the ER, where it triggers release of the ER's calcium storage pool. DAG meanwhile remains in the phospholipid bilayer, where it activates protein kinase C (PKC) and the RAS/RAF/MEK signaling pathways [73–75]. DAG also activates TRPC6, and in podocytes this leads to increased calcium influx and the production of reactive oxidative species by NOX2 [24]. A renal phenotype has not been found in *PLCE1* knockout mice [72]. Enhanced podocyte PLC signaling in transgenic mice, however, results in podocyte injury and proteinuria [76]. PLCE1 likely also affects podocyte differentiation. *PLCE1* is expressed in the S-shaped body and capillary loop glomeruli. Children with *PLCE1* mutations have immature capillary loop glomeruli and a decreased expression of proteins that are characteristic of terminally differentiated podocytes such as NPHS1 and NPHS2 [72].

Recent findings support the possibility of cross-talk between the actin cytoskeleton regulators, slit diaphragm proteins, and podocyte calcium signaling. PLCE1 has a guanine nucleotide exchange factor domain on the N-terminus which allows PLCE1 to be stimulated by small GTPases that regulate the actin cytoskeleton, such as RAS and RHO [73]. PLCE1 forms a complex with Ras GTPase-activating-like protein IQGAP1 in podocytes [72]. IQGAP1 can form a complex with podocyte slit diaphragm proteins, including NPHS1 and NPHS2 [77], and is also regulated by binding to members of the RHO GTPase family. It can shift the balance between cell adhesion and migration, as it interacts with cell–cell adhesion molecules and the actin cytoskeleton. Silencing of IQGAP1 in podocytes leads to the depolymerization of F-actin and inhibits migration [77]. Thus, *PLCE1* mutations likely have multiple mechanisms of inducing podocyte injury, including effects on calcium signaling, the actin cytoskeleton, and podocyte differentiation.

Mutations in genes encoding mitochondrial proteins

The identification of mutations in mitochondrial genes led to the recognition of the importance of mitochondria to podocyte health. This includes a discovery of an A3243G mutation in the *MT-TL1* gene encoding leucine tRNA that causes a respiratory chain defect and induces FSGS [78]. Several genetic defects in the synthesis of mitochondrial coenzyme Q10 (CoQ_{10}) have been described that result in podocytopathies: mutations in *COQ2* gene (which encodes para-hydroxybenzoate-polyprenyl-transferase) were identified in some patients with early-onset nephrotic syndrome with or without neuromuscular symptoms [79]. Mutations in *PDSS2*, a gene coding the subunit 2 of the enzyme decaprenyl diphosphate synthase, were identified in some patients with Leigh syndrome with nephrotic-range proteinuria [80]. Mutations have also been identified in the *COQ6* gene, which encodes CoQ_{10} biosynthesis monooxygenase 6, in families with early-onset SRNS and sensorineural deafness [81].

How do mitochondria play a role in maintenance of podocyte health? CoQ_{10} is a component of the electron transport chain that is required for the synthesis of ATP. The finding of podocytopathy with CoQ_{10} deficiency suggests that podocytes may have a relatively high energy requirement to maintain podocyte health. In addition to energy production, the mitochondrial electron transport chain is the source of reactive oxygen species (ROS). CoQ_{10} acts to scavenge oxygen free radicals and limits the oxidation of DNA, RNA, and proteins by ROS. Genetic defects in CoQ_{10} synthesis are therefore likely to induce mitochondrial dysfunction and excessive

generation of ROS, resulting in podocyte injury and apoptosis. Congruent with this concept, knockdown of *COQ6* in podocyte cell lines and in zebrafish embryos caused apoptosis that was partially reversed by CoQ_{10} treatment [81].

Mutations in genes encoding lysosomal proteins

Homozygous truncating mutations of *SCARB2*, the gene that encodes lysosomal integral membrane protein LIMP-II, a β-glucocerebrosidase receptor, have been associated with action myoclonus–renal failure syndrome [82]. This is an autosomal recessive (AR) syndrome that presents in adolescents and young adults as collapsing FSGS and progressive myoclonic epilepsy [82]. The neurologic phenotype is similar to that seen with lysosomal storage diseases. Defects in autophagy, a cellular process of degradation of cell components that allows for recycling of cellular material, are associated with lysosomal storage diseases [83]. The components to be broken down are first engulfed in autophagosomes that then fuse with lysosomes. In lysosomal storage diseases, the autophagosomes are unable to fuse with the lysosomes, resulting in the accumulation of unfolded proteins, mitochondrial dysfunction, and cell death [83]. A role for autophagy in the maintenance of podocyte health is supported by genetic studies in mice. In one study, deletion of ATG5 (a major component of the autophagy machinery) in podocytes was found to increase susceptibility to glomerular disease [84]. Similarly, in another study, disruption of podocyte mammalian target of rapamycin (mTOR) signaling, a regulator of autophagy, resulted in disturbed autophagic flux and induced glomerulosclerosis in mice [85]. Thus, the dysregulation of autophagy can be considered as a potential mechanism for *SCARB2*-mediated podocyte injury.

Mutations affecting cell polarity

During embryogenesis, podocytes evolve from columnar epithelial cells of the S-shaped body into mature arborated cells with a complex polarity. Namely, mature podocytes have basal domains that attach to the GBM, apical domains that face the urinary space, and junctional domains of cell–cell contact at the slit diaphragm. These domains express distinct sets of membrane proteins, as is characteristic of polarized cells. The membrane on the apical side of foot processes contains negatively charged proteins, such as podocalyxin, podoplanin, podoendin, and protein tyrosine phosphatase receptor type O (PTPRO, also known as glomerular epithelial protein or GLEPP-1), which form a glycocalyx [86]. Podocalyxin is linked to the actin cytoskeleton and is necessary for normal foot process structure in mice [87]. Integrins are expressed in the basal domains and slit diaphragm proteins at the junctional domains. Consequently, polarized expression of proteins in podocytes may support proper cell–matrix and cell–cell adhesion.

Studies in mice have identified a role for the apico-basal polarity proteins partioning defective (PARD3/PAR6) and atypical protein kinase C (aPKC λ/ι) in establishing podocyte structure during nephrogenesis and in the development of glomerulosclerosis [88–90]. Mutations of the apical protein, PTPRO, have been identified in children with AR SRNS [91]. Another apical polarity protein, Crumbs (CRB2B), is required for proper podocyte structure and NPHS1 localization to the slit diaphragm in zebrafish [92]. Mutations in the human crumbs homolog *CRB2*, identified by exome sequencing in patients with FSGS, have recently been reported [93]. Actin dynamics may also affect podocyte polarity, as the deletion of podocyte RHO GTPase CDC42 in mice led to congenital nephrotic syndrome with decreased expression of NPHS1, Pard3, and aPKC [94]. Together, these data indicate that defects in cell polarity may induce podocyte injury and loss.

Genetic mutations in transcription factors

Mutations in WT-1, a nuclear transcription factor, are associated with both syndromic and sporadic SRNS. WT-1 is required for renal development, but its function in the mature podocyte remains incompletely understood. WT-1 likely affects podocyte differentiation, as *NPHS1* and podocalyxin genes are downregulated in mice with decreased levels of WT-1 [95]. WT-1 defects also induce podocyte apoptosis and loss [96].

The type of podocyte injury induced by WT-1 likely depends upon the location of the mutations. Mutations in exons 8 and 9, which code for zinc finger domains 2 and 3, are associated with Denys–Drash syndrome. Denys–Drash is characterized by the triad of congenital or infantile SRNS with diffuse mesangial sclerosis, XY pseudohermaphroditism (male-to-female sex reversal), and a high prevalence of Wilms tumors. Such mutations may lead to a truncation of WT-1 [97]. Truncated WT-1 may act as a dominant negative suppressor of wild-type WT-1, explaining the early onset and developmental phenotype [97].

In contrast, Frasier syndrome [98] is caused by the mutations in the donor splice site at intron 9 of the WT1 gene [99] and is characterized by FSGS, XY pseudohermaphroditism, and high risk of gonadoblastoma. The donor splice site mutations lead to a change in the balance of two splice variants (+KTS and −KTS). The balance of +KTS/−KTS is usually 2:1. Mutations at intron 9 changes the balance with increased −KTS versus +KTS variants [99]. The two KTS variants have distinct roles in the podocyte, with the −KTS variant tending to bind DNA and the +KTS variant being more prone to bind RNA than DNA [100]. Thus, the −KTS variant cannot

compensate for loss of the +KTS variant. The +KTS variant binds alpha-actinin1 mRNA; thus, dysregulation of the actin cytoskeleton may be the mechanism by which these WT-1 mutations induce podocyte injury [100].

LMX1B mutations are associated with the rare AD disorder Nail–Patella syndrome that is characterized by glomerulosclerosis and hereditary onychoosteodysplasia. LMX1B is a LIM homeodomain transcription factor. Mutations in this transcription factor typically occur in either its protein-binding LIM domain or its DNA binding domain. Loss of LMX1B leads to defective podocyte differentiation and GBM formation in mice [101]. Studies with podocyte-specific *LMX1B* knockout mice suggest that LMX1B also regulates podocyte motility, possibly via effects on the transcription of actin cytoskeleton-associated proteins [102].

Mutations in the GBM components

Podocyte injury can be the result of defects in other parts of the glomerular filtration barrier, such as in components of the GBM. *LAMB2* mutations were first described in patients with CNS characterized by DMS, in combination with complex ocular abnormalities and severe neuro-developmental deficits, known as Pierson syndrome [103]. *LAMB2* encodes laminin β2, an important glycoprotein component of the GBM, which binds α3β1 integrin, thereby linking podocytes to the GBM [104, 105]. Laminin binding to the GBM may also induce modulation of the actin cytoskeleton, as α3β1 integrin is coupled to the actin cytoskeleton through focal adhesion complexes. The original studies of *LAMB2*$^{-/-}$ mice suggested that podocyte injury occurs subsequent to GBM abnormalities, possibly due to excessive endocytosis of the filtered albumin [106].

The full Pierson syndrome phenotype is present when truncating mutations in *LAMB2* occur, whereas patients with missense mutations, such as R246Q and C321R, have nephrotic syndrome with significantly milder extra-renal defects [107]. Transgenic mice expressing R246Q mutant *LAMB2* have impaired laminin secretion [108]. The retention of mis-folded LAMB2 has been found to induce podocyte ER stress (detected by the production of the unfolded response protein CHOP) and autophagy activation [109]. Thus, increased podocyte ER stress is an alternative mechanism by which this genetic defect may induce podocyte injury.

Genetic variants associated with FSGS

Genetic variants in *APOL1* were identified initially in a genome-wide association study (GWAS) examining the association of single nucleotide polymorphisms (SNPs) with the development of hypertensive end-stage kidney disease in African Americans [110]. The initial analysis of the GWAS identified an association of this disease with SNPs in *MYH9*, which encodes a non-muscle myosin IIA heavy chain [111]. Missense mutations of *MYH9* have been found to be associated with AD giant-platelet syndromes, which may include sensorineuronal deafness, cataracts, and FSGS, consistent with a role for MYH9 in podocyte health [112].

However, mutations in MYH9 were not identified in the GWAS study, and further analysis revealed stronger linkage to two SNPs in the *APOL1* gene, termed G1 (S342G and I384M substitutions) and G2 (deletion of two amino acid residues, N388 and Y389) [110, 113]. These variants likely provide a selective advantage in Africa, where homozygous or compound heterozygous carriers of the *APOL1* G1 and G2 alleles have an improved capability to lyse the parasite *Trypanosoma brucei rhodensiense*, the cause of human African sleeping sickness [110]. *APOL1* risk alleles were subsequently identified in patients with FSGS.

The physiologic functions of APOL1 are not fully understood beyond its anti-trypanosomal effect. *APOL1* is widely expressed in different tissues, including podocytes, and also circulates as a component of high-density lipoprotein. There is some evidence that *APOL1* overexpression promotes autophagic cell death [114], but it is not clear whether circulating or podocyte-specific APOL1 is responsible for glomerular disease. However, glomerular staining for APOL1 was found to be decreased in cases of FSGS and human immunodeficiency virus-nephropathy [115]. It was also reported that transplanted kidneys with two *APOL1* risk alleles experience higher rates of early failure than kidneys with other genotypes [116]. These data suggest that the APOL1 expressed in the kidney may play some role in the development of glomerular disorders.

Conclusions and implications for future therapeutics

One of the most exciting prospects of the contributions of genetics to our improved understanding of the mechanisms that maintain podocyte health is the potential for new therapeutic options and personalized medicine. Therapeutics targeting regulation of the actin cytoskeleton, calcium signaling, ER stress, and autophagy are potential areas for investigation opened up by this knowledge. Furthermore, the increasingly less expensive potential to perform next-generation sequencing is likely to revolutionize our approach to the care of patients with FSGS and suggests the possibility for developing personalized treatment for specific genetic mutations [117]. However, some barriers remain to translating our understanding of genetics and podocyte health into optimization of patient care and clinical outcomes. We are only

now starting to have large-scale studies of ethnically diverse populations of children with nephrotic syndrome and FSGS to provide us with a detailed understanding of genotype–phenotype–environmental correlations, including response to therapy, risk for end-stage kidney disease, and recurrence after transplant.

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