Genetics of nephrotic syndrome: connecting molecular genetics to podocyte physiology

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Urinary losses of macromolecules in nephrotic syndrome (NS) reflect a dysfunction of the highly permselective glomerular filtration barrier. Genetic studies of hereditary forms of NS have led to the identification of proteins playing a crucial role in slit-diaphragm signalling, regulation of actin cytoskeleton dynamics, maintenance of podocyte integrity and cell–matrix interactions. This review will focus on recent molecular and clinical findings in the field of genetics of NS, thereby providing a better understanding of the complex glomerular filtration barrier physiology.

INTRODUCTION

Nephrotic syndrome (NS) is a heterogeneous group of disorders characterized by heavy proteinuria with hypoalbuminemia, edema and dyslipidemia. Urinary losses of macromolecules, such as albumin, reflect a dysfunction of the normally highly permselective glomerular filtration barrier (GFB) (1). The GFB consists of three interacting layers (Fig. 1): the glomerular fenestrated endothelium, the glomerular basement membrane (GBM) and the podocytes, with their interdigitated foot processes interconnected by the slit diaphragm (SD), a multiprotein structural and signalling complex. Two additional layers, the endothelial surface layer and the subpodocyte space, are now also considered as part of the major determinants of glomerular permeability (1,2). The GFB mainstone is the podocyte, which contains a highly dynamic cytoarchitecture exhibiting enormous plasticity in response to harmful events. Indeed, the profound morphologic changes (complete foot-process effacement, dedifferentiation and focal detachment) occurring during NS may be reversible in cases without a primary podocyte defect. GFB dysfunction may be secondary to an immune disorder or due to intrinsic podocytes defects. Accumulating data suggests that steroid-sensitive NS, as well as a subset of steroid-resistant NS (SRNS), particularly those with response to immunosuppressive agents and/or relapsing after kidney transplantation, have an underlying immune defect. Indeed, immediate and iterative recurrence of proteinuria after transplantation and the favourable effect of plasma exchange (3) or immunoadsorption (4,5) support the putative role of an unrecognized circulating permeability factor (6), whose production seems to follow T cell dysfunction, among immune forms of NS (7). Instead, SRNS cases without relapse after transplantation (8–10) as well as familial forms of SRNS, are generally due to a primary defect in the GFB, are resistant to other immunosuppressive agents and almost invariably progress to end-stage kidney disease (ESKD).

Whereas most of the cases with SSNS exhibit minimal glomerular changes distinguished by normal glomeruli at light microscopy and diffuse podocyte foot-process effacement on electron microscopy, cases with SRNS present with either focal segmental glomerulosclerosis (FSGS) or diffuse mesangial sclerosis (DMS). In addition to sclerosis, FSGS consists of foot process effacement in absence of glomerular immune complex deposits, although DMS is characterized by mesangial matrix expansion accompanied by hypertrophy and mild cobbblestone hyperplasia of podocytes. Indeed, DMS and FSGS result from a more sustained and severe injurious process which eventually leads to progressive podocyte loss and glomerular scarring.

Until the familial pattern of some glomerular diseases was recognized, little was known on hereditary NS (11). In the last decade, studies of familial cases of SRNS have led to the
identification of genes encoding proteins highly expressed in podocytes, but also elsewhere in the glomerular capillary wall, unravelling the basis of NS and GBF physiology (Table 1). Structural elements of the SD (nephrin, podocin and CD2AP) and actin cytoskeleton (α-actinin-4) (12–15) control podocyte differentiation and survival (16), cell polarity (17) and cytoskeletal dynamics (18) (Fig. 2). Podocyte and glomerular development are critically regulated by the transcription factor WT1 and phospholipase Cε1 (PLCε1) mediated signals (19,20). The calcium channel TRPC6, which localizes in membrane lipids supercomplex along podocin, regulates mechanosensation sensed at the SD (21), whereas the structural component of the GBM, laminin-β2, is essential for podocyte cell–matrix interactions (22). Podocyte integrity may also be affected by derangements in proteins involved in varied subcellular processes including the mitochondrial respiratory chain, DNA restructuring and repair and lysosomal function. Finally, identification of novel genetic determinants in glomerular disease, such as high risk haplotypes in the MYH9 gene (23,24) may also explain the increased risk of some adult patients to glomerular injury.

Advances in genetics of SRNS have significantly increased our understanding of GBF physiology providing insights into future promising therapeutic strategies. Genotype-phenotype correlations and recent molecular findings in the field of hereditary NS will be reviewed here.

**GENETIC OVERVIEW**

**Main autosomal recessive forms of NS**

Positional cloning has allowed identifying the main GBF players. Mutations in genes encoding nephrin, podocin and PLCε1 are responsible for most of the severe cases of congenital and early onset NS (Table 1, Fig. 3); however, it has been recently shown that mutations may be associated with less severe phenotypes, either given the type of mutation (mild mutation or non-silent polymorphisms) and/or because of modifier genes affecting the final phenotype (Fig. 3).

**NPHS1** encodes nephrin, the principal component of the SD, and has been identified as the major gene involved in congenital nephrotic syndrome (CNS) of the Finnish type, with the Finmajor (c.121delCT; p.L41fs) and Finminor (c.3325C>T; p.R1109X) mutations accounting respectively for 78 and 16% of the mutated alleles in Finnish patients (12). **NPHS2**, encoding podocin, is responsible for most of infantile SRNS cases. Recessive mutations in this gene account for 42% of familial and 10% of sporadic cases of childhood-onset SRNS (8.25) and have also been found in 39% of patients with CNS (26). Recessive truncating and missense mutations in **PLCE1**, encoding PLCε1, have been detected in early-onset NS showing DMS or FSGS on renal histology, respectively (20). Subsequent mutational analysis among children with DMS demonstrated that 28.6% of cases had **PLCE1** mutations (27), whereas no mutations had been found among adults with FSGS (28).

Interestingly, some **NPHS1** mutations have been associated with a milder clinical course characterized by preserved renal function and proteinuria reduction towards adolescence; usually cases are females, suggesting a gender modifier effect (29). Recently, **NPHS1** mutations have also been identified in patients with childhood-onset SRNS (30). Affected cases were compound heterozygotes for at least one mild missense mutation which exhibited normal trafficking to the plasma membrane. This contrasts with most of the nephrin and podocin missense mutants found in cases with very early-onset of hereditary NS (31,32), which are retained in the endoplasmic reticulum, thus acting as a null allele, and consequently leading to a severe phenotype. Therapeutic strategy relying on chemical chaperones allowing targeting of the mutant protein to the SD (33) may eventually ameliorate the clinical course of the disease. Intriguingly, compound heterozygous missense mutations were identified in two cases presenting subnephrotic persistent proteinuria and self-limited intermittent nephrotic flares triggered by upper respiratory tract infections (34). In vitro studies showed that one of these mutants, which was predominantly targeted to the plasma membrane, was unable to assemble into functioning membrane microdomains (35), thus probably hampering nephrin signalling and SD complex anchoring to the actin cytoskeleton. This observation raises the possibility that mild structural defects in the SD complex may predispose to progressive glomerular disease following intermittent environmental injurious events.

Similarly, genotype-phenotype correlations among cases with **NPHS2** mutations revealed that compound heterozygotes for one pathogenic **NPHS2** mutation and the p.R229Q variant (most frequent non-synonymous **NPHS2** polymorphism among European derived populations) may cause juvenile or adult-onset NS (36). Moreover, the renal phenotype variability among patients bearing podocin mutations suggests a role for modifiers genes. Analysis of **Nphs2** null mice phenotype revealed that glomerular disease progression and severity of histological lesions strongly depend on the genetic background and the maternal environment in which mice are nourished (37). In addition, it has recently been shown in mice that the transcript level of the Nphs2 gene is heritable and controlled...
by an ancestral *cis*-eQTL (38). These novel findings highlight the importance of putative modifier genes within podocyte-expressed genes in glomerular disorders and progression towards ESKD.

Table 1. Hereditary forms of Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Protein</th>
<th>Function</th>
<th>Phenotype or Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slit-Diaphragm protein complex</td>
<td>NPHS1</td>
<td>19q13.1</td>
<td>AR Nphrin</td>
<td>Main component of the SD. Anchors the SD to the actin cytoskeleton. Modulate signalling events related with actin cytoskeleton dynamics, cell polarity and survival</td>
<td>CNS of the Finnish type. Early-onset SRNS in cases carrying at least one mild mutation</td>
</tr>
<tr>
<td></td>
<td>NPHS2</td>
<td>1q25–31</td>
<td>AR Podocin</td>
<td>Scaffold protein linking plasma membrane to the actin cytoskeleton. Modulates mechanosensation</td>
<td>CNS. Early and late onset AR SRNS. Juvenile and adult SRNS in cases bearing the R229Q variant in compound heterozygous state with a pathogenic mutation</td>
</tr>
<tr>
<td></td>
<td>PLCE1</td>
<td>10q23</td>
<td>AR Phospholipase C1</td>
<td>Involved in cell junction signalling and glomerular development</td>
<td>Early-onset SRNS with DMS and FSGS</td>
</tr>
<tr>
<td></td>
<td>CD2AP</td>
<td>6p12.3</td>
<td>AR CD2 associated protein</td>
<td>Adapter protein, may anchor the SD to the actin cytoskeleton</td>
<td>Not precisely defined in humans, may cause early-onset SRNS and FSGS. Mice model exhibits a severe phenotype resembling CNS in humans</td>
</tr>
<tr>
<td></td>
<td>TRPC6</td>
<td>11q21–22</td>
<td>AD TRPC6</td>
<td>Receptor-activated non-selective calcium permeant cation channel. Involved in mechanosensation</td>
<td>Adult-onset SRNS with FSGS</td>
</tr>
<tr>
<td>Actin cytoskeleton components</td>
<td>ACTN4</td>
<td>19q13</td>
<td>AD α-actinin-4</td>
<td>F-actin cross-linking protein</td>
<td>Late-onset SRNS with incomplete penetration and slow progression to ESRD</td>
</tr>
<tr>
<td></td>
<td>MYH9</td>
<td>22q12.3</td>
<td>complex NMMHC-A</td>
<td>Cellular myosin that appears to play a role in cytoskeleton and cell shape</td>
<td>High risk haplotypes associated with increased risk of FSGS and ESKD in African-Americans</td>
</tr>
<tr>
<td>Nuclear proteins</td>
<td>LMX1B</td>
<td>9q34.1</td>
<td>AD LIM/homeobox protein</td>
<td>Podocyte and GBM development and maintenance</td>
<td>Nail-patella syndrome. NS in 40% of cases</td>
</tr>
<tr>
<td></td>
<td>SMARCAL1</td>
<td>2q35</td>
<td>AR LMX1B protein hHARP</td>
<td>ATP-dependent annealing helicase that rewind stably unwound DNA</td>
<td>Schimke immuno-osseus dysplasia</td>
</tr>
<tr>
<td></td>
<td>WT1</td>
<td>11p13</td>
<td>AD Wilms’ tumour 1</td>
<td>Zinc finger transcription factor that functions both as a tumour suppressor and as a critical regulator of kidney and gonadal development</td>
<td>Denys–Drash syndrome, Frasier syndrome, WAGR syndrome, isolated FSGS and DMS</td>
</tr>
<tr>
<td>Glomerular basement membrane proteins</td>
<td>LAMB2</td>
<td>3p21</td>
<td>AR Laminin-β2</td>
<td>GBM component, scaffold for type IV collagen assembly. Interactions with integrin α3β1 links the GBM to the actin cytoskeleton</td>
<td>Pierson syndrome</td>
</tr>
<tr>
<td></td>
<td>ITGB4</td>
<td>17q25.1</td>
<td>AR Integrin-β4</td>
<td>Cell-matrix adhesion, critical structural role in the hemidesmosome of epithelial cells</td>
<td>Epidermolysis bullosa. Anecdotic cases presenting with NS and FSGS</td>
</tr>
<tr>
<td>Mitochondrial proteins</td>
<td>COQ2</td>
<td>4q21–q22</td>
<td>AR Polypeptidyltransferase</td>
<td>CoQ10 biosynthesis, which transfers electrons from the mitochondrial respiratory chain</td>
<td>COQ10 deficiency, early-onset SRNS, with or without encephalomyopathy</td>
</tr>
<tr>
<td></td>
<td>PDSS2</td>
<td>6q21</td>
<td>AR Decaprenyl diphosphate synthase-2 tRNA-LEU</td>
<td>CoQ10 biosynthesis, which transfers electrons from the mitochondrial respiratory chain</td>
<td>COQ10 deficiency, Leigh syndrome and SRNS</td>
</tr>
<tr>
<td></td>
<td>MTTL1</td>
<td>mtDNA</td>
<td></td>
<td>Mitochondrial tRNA for leucine</td>
<td>MELAS syndrome. Mitochondrial diabetes, deafness and FSGS, with or without nephrotic syndrome</td>
</tr>
<tr>
<td>Lysosomal proteins</td>
<td>SCARB2</td>
<td>4q13–21</td>
<td>AR LIMP II</td>
<td>May act as a lysosomal receptor</td>
<td>Action myoclonus renal failure</td>
</tr>
</tbody>
</table>

(AR) autosomal recessive, (AD) autosomal dominant. In certain cases, mutations in *WT1*, *LAMB2*, *COQ2* and *PDSS2* can be associated with isolated SRNS. A locus for SSNS has been mapped on chr 2p12–13.2. Two loci on chr 14q24.2 and 11q24 have been mapped in cases with SRNS and deafness of AR and AD inheritance, respectively.

*a*Only protein functions directly related with podocyte physiology and NS are listed.

Milder phenotypes have also been described with *PLCE1* mutations, including sustained complete remission in two cases with truncating mutations (20,39). A striking observation has been the identification of unaffected siblings bearing inactivating
mutations in both alleles as the corresponding index case (20). We have also identified three asymptomatic adults from three unrelated families bearing homozygous mutations with at least one affected sibling haploidentical to the unaffected cases (Antignac, unpublished). These observations open the question of whether incomplete penetrance or therapy response particularly at critical phases during podocyte development may be due to the modifier role of podocyte specific genes or to individual differences due to the compensatory effect of other PLCs highly expressed on podocytes.

The undefined phenotype of mutations in CD2AP

CD2AP encodes the CD2 adaptor protein (CD2AP). In spite of a clear association of CD2AP defects with glomerular disease in animal models (40), little is known about the human phenotype associated with CD2AP mutations. Cd2ap knockout mice have a severe phenotype, in contrast to Cd2ap haploinsufficient mice which develop minor glomerular changes, without proteinuria (14). One heterozygous splice-site mutation in two patients with primary FSGS leading to a reduced expression of CD2AP in lymphocytes has been described (14). A recent study found three unrelated cases bearing heterozygous mutations associated with defective CD2–CD2AP interaction in T-lymphocytes as well as down-regulation of CD2AP, podocin and nephrin glomerular expression on renal biopsies (41). Interestingly, a homozygous mutation has been found in a 10-month-old patient with FSGS, resulting in a decreased F-actin binding efficiency in vitro and no expression of the mutated allele in lymphocytes. Both heterozygous parents were clinically unaffected (42). Because CD2AP mutations reports are scarce and complete segregation data are not available in cases with CD2AP heterozygous mutations, the phenotype and pattern of inheritance of CD2AP mutations or its putative role in the susceptibility to develop glomerular disease in humans remain uncertain.
Autosomal dominant forms of FSGS

Familial forms of NS of autosomal dominant (AD) inheritance are rare, occurring mostly among juvenile and adult cases. So far, mutations in the \textit{ACTN4} and \textit{TRPC6} genes, encoding \(\alpha\)-actinin-4 and the transient receptor potential cation channel 6 (TRPC6), respectively, have been involved in this form of NS (15,43). Nevertheless, most families with AD FSGS do not have mutations in these two genes (21,44).

Recently, an additional locus to AD FSGS and deafness has been mapped to chromosome 11q24 (45). Individuals bearing \textit{ACTN4} missense mutations have FSGS with an incompletely penetrant phenotype: proteinuria develops within the second decade of life and disease progresses to ESKD by 50 years of age (15,44,46,47). On the other hand, patients with \textit{TRPC6} mutations also exhibit an incomplete penetrant phenotype, but present with FSGS in their third or fourth decade of life (48).

FUNCTIONAL ROLES OF THE MAIN PODOCYTE PROTEINS

Slit-diaphragm signalling complex and regulation of the actin cytoskeleton dynamics

Previously seen as a static molecular sieve, the SD is now known as a dynamic signalling complex interacting with the submembranous cytoskeleton for maintaining the podocyte architecture and the function of the glomerular filter of the kidney (Fig. 2). Nephrin, podocin and CD2AP are considered as the main structural elements of the SD. Nephrin, a single-pass transmembrane protein of the immunoglobulin superfamily, homodimerizes and forms heterodimers with its homolog NEPH1, thus connecting adjacent foot-processes and transducing signals that control glomerular permeability (49). Nephrin interacts through its C-terminal part with podocin, a transmembrane harpin-like scaffolding protein, and with CD2AP, an adapter protein also found on the surface of T-cells and natural killer cells. The nephrin/NEPH1 complex transduces phosphorylation-mediated signals that assemble an actin polymerization complex at the podocyte intercellular junction. Indeed, nephrin/NEPH1 complex recruits Grb2 and Nck1/2 adaptor proteins (18), which mediate downstream activation of the cytoskeletal regulators N-WASp and Pak (50). In addition, nephrin phosphorylation by Fyn kinase increases its interaction with phosphatidylinositol 3-kinase (PI3K) and the subsequent PI3K-dependent activation of Akt and Rac modifies actin cytoskeleton (51), confirming the determinant role of nephrin signalling on podocyte morphology. Similarly, CD2AP has been implicated in the PI3K/AKT survival pathway (52) and in dynamic actin remodelling (53). Another function of the nephrin/NEPH1 complex is the regulation of podocyte cell polarity, via its binding with Par3, Par6 and atypical protein kinase C (aPKC) complex (17). The aPKC signalling is fundamental to glomerular maintenance and development, as shown in mice with podocyte-specific deletion of aPKC\(\alpha\), resulting in mislocalization of the SD and NS (54).

The critical importance of an intact podocyte actin cytoskeleton has been highlighted by the fact that mutations in the actin-bundling protein \(\alpha\)-actinin-4 lead to AD FSGS. Exposure
Thus, the calcineurin-NFAT pathway may be a potential mechanism that enhances basal NFAT-mediated transcription in cultured podocytes (64). The absence of PLC-β1, a protein and interacting partner of nephrin implicated in cell adhesion (59), the TRPC6 channel activity, it has also been suggested that nephrin are a target of the tyrosine kinase Fyn, which increases calcium signals. Interestingly, mutations in TRPC6 among cases with AD FSGS (43), unexpectedly added an ion channel to the list of SD signalling molecules and provided new insight into mechanosensation. In addition to its role in ion homeostasis, cell growth and PLC dependent calcium entry into cells (60), TRPC6 is a sensor of mechanically and osmotically induced membrane stretch (61) and is regulated by a podocin–lipid complex that might translate mechanical tension to ion channel action (62). As both TRPC6 and nephrin are a target of the tyrosine kinase Fyn, which increases the TRPC6 channel activity, it has also been suggested that TRPC6 is assembled in a complex together with nephrin and Fyn at the SD (63). In vitro experiments revealed that several TRPC6 mutants show increased current amplitudes; in addition, TRPC6P112Q exhibited an augmented angiotensin II-dependent calcium influx (43), leading to the hypothesis that mutations may disrupt podocyte cell function by amplifying calcium signals. Interestingly, TRPC6 mutations also enhance basal NFAT-mediated transcription in cultured podocytes, a pathway that can be blocked by inhibitors of calcineurin, calmodulin-dependent kinase II, and PI3K (64). Thus, the calcineurin-NFAT pathway may be a potential mediator of FSGS and calcineurin inhibitors may have a therapeutic role by blocking TRPC6 downstream signalling events.

Podocyte mechanosensation and modulation of signals leading to glomerular disease

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DERANGEMENTS OF PODOCYTE CELL–MATRIX INTERACTIONS

Laminins are heterotrimeric extracellular matrix proteins consisting of α, β and γ subunits that provide the basic scaffold for assembly of type IV collagen, nidogen/entactin and sulphated proteoglycans in GBM (65). Laminin-521 (α5, β2 and γ1) is the most important β2-containing laminin isofrom and is specifically expressed in the GBM and at some other sites, including intraocular muscles (66). Mutations in LAMB2 gene cause Pierson syndrome (67), an autosomal recessive (AR) disorder initially described as a severe lethal phenotype, characterized by CNS with DMS, rapidly progressing renal dysfunction and ocular malformations with microcoria as the leading feature. Blindness and neurodevelopmental deficits were noted in patients surviving infancy (68,69). The clinical spectrum of Pierson syndrome has been extended to milder phenotypes, including infantile- or childhood-onset NS (70,71), variable or even lacking ocular abnormalities (71,72) and renal survival at 16 years of age (71). This suggests that genetic modifiers may play a role in the phenotypic variability of cases with Pierson syndrome. Laminin receptors expressed on the basal side of podocytes foot processes include integrin α3β1 and dystroglycan which link the GBM to the intracellular actin cytoskeleton through a set of integrin and actin-associated proteins that include paxillin, talin, vinculin, α-actinin and filamin (22) (Fig. 2). The importance of podocyte cell–matrix interactions, although extensively confirmed by the severe disease phenotype of LAMB2 mutations in humans, has been emphasized by a conditional mouse model exhibiting podocyte-specific deletion of integrin-linked kinase (ILK), which is a downstream mediator of integrin β1 activity (73). In this model, GBM alterations preceded podocyte damage and the development of glomerulosclerosis, suggesting that alteration in matrix assembly subsequent to ILK deletion via modified integrin is responsible for the renal phenotype (73).

INHERITED DEFECTS OF MITOCHONDRIAL AND LYSOSOMAL COMPONENTS LEADING TO PROFOUND PODOCYTE DYSFUNCTION

Renal dysfunction due to mitochondrialopathies is infrequent, and may be a consequence of mutations in the mitochondrial or nuclear genomes (Table 1). Coenzyme Q10 (CoQ10) is a lipophilic molecule that transfers electrons from mitochondrial respiratory chain complexes I and II to complex III (74). Deficiency of CoQ10 has been associated with encephalomyopathy and multisystemic involvement, including NS (75–77). The COQ2 gene encodes the para-hydroxybenzoate-polyphenyltransferase enzyme, which is part of the CoQ10 pathway (74,78). COQ2 mutations have been identified in patients presenting with early-onset NS, severe oliguric renal failure, collapsing glomerulopathy with or without neuromuscular symptoms (79). The PDSS2 gene encodes a subunit of decaprenyl diphosphate synthase, the first enzyme of the CoQ10 biosynthetic pathway (80). Mutations in the PDSS2 gene have been recently described in a patient with Leigh syndrome, CoQ10 deficiency and NS (80). CoQ10 supplementation rescues the renal disease in Pdss2kd/kd mice (81). Thus, early CoQ10 supplementation may be crucial for renal symptoms resolution and prevention of neurological damage, as recently demonstrated in patients with CoQ10 deficiency due to COQ2 mutations (82). Finally, mutations in the tRNALeu(UUR) gene are associated with MELAS syndrome (83), which may include FSGS nephropathy (84,85).
Homozygous truncating SCARB2 mutations have been associated with action myoclonus-renal failure syndrome (86), an AR disorder presenting in young adults and characterized by collapsing FSGS and progressive myoclonic epilepsy. SCARB2 encodes the lysosomal integral membrane protein LIMP-2, which is a receptor for lysosomal mannose-6-phosphate-independent targeting of β-glucocerebrosidase (βGC) (87). βGC is a lysosomal enzyme deficient in most cases of Gaucher disease, leading to the accumulation of its substrate, glucosylceramide (GlcCer). Although decreased βGC activity and protein expression have been shown in LIMP-2 deficient mice (87), residual βGC activity may be sufficient to prevent GlcCer accumulation to levels at which more significant Gaucher-like pathologies might be seen. The pathophysiological events leading to glomerular disease in cases with SCARB2 mutations remain unknown.

COMPLEX GENETIC DETERMINANTS OF GLOMERULAR DISEASE: THE ROLE OF MYH9

An exceptional example of the genetic complexity of NS was shown by two independent studies demonstrating a strong association of common genetic variants in the MYH9 gene with FSGS and non-diabetic ESKD (23,24). Pathogenic mutations in the MYH9 gene, encoding the molecular motor protein non-muscle myosin heavy chain type II isoform A (NMMHC-A), are associated with the AD giant-platelet disorders which may include sensorineural deafness and glomerular disease. Recently, multiple linked non-coding SNPs in MYH9 were found to confer two to four times increased risk of ESKD in African Americans compared with European Americans (23). Moreover, the presence of the same risk haplotype was associated with almost a 5-fold increased risk of FSGS (24), accounting for a large proportion of the excess risk of ESKD and FSGS observed in African compared with European Americans. It has been demonstrated that NMMHC-A acts as a component of the podocyte cytoskeleton, contributing to its contractile functions (88,89); however, the underlying pathophysiological events occurring at the podocyte cytoskeleton associated with MYH9 high-risk haplotypes remain unknown.

CONCLUSION

In the last decade, it has been shown that the vast majority of patients with congenital onset of NS and a major proportion of those presenting in early childhood have an underlying Mendelian disorder. Among adults, hereditary forms of NS are uncommon, although oligogenic and complex inheritance may account for a significant percentage of cases previously regarded as idiopathic, as recently shown in African-Americans with FSGS and non-diabetic ESKD. Moreover, cases thought to be of immune origin may have a primary underlying genetic defect, as suggested by individuals presenting with familial forms of steroid-sensitive NS (90–92), as well as animal models exhibiting AR FSGS and relapsing proteinuria after kidney transplantation (93,94). Independent of the subjacent etiology of NS, unravelling the complexity of the pathophysiological events altering the stability of the glomerular permselectivity barrier may elucidate potential strategies to treat this devastating syndrome; such is the case of chemical chaperones experimentally used in vitro to redirect nephrin and podocin missense mutants to the plasma membrane which are abnormally retained in the endoplasmic reticulum.

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Conflict of Interest statement. All the authors state that they do not have any personal or professional potential conflict of interest. The Institut national de la santé et de la recherche médicale (INSERM) has submitted a French patent (INPI n° FR00 00709 and an international patent (FR01/00188), entitled “Identification of the NPHS2 gene implicated in the steroid-resistant nephrotic syndrome an its potential applications” filed on the 20.01.2000. A “License Agreement” (99301) was reached with Athena Diagnostics on 18.11.2001.

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