

# The Genetic Basis of FSGS and Steroid-Resistant Nephrosis

By Martin R. Pollak

Studies of Mendelian forms of focal segmental glomerulosclerosis (FSGS) and nephrotic syndrome have provided new insights into the mechanism of these diseases. Congenital nephrotic syndrome and familial forms of FSGS form a spectrum of podocyte diseases of varying severity and age of onset. Mutations in both nephrin gene (NPHS1) alleles lead to congenital nephrosis, podocyte foot process effacement, and loss of slit-diaphragm structure. Mutations in both podocin gene (NPHS2) alleles lead to a wide range of human disease, from childhood-onset steroid-resistant FSGS and minimal change disease to adult-onset FSGS. Dominantly inherited mutations in ACTN4, the  $\alpha$ -actinin-4 gene, can lead to a slowly progressive adult-onset form of FSGS. In addition, FSGS is observed as part of several rare multisystem inherited syndromes. Here we review recent progress in understanding the genetic basis of FSGS in humans.

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**T**HE ROLE OF GENETIC factors in the development of focal segmental glomerulosclerosis (FSGS) in humans has become increasingly apparent in recent years. Genetic studies also have helped strengthen the notion that glomerular visceral epithelial cell (or podocyte) disorders lead to a spectrum of clinical presentations, from congenital nephrotic syndrome (CNF), to minimal change disease (MCD), and FSGS. Here we review recent progress in the understanding of the role of genetic factors in these related disorders of podocytes.

## MENDELIAN DISEASE

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 some time, though recognition of familial nephrosis has not been widespread. For over half a century, there have been scattered reports in the medical literature of familial nephrosis.<sup>1</sup> Four siblings with nephrotic syndrome were described in a 1957 report.<sup>2</sup> 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.<sup>3-8</sup> Of course, familial disease need not be 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 syndrome (Table 1). 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 past several years, novel

proteins have been identified in 2 childhood forms of nephritic syndrome using purely positional genetic approaches.

## GENETICS

Congenital nephrotic syndrome of the Finnish type, or CNF, is a geographically widespread disease characterized by the development of severe nephrosis in utero and autosomal-recessive inheritance.<sup>9</sup> Affected neonates have on the order of 20 to 30 g/d proteinuria and typically die from complications of the nephrotic syndrome at a young age unless nephrectomy and renal transplantation are performed. Without renal transplantation, mortality is essentially 100%. Typical problems include infection, growth retardation, prematurity, and the development of renal insufficiency.<sup>10</sup> CNF presents neonatally but is present prenatally. Parents of CNF infants (and therefore obligate heterozygotes) have no apparent phenotype, though prenatal proteinuria is detectable in a substantial fraction of heterozygotes before birth.

Subsequent to mapping the CNF gene to chromosome 19q13 by a means of a genome-wide linkage analysis, the CNF gene NPHS1 was cloned by positional methods.<sup>11,12</sup> NPHS1 spans 26 kb of genomic DNA and contains 29 exons.<sup>13</sup> Nephrin, the gene product, is a 185-kd protein containing a fibronectin III-like domain, 8 immunoglobulin C2 motifs, and a single transmembrane segment. Nephrin localizes to the slit diaphragm in the podocyte.

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**Table 1. Identified Nonsyndromic FSGS/NS Genes**

Disease	Locus	Inheritance	Gene	Protein	MIM Number*	Study
Congenital nephrotic syndrome	19q13.1	Autosomal recessive	NPHS1	Nephrin	602716	Kestila et al <sup>12</sup>
Steroid-resistant-NS	1q25-32	Autosomal recessive	NPHS2	Podocin	604766	Boute et al <sup>31</sup>
FSGS	19q13	Autosomal dominant	ACTN4	$\alpha$ -actinin-4	604638	Kaplan et al <sup>44</sup>

\* Mendelian inheritance in man number.

cyte.<sup>14-17</sup> Nephrin appears to play a role in regulating signaling pathways.<sup>18</sup> Localization to signaling domains known as lipid rafts has been shown recently.<sup>17,19</sup>

Most of the congenital nephrotic syndrome in Finland is caused by 2 specific NPHS1 mutations, Fin major (the deletion of nucleotides 121–122 leading to a frameshift) and Fin minor (encoding a premature termination signal at amino acid 1109).<sup>12</sup> A growing list of disease-associated mutations includes missense, splicing, and truncation mutations.<sup>20-23</sup> Some nephrin mutations have been shown to cause defective trafficking of the protein.<sup>24</sup> In addition to the high prevalence in Finland, NPHS1 mutations are frequent in Mennonites from Lancaster County, Pennsylvania.<sup>25</sup> Eight percent of the Groffdale Conference Mennonites carry a specific altered NPHS1 allele. The incidence of CNF is 1 in 500 live births in this group.

The identification of NPHS1 has improved the antenatal diagnosis of CNF. Prenatal proteinuria and elevated  $\alpha$ -fetoprotein levels are observed in fetuses both heterozygous and homozygous for NPHS1 defects, making  $\alpha$ -fetoprotein levels a poor screening tool.<sup>26</sup> In Finland, where 2 mutations account for 95% of disease, testing for these 2 alleles can provide an inexpensive and highly sensitive screen.

Mice homozygous for targeted disruption of nephrin have neonatal nephrosis.<sup>27-29</sup> Nephrin knockout mice initially have normal-appearing podocytes, despite abnormal appearing slit-diaphragms, suggesting that nephrin's primary role in the kidney is in slit diaphragm function rather than in podocyte development.<sup>29</sup>

#### RECESSIVE FSGS

Fuchshuber et al<sup>30</sup> described a form of nephrosis characterized by recessive transmission, early onset, resistance to steroid therapy, and rapid progression to end-stage kidney failure. The majority of the affected children showed an FSGS pattern

on renal biopsy examination, though some showed MCD. The gene for this recessive form of FSGS was mapped to chromosome 1q25-31 and subsequently cloned.<sup>30,31</sup> NPHS2, the responsible gene, encodes podocin, a 383 amino acid integral membrane protein. Podocin is homologous to stomatin family proteins and to MEC-2, part of the *Caenorhabditis elegans* mechanosensing apparatus.<sup>32</sup> Podocin localizes to the slit-diaphragm and has been shown to interact directly with nephrin.<sup>17,18,33,34</sup>

The relatively small number of NPHS2 exons (8) facilitates mutational analysis of human DNA. Several recent reports have helped define the spectrum of NPHS2-associated disease. Many of the disease-associated mutations create truncated proteins, suggesting that disease results from a loss of function of NPHS2.<sup>35-39</sup> 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.<sup>35</sup> Our data suggests that an R229Q variant, common in the general population, can cause late-onset FSGS when it occurs together with a second mutant (and probably more severe) allele. Podocin mutations underlie disease in a sizable fraction of both familial and nonfamilial instances of childhood-onset recessive FSGS. Fuchshuber et al<sup>36</sup> found NPHS2 mutations in 46% of such families. Other studies suggest that NPHS2 mutations cause disease in 20% to 30% of children with sporadic steroid-resistant nephrotic syndrome.<sup>39,40</sup>

Recent reports suggests a podocin-nephrin interaction at a protein-protein and at a genetic level. Direct physical interactions between the proteins have been shown.<sup>17,18</sup> Human data also suggest a genetic interaction. Koziell et al<sup>22</sup> have reported that the presence of a single NPHS2 may modify

the course of NPHS1-associated congenital nephrosis.

Recessive and steroid-resistant nephrotic syndrome (NS) is genetically heterogeneous. Fuchshuber et al identified one large family unlinked to the chromosome 1q locus in their report of locus identification.<sup>30</sup> Our unpublished data also suggests heterogeneity in recessive disease. Genetic heterogeneity in human disease is not surprising, given the existence of several recessive loci for NS in mice.

#### DOMINANT FSGS

Autosomal-dominant forms of FSGS typically present later and are more slowly progressive than recessive forms.<sup>41-43</sup> Mutations in ACTN4, encoding  $\alpha$ -actinin-4, cause a slowly progressive form of disease with dominant inheritance, nonnephrotic proteinuria, and renal insufficiency.<sup>44</sup> The penetrance of ACTN4-associated disease is high but not 100%: in these families, several individuals carry disease-associated mutations but have no proteinuria or renal insufficiency.

ACTN4 is one of 4  $\alpha$ -actinin genes. These genes encode biochemically similar, highly homologous proteins. The  $\alpha$ -actinins form approximately 100-kd head-to-tail homodimers. ACTN4 is the only actinin expressed significantly in the human glomerulus.<sup>44</sup> The ACTN4 mutations identified in FSGS families are all missense and increase the affinity of the encoded protein to actin filaments.<sup>44</sup>  $\alpha$ -actinin/actin affinity affects mechanical properties of actin gels, suggesting that these mutations may alter the mechanical properties of the podocyte.<sup>45</sup> This form of disease appears to be rare compared with NPHS1- and NPHS2-associated nephrosis.

ACTN4 mutations appear to explain only a fraction of dominant FSGS. Another locus on chromosome 11q has been reported.<sup>46</sup> Most families do not show evidence of linkage to either the chromosome 19q13 (ACTN4) or this 11q locus. It remains unknown whether disease in most of these families is caused by inherited podocyte defects.

#### SYNDROMIC FSGS

FSGS and related podocyte disorders also are seen as part of well-defined inherited syndromes. The spectrum of disease seen with WT1 mutations is the best studied of these disorders. The WT1 transcription factor was cloned on the basis of its

role in the development of Wilms tumor.<sup>47,48</sup> Frasier syndrome and Denys-Drash syndrome are related and overlapping syndromes caused by mutations in WT1.<sup>49-52</sup> Both syndromes are characterized by glomerular disease and the development of male pseudohermaphroditism. Frasier syndrome is caused by donor splice mutations in intron 9 of WT1. An FSGS pattern is seen on renal biopsy examination. Frasier syndrome can present as FSGS in 46,XX females in association with gonadal malignancy.<sup>53,54</sup> WT1 mutations are not a significant cause of glomerular disease in the absence of other genitourinary features.<sup>55</sup> Denys-Drash syndrome is defined by diffuse mesangial sclerosis on renal biopsy examination, genitourinary tumors, and pseudohermaphroditism. A different spectrum of mutations is seen in Denys-Drash syndrome, most commonly within exon 9 of WT1.<sup>49,56</sup>

Nail-Patella syndrome generally is regarded as a disease of the basement membrane rather than the podocyte, though it is probably both. Affected individuals typically show nephropathy, as well as dysplastic nails, and absent or hypoplastic patellae. An altered glomerular basement membrane typically predominates on histologic analysis, the glomerulopathy is variable and can present as nephrotic syndrome.<sup>57</sup> Defects in the *lmx1b* transcription factor are responsible for disease.<sup>58,59</sup> *Lmx1b* helps control the transcriptional regulation of matrix proteins by the podocyte as well as the podocyte genes CD2AP and NPHS2.<sup>60-63</sup> A variety of other inherited syndromes are associated with an increased frequency of FSGS. For example, Charcot-Marie Tooth disease and Galloway-Mowat syndrome are both inherited neuropathies in which nephrosis and/or FSGS are seen with increased frequency.<sup>64,65</sup>

#### SECONDARY FSGS

The role of human FSGS and NS genes in acquired disease is a subject of ongoing investigation. Some studies have reported increased nephrin expression in animal models of disease, others have reported decreased expression in other models.<sup>66-70</sup> Results from human studies have not yet provided a clear picture of the nature and role of nephrin expression in acquired glomerulopathies.<sup>71,72</sup>

### CLINICAL SPECTRUM OF DISEASE

Different defects in the podocyte lead to different clinical presentations. Further elucidation of the molecular mechanisms of these diseases are required to fully understand these differences.

Disease caused by defects in NPHS1, NPHS2, and ACTN4 forms a spectrum from prenatal-onset, to childhood-onset, to adult-onset disease. In addition, the disease severity caused by defects in any one of these genes is quite variable as well. It is unclear if the difference between FSGS and NS genes has to do simply with the severity of the resulting podocyte defect, or if FSGS genes perturb a different biologic pathway than NS genes. Interestingly, one recent report observed that patients with 2 defective NPHS1 alleles and a third mutation in NPHS2 showed a congenital FSGS phenotype.<sup>22</sup> Some genes (such as NPHS1) 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 (such as ACTN4). Defects in genes that alter the filtration barrier also may alter the podocyte's production of glomerular basement membrane matrix proteins, leading to variations in glomerulosclerosis.

### SPORADIC FSGS

What causes most cases of FSGS and MCD? A significant fraction of sporadic FSGS in children is caused by NPHS2 mutations. However, a greater fraction still remain unexplained by defects in known genes. Likely, complex combinations of genetic and environmental factors contribute to the development of much of this disease. For example, it has been suggested that parvovirus infection is associated with the development of FSGS.<sup>73,74</sup> Human immunodeficiency virus infection also is associated with an FSGS-like lesion.<sup>75</sup> Although purely speculative, it may be the case that some moderately frequent variants in podocyte proteins alter the response of these cells to an altered T-cell repertoire.

### IMPLICATIONS

Prenatal and presymptomatic diagnosis is possible for inherited diseases with known genetic bases. The practical value of such testing depends on the specifics of the disease. As noted earlier,

prenatal testing for specific identification of CNF-associated NPHS1 alleles already has been shown to be a useful clinical tool. The use of NPHS2 testing to determine response to treatment still needs to be verified. The value of genetic testing for other forms of FSGS or NS will depend on the frequency of these forms of disease and their implications for response to specific treatments. At present, genetic testing for FSGS and NS genes remains primarily a research tool, rather than a clinical test. In the next several years, testing for at least some of these genes likely will evolve into useful clinical tools. As with other forms of inherited kidney disease, care must be taken to avoid using an affected relative as a renal transplant donor. Because the familial pattern of inheritance may not always be obvious in inherited FSGS, clinicians should take particular care. As a practical matter, at the present time, the best method for ensuring this is to be certain that the potential donor has absolutely no microalbuminuria in multiple repeated measurements.

Does the human variation in the renal response to primary insults (such as diabetes, hypertension, reflux) involve common differences in genes that regulate podocyte structure and function? Variations in some genes may be involved in the heritable response to podocyte injury, whereas other variations may cause altered podocyte function directly. Progress in the genetic and biologic understanding of inherited podocytopathies will continue. Ultimately, we may come to regard much of the NS/FSGS group of diseases as a collection of inherited defects in the podocyte, the immune system, and genes involved in the response to injury.

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