

Inherited Podocytopathies: FSGS and Nephrotic Syndrome from a Genetic Viewpoint

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Recent progress in defining the genetic basis of inherited glomerular disease has helped illuminate inadequacies in the way we describe many of these diseases. Too often, we talk about histologic patterns of injury, such as focal and segmental glomerulosclerosis (FSGS), as if they were diseases rather than descriptions of kidney biopsy specimens at particular points in time. Some patients “with FSGS” respond to steroids, some do not; some patients present with nephrotic syndrome (NS), others with mild proteinuria; some present in childhood, some as adults. FSGS can be primary or secondary to other primary processes. Pathologists may further subdivide FSGS (for example, into collapsing nephropathy, glomerular tip lesion, cellular variant). Some, but not all, FSGS recurs in transplanted kidneys. Do these phenotypic differences reflect differences in the underlying biology of the disease? Is the phrase “focal segmental glomerulosclerosis” as a clinical diagnosis very meaningful, or is it too far downstream from the biologically important disease process? Will genetics help us to understand the biologic basis of the similarities and differences between individuals diagnosed with proteinuric disease? Will genetic testing help guide our therapy?

These questions are clinically significant. FSGS, broadly defined as a pattern of injury, is a major cause of renal failure and is increasing in frequency (1). We need to know how many biologically distinct diseases cause the histopathology we call FSGS and how best to distinguish these diseases to determine how best to treat patients whose biopsies show this lesion. Certainly FSGS and non-glomerulosclerotic disorders of the podocyte are complex and overlapping phenotypes involving the interplay of genetic and environmental factors. Here we will review recent progress in the understanding of the genetic basis of FSGS and NS. The forms of FSGS we will focus on in our discussion here belong to that subset of patients in whom the FSGS lesion is a downstream response to podocyte injury.

Mendelian Genetics

Studies of Mendelian forms of disease have provided (and will continue to provide) some of the most novel insights into

the mechanisms of human disease. Clinicians have observed familial aggregation of proteinuric disease for quite some time, though recognition of these entities have not been widespread. For over half a century, there have been scattered reports in the medical literature of familial nephrosis (2). Four siblings with nephrotic syndrome were described in a 1957 report (3). Pathology showed minimal change disease in some children, FSGS in others. The absence of disease in the parents suggested recessive inheritance. Additional scattered reports of both single-generation and multigeneration disease have continued to appear in the case literature (4–9). Of course, familial disease is not always inherited; multiple members of a family may be exposed to the same environmental insults. However, recent studies of Mendelian disease have begun to clarify the clinical spectrum of the group of disorders that make up familial FSGS and familial nephrotic syndromes. Studies involving genetic manipulations in mice have identified additional genes involved in regulating the normal podocyte phenotype and in the development of FSGS. In the last several years, entirely novel proteins have been identified by purely positional genetic approaches taken to identify the most upstream cause of two childhood forms of nephrotic syndrome (Table 1).

Genetics

Congenital nephrotic syndrome of the Finnish type (CNF), a disease of in fact widespread geographical distribution, is characterized by autosomal recessive inheritance and the development of severe nephrosis *in utero* (10). The nephrosis in CNF is massive; neonates have on the order of 20 to 30 g/d proteinuria and typically die from nephrotic complications (rather than renal failure) at a young age unless nephrectomy and renal transplantation are performed. In the absence of renal transplantation, mortality approaches 100%. Infection, growth retardation, prematurity, and the development of renal insufficiency are common (11). Obligate heterozygotes (parents of CNF infants) have no apparent phenotype, though prenatal proteinuria (evidenced by elevated AFP) is observed in a substantial number of heterozygotes.

Kestila *et al.* (12) mapped the CNF gene to chromosome 19q13 by means of a genome-wide linkage analysis. Subsequently, NPHS1, the CNF gene, was cloned by positional methods (13,14). The NPHS1 gene spans 26 kb of genomic DNA and contains 29 exons (15). The gene product, called nephrin, is a 185-kD protein containing eight Ig C2 motifs, a fibronectin III-like domain, and a single transmembrane seg-

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Table 1. Known genes for non-syndromic podocytopathies

Disease	Locus	Inheritance	Gene	Protein	MIM Number*	Reference
Congenital nephrotic syndrome	19q13.1	AR	NPHS1	nephrin	602716	[14]
Steroid-resistant NS	1q25-32	AR	NPHS2	podocin	604766	[36]
FSGS	19q13	AD	ACTN4	α -actinin-4	604638	[50]

* Mendelian Inheritance in Man number.

ment. Nephrin is predominantly expressed in the podocyte, where it localizes to the slit diaphragm (16–19).

Evidence now suggests a role for nephrin in regulating signaling pathways. Nephrin activation can stimulate mitogen-activated protein kinases, and this signaling is enhanced by podocin (see below) (20). Localization to the signaling domains known as lipid rafts has been demonstrated (19,21).

Two NPHS1 mutations, termed Fin major (the deletion of nucleotides 121 to 122 leading to a frameshift) and Fin minor (encoding a premature termination signal at amino acid 1109) cause most of the congenital nephrotic syndrome in Finland. However, a long and growing list of disease-associated mutations exists and includes missense and splicing as well as truncation mutations (22–25). Defective nephrin trafficking has been demonstrated experimentally for some nephrin mutations (26). Frank disease is evident only in individuals with defects in both nephrin alleles. However, *in utero* proteinuria has been described in heterozygotes for nephrin mutations (27). In addition to the high prevalence in Finland, NPHS1 mutations are common in Mennonites in Lancaster County, Pennsylvania (28). In the Groffdale Conference Mennonites, the incidence is 1 in 500 live births, and 8% of this population carry a mutant NPHS1 allele.

In a significant fraction of affected children, the development of less severe proteinuria is observed post-renal transplantation. In recent studies, NS developed in 20 to 25% of kidneys transplanted into Finnish children with CNF. A high percentage of these patients displayed anti-glomerular and anti-nephrin antibodies (29,30). The development of anti-nephrin antibodies is certainly a plausible disease mechanism, as the nephrosis-inducing monoclonal antibody mAb 5-1-6 has been shown to identify the extracellular domain of nephrin (31).

The ability to perform antenatal diagnosis of CNF is much improved with the identification of NPHS1. In Finland, where CNF is frequent, high concentrations of alpha-fetoprotein have traditionally been used for prenatal diagnosis of CNF. However, prenatal proteinuria and elevated AFP is observed in fetuses both heterozygous and homozygous for NPHS1 defects (27). Particularly in Finland, where two mutations account for 95% of disease, testing for just these two alleles can provide a low-cost and highly sensitive screening test. Carrier status of the Fin major and Fin minor alleles can be easily identified before conception, and prenatal testing offered if appropriate.

Like humans with two mutant NPHS1 alleles, mice homozygous for targeted disruption of nephrin have neonatal nephrosis (32–34). Interestingly, nephrin knockout mice initially show

fairly normal-appearing podocytes despite abnormal-appearing slit diaphragms, suggesting that nephrin's primary role is functional rather than developmental (34).

Familial NS: Recessive

A distinct form of NS was described by Fuchshuber *et al.* (35,36) characterized by recessive disease, early onset, resistance to steroid therapy, and rapid progression to end-stage kidney failure. Most affected children showed an FSGS pattern on renal biopsy, though some showed minimal change disease (MCD). The gene for this second recessive podocytopathy was mapped to chromosome 1q25–31 and subsequently cloned. The responsible gene, NPHS2, encodes a membrane protein named podocin. Podocin is predicted to encode a 383-amino acid integral membrane protein of approximately 42 kD. It exhibits homology to stomatin family proteins and MEC-2, part of the mechanosensing apparatus of *C. Elegans*, thought to link ion channels to the cytoskeleton (37). Podocin has been localized to the slit diaphragm and has now been shown to interact directly with nephrin (19,20,38,39).

The NPHS2 gene is encoded by eight exons. This relatively small number facilitates mutational analysis of human DNA. Several papers have helped define the mutational spectrum of NPHS2-associated disease. A substantial number of the reported mutations encode truncated proteins, suggesting that disease results from a loss of function of NPHS2 (40–44). Most affected individuals in these reports presented with disease in early childhood. R138Q appears to be a common disease-causing variant, and has been observed in several families without recent common ancestors. R138X seems to be particularly common in Arab-Israeli children with steroid-resistant nephrosis (40).

Podocin is responsible for disease in a sizable fraction of both familial and nonfamilial instances of childhood-onset recessive FSGS. Fuchshuber *et al.* (44,45) found NPHS2 mutations in 46% of such families. Recent studies suggest that NPHS2 mutations underlie disease in 20 to 30% of children with sporadic steroid-resistant nephrotic syndrome.

A recent report described assays of glomerular permeability in five patients with recessive NPHS2-associated NS (46). Plasma permeability activity was high in all cases. On the basis of assays performed on urine, the authors concluded that there is loss of plasma permeability inhibitors in these individuals. Two of four patients receiving a renal allograft had recurrent proteinuria that responded to treatment with plasmapheresis. This observation complicates our interpretation of glomerular

permeability assays, as they suggest that alterations in this activity may be an effect, in addition to being a cause, of NS. It also illustrates that while recurrent FSGS is more rare in familial forms of disease, it does occur.

Growing evidence suggests a podocin-nephrin interaction at both a protein-protein and at a genetic level. Direct physical interactions have been demonstrated (19,20). There is also evidence of a genetic interaction. Koziell *et al.* (24) have presented genetic data suggesting that the presence of a single NPHS2 may modify the course of NPHS1-associated congenital nephrosis.

Recessive steroid-resistant NS is genetically heterogeneous. In their initial article mapping SRN to chromosome 1q25–32, Fuchshuber *et al.* (35) identified one large family unlinked to this locus. Our own unpublished data also suggests heterogeneity in recessive disease. Given the existence of several recessive loci for NS in mice, genetic heterogeneity in human disease is not surprising. Electron micrographs from patients with ACTN4 and NPHS2 associated disease are shown in Figure 1.

Steroid-Responsive Nephrotic Syndrome

Fuchshuber *et al.* (41) recently reported a group of families with familial steroid-responsive nephrotic syndrome and apparent autosomal recessive inheritance. Age of onset is typically low, with a median age of onset at 3.4 yr in this report. Exclusion of NPHS2 as a cause for disease demonstrated that this disease is biologically and genetically distinct from the other forms of recessive childhood nephrosis. It is unknown whether this disease is a primary podocytopathy *versus* an extrarenal abnormality (*e.g.*, an inherited T cell disorder).

Autosomal Dominant Disease

Autosomal dominant forms of FSGS are typically of later onset and more slowly progressive than recessive forms (47–49). Two genetic loci have been identified, but these loci seem to be responsible for only a fraction of dominant disease. Mutations in ACTN4, the α -actinin-4 gene, cause a slowly progressive form of disease characterized by dominant inher-

itance, generally subnephrotic proteinuria, and renal insufficiency. The penetrance of ACTN4-associated disease is high but not 100%; in these families, a small number of individuals carry disease-associated mutations but have no proteinuria or renal insufficiency.

ACTN4 is one of four actinin genes. The four genes encode highly homologous proteins, which are biochemically similar (except for the difference in the calcium sensitivity of a C-terminal EF hand). The α -actinins all encode approximately 100-kD head-to-tail homodimers. ACTN4 is the only actinin significantly expressed in the human glomerulus (50). The identified ACTN4 mutations are all missense, and increase the affinity of the encoded protein to filamentous actin (50). α -actinin/actin affinity affects mechanical properties of actin gels, these mutations, among other effects, may alter the mechanical properties of the podocyte (51). This form of disease appears to be more rare than NPHS1- and NPHS2-associated nephrosis.

Most families with autosomal dominant FSGS do not map to ACTN4. Winn *et al.* (52) mapped a family with dominant disease to chromosome 11q. Most families large enough for Mendelian genetic methods to be useful exclude both the ACTN4 locus on chromosome 19q13 and this 11q locus. It is unknown whether or not disease in most of these families is due to inherited podocyte defects or defects in genes which alter the response to some primary injury (*e.g.*, mediators of cell growth, cell division, fibrosis, etc.)

Syndromic Disease

Podocyte disease is also seen as part of well-defined inherited syndromes. The best described of these is the spectrum of disease seen with WT1 mutations. WT1, a transcription factor, was positionally cloned on the basis of its role in the development of Wilms tumor (53,54). Frasier syndrome and Denys-Drash syndrome are related and overlapping syndromes caused by mutations in WT1 (55–58). Both syndromes are characterized by the development of male pseudohermaphroditism and glomerular disease. Frasier syndrome is caused by donor splice mutations in intron 9 of WT1. An FSGS pattern is seen on renal biopsy. Frasier syndrome can present as FSGS in 46,XX females in association with gonadal malignancy (59,60). WT1 mutations do not appear to be a significant cause of isolated glomerular disease in the absence of other genitourinary features (61). Denys-Drash syndrome (DDS) is a related disorder characterized by diffuse mesangial sclerosis on renal biopsy, genitourinary tumors, and pseudohermaphroditism. A different spectrum of mutations is associated with DDS, most commonly in exon 9 of the WT1 gene (55,62).

Although Nail-Patella Syndrome is typically thought of as a disease of the basement membrane rather than the podocyte, it is probably both. Individuals with this autosomal dominant disorder typically demonstrate dysplastic nails, absent or hypoplastic patellae, and nephropathy. Although altered GBM typically predominates on histologic analysis, the renal disease is highly variable and can present as nephrotic syndrome (63). The responsible gene is the *lmx1b* transcription factor (64,65). *Lmx1b* contributes to the transcriptional regulation of matrix proteins by the podocyte (66,67) as well as regulation of the

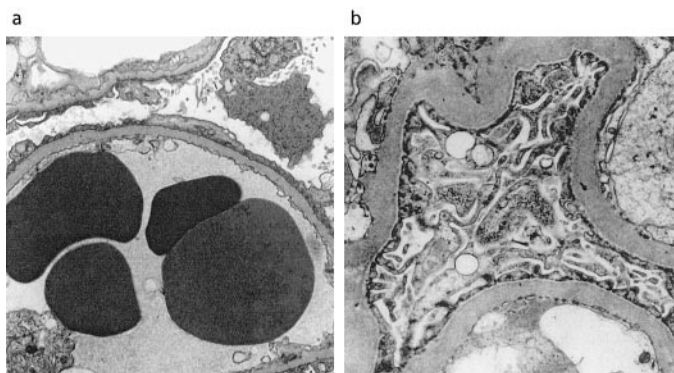


Figure 1. Electron micrographs from FSGS patients with (a) two mutant NPHS2 (podocin) alleles and (b) one mutant ACTN4 allele. EM (a) courtesy of Drs. Bernard Kaplan and Pierre Russo. EM (b) courtesy of Dr. Helmut Rennke.

podocyte genes CD2AP and NPHS2 (68,69). Other rare inherited syndromes are associated with an increased incidence of FSGS lesions. Charcot-Marie Tooth disease (70) and the Galloway-Mowat syndrome (71) are both forms of inherited neuropathy in which nephrosis and/or FSGS are seen with increased frequency.

The Possible and the Actual: Animal Models

Observing natural variation in humans helps elucidate the actual causes of disease that may have developed as past mutational “accidents.” Understanding this variation helps understand disease pathways, even when these variations are quite rare. On the other hand, experiments in model organisms (like mice) allow us to investigate the role of genes and gene products in biologic pathways, whether or not actual genetic variation in these genes mediate human disease. Multiple genes have been identified that encode products critical to the normal podocyte phenotype in mice.

Mice with a targeted disruption of CD2AP develop severe nephrosis. CD2AP was originally identified as an approximately 80-kD SH3 domain-containing protein involved in stabilizing contacts between T cells and antigen-presenting cells (72). However, the major phenotype in CD2AP deficient mice is renal; mice die at 6 to 7 wk from kidney failure. Histology shows podocyte foot process effacement, mesangial cell hyperplasia, and glomerulosclerosis (73). CD2AP localizes to the slit diaphragm and directly interacts with the C-terminal portion of nephrin (39,74). Together, these results support a role for CD2AP in mediating nephrin signaling.

Mice lacking NEPH1, a nephrin homolog sharing structural features as well as high renal expression with nephrin, develop severe nephrosis and die perinatally (75). Electron microscopy studies showed podocyte expression of NEPH1, and, in NEPH1-deficient mice, diffusely effaced foot processes. Other nephrin homologs may be similarly important in slit diaphragm function. Studies of nephrin family members in model organism (*e.g.*, hibiris and sticks-and-stones in drosophila [76,77]) may help clarify the biology of these molecules. Despite the high degree of homology, human and mouse genetics suggests that the functions of these molecules are non-redundant.

A variety of other mouse models develop podocyte abnormalities. Mice deficient in RhoGDI α , a regulator of the Rho GDP dissociation inhibitor family, develop massive nephrosis (78). The importance of the Rho pathway in mediating cytoskeletal rearrangements again points to a dysregulated cytoskeleton as the cause of this phenotype. Mice deficient in Fyn, a member of the Src family of tyrosine kinases, develop a lymphocyte-independent form of proteinuria (79). Mice with an interruption in the MPV17 gene, which encodes a preoxisomal protein that regulates MMP2 production, develop FSGS (80–82). Podocalyxin-deficient mice exhibit multiple renal and nonrenal abnormalities, including failure of the podocytes to form foot processes (83). Mice deficient in GLEPP1, a tyrosine phosphatase on the podocyte surface, have severely altered podocyte morphology. Foot processes are widened, intermediate filament distribution is altered, and mice have lower GFR despite the absence of albuminuria. This model in

particular supports the notion that specific and separable functions can be assigned to the various gene products that cause mouse and human podocytopathies (84).

TGF- β transgenic mice have increased plasma levels of TGF- β and exhibit glomerulosclerosis (85). Although the primary defect is not in the podocyte, podocyte depletion appears in these mice as a direct effect of Smad7-amplified TGF- β signaling (86). Thus, podocyte damage may not just initiate fibrotic pathways, their structure may be directly affected as well, accelerating the process.

A variety of rat models develop proteinuria and progressive kidney disease. Among the most interesting is the Buffalo/Mna rat. These rats develop proteinuria and FSGS histology at 2 mo of age. Disease recurs in transplanted kidneys; however, when Buf/Mna serve as kidney donors, the glomerulopathy regresses (87). One locus partially responsible for the glomerulopathy has been mapped to a region of rat chromosome 13 named *Purl* and partially overlaps the rat region syntenic to the NPHS2 locus (88). These rats also develop thymoma and anti-ryanodine receptor antibodies. This phenotype supports the notion that a circulating factor is responsible for the kidney lesion. Genetic differences that alter the activity of a circulating factor in rats increase the suspicion that variation in genes involved in the encoding or the metabolism of such factor(s) may also be important in human disease (89,90).

Genetic models relevant to NS/FSGS are not limited to rodents. For example, a very high percentage of cheetahs, a species with minimal genetic diversity, develop glomerulosclerosis and renal failure (91).

Secondary Disease

The role of human podocytopathy genes in acquired disease is a subject of ongoing investigation. Some of these studies have noted increased nephrin expression in specific animal models of disease, others decreased expression in a different set of models (92–96). Results from human studies have not yet provided a clear unifying picture of the nature and role of nephrin expression in acquired glomerular disease (97,98).

Clinical Spectrum of Disease

Why do different defects in the podocyte lead to different clinical presentations? NPHS1-, NPHS2-, and ACTN4-associated disease forms a spectrum from onset before birth, to childhood onset, to adult onset disease. One simple hypothesis to explain the clinical presentations could be presented essentially as follows. Severe structural defects in the podocyte (*e.g.*, no nephrin) present as severe nephrosis; individuals with more subtle defects in the podocyte (*e.g.*, α -actinin-4 mutations) present with chronic, milder proteinuria, and the secondary glomerulosclerotic response is the major clinically apparent phenotype. This is not the only reasonable hypothesis, however. Perhaps mutations in FSGS genes perturb a different biologic pathway than NS genes. This possibility is raised by the suggestion that patients with two defective NPHS1 alleles and a third mutation in NPHS2 show a congenital FSGS phenotype, rather than simple congenital NS (24). Some genes may encode proteins whose major (or sole) function is to

maintain the glomerular filtration barrier, whereas others encode proteins that function primarily to establish or maintain the normal podocyte architecture. This may still oversimplify the situation; some genes that affect the filtration barrier may also, to greater or lesser extent, alter the podocyte's production of GBM matrix proteins, accounting for variations in sclerosis. Furthermore, differences in genes encoding members of other biologic pathways, as well as differences in environmental factors, may introduce further phenotypic variability.

Sporadic FSGS

We are left with the basic question: what causes “typical” FSGS and MCD? How much is genetic? It is now clear that a significant fraction of sporadic FSGS in children is due to NPHS2 mutations. It is important to emphasize that a clinician cannot say on clinical grounds that a given sporadic (*e.g.*, nonfamilial) case of NS/FSGS is not inherited. This point simply reflects the fact that in most families without large sibships, recessive disease will be apparent in only one child. In addition, a sizable subset of “sporadic” disease may turn out to be oligogenic, due to combined defects in a few different genes.

It is still reasonable to assume that most podocytopathies are not inherited as Mendelian traits. Complex genetic factors are undoubtedly critical to the development of non-Mendelian podocyte disease, including disease triggered by environmental factors. It has been suggested, for example, that parvovirus infection is associated with the development of FSGS (99,100). HIV infection is associated with a distinct podocytopathy (see review by Ross and Klotman in this issue [101]). We will ultimately need to explain why some people with HIV infection (and perhaps parvovirus) develop disease and others do not. It may be the case that some moderately frequent variants in podocyte proteins alter the response of these cells to an altered immune function, or the podocytes themselves demonstrate genetically mediated variation in susceptibility to direct insults.

Implications for Clinical Care

Prenatal diagnosis is theoretically possible for any inherited disease with known genetic basis. Certainly, NPHS2-associated disease appears to be a frequent enough cause of childhood disease to make such testing useful. As noted above, clinical prenatal testing for CNF alleles has already been shown to be a useful tool. The utility of NPHS2 testing to determine response to treatment still needs to be verified. NPHS2 was cloned on the basis of a shared steroid-resistant phenotype within families. While the nature of the NPHS2 product, podocin, strengthens the hypothesis that NPHS2-associated disease will be steroid-resistant, this needs verification by testing steroid-sensitive populations of sporadic NS. If NS individuals with two mutant NPHS2 alleles are, as a rule, steroid-resistant, then genetic testing will be of great value in tailoring therapy. The societal value of genetic testing for other podocytopathies will depend on the frequency of these forms of disease as well as their implications for response to specific treatments.

Future Genetics of the Podocyte

What is the role of the podocyte and inherited variation in podocyte proteins in common disease? Does the human variation in response to primary insults (such as diabetes, hypertension, reflux) involve common differences in genes that regulate podocyte structure and function? It seems reasonable to hypothesize that variations in some genes are involved in the (heritable) response to podocyte injury, while other genetic variation causes altered podocyte function directly. Progress in the genetic and biologic understanding of inherited podocytopathies will continue. Ultimately, we may regard much of the NS/FSGS group of diseases as a collection of inherited defects in the podocyte, as well as perhaps the immune system and genes involved in the response to injury. We can hope such progress will aid the development of novel, biologically based, and genetically targeted therapies that will be tested in rigorous clinical trials.

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