

Familial focal segmental glomerulosclerosis

Joshua Kaplan and Martin R. Pollak

There is increasing recognition of the importance of genetic factors in the development of focal segmental glomerulosclerosis and related proteinuric disorders. Recently, four genes have been identified which, when defective, cause focal segmental glomerulosclerosis or nephrosis. All of these genes appear to be important in the maintenance of glomerular podocyte function. However, not all cases of familial nephrosis or proteinuria are explained by defects in these genes. *Curr Opin Nephrol Hypertens* 10:183–187. © 2001 Lippincott Williams & Wilkins.

Renal Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Martin Pollak, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA 02115, USA
e-mail: mpollak@rics.bwh.harvard.edu

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Abbreviations

CNF congenital nephrotic syndrome of the Finnish type
FSGS focal segmental glomerulosclerosis
TGF- β 1 transforming growth factor beta 1

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Introduction

The importance of genetic factors in kidney dysfunction characterized by cystic disease, basement membrane abnormalities, and electrolyte disturbances is well recognized. However, progress in understanding mendelian forms of proteinuria has, until recently, lagged behind. Similarly, a general appreciation among clinicians of familial proteinuric disease has been slow to develop. Nevertheless, some clinical reports of families with proteinuric disease are quite old. Reports of the familial clustering of nephrotic syndrome appear as early as 1942 [1]. In 1957, Vernier *et al.* [2] described four siblings with proteinuria. Their parents showed no evidence of kidney disease, suggesting autosomal recessive disease. The disease manifestations ranged from a spontaneously remitting proteinuria with onset at 5 years to nephrotic syndrome with onset at 4 months, hypertension, progressive renal insufficiency, resistance to treatment, and death at 7 years. Pathology showed minimal change disease in some cases, and changes consistent with focal segmental glomerulosclerosis (FSGS) in others.

Recent reports [3,4*,5–10] have helped clarify the clinical spectrum of the group of diseases that make up familial FSGS. Just as the clinical spectrum of human disease displaying FSGS on biopsy is quite variable, familial FSGS is also highly heterogeneous. Families with many members with FSGS have been reported, with disease segregation consistent with both autosomal recessive and dominant inheritance. Disease following dominant patterns of inheritance tends to present at a later age than in families with disease in a single generation (and more likely recessive). As a rule, FSGS does not recur in transplanted kidneys in end-stage renal failure patients with familial FSGS [4*].

Genetics

Recently, considerable progress has been made in elucidating the genetic mechanisms of this set of diseases. We include congenital nephrotic syndrome of the Finnish type (CNF) in this discussion because of its biological relationship to the familial forms of FSGS. CNF, which in fact is not limited to Finland in its geographical distribution, is characterized clinically by autosomal recessive inheritance, the development of severe nephrotic syndrome *in utero*, and death in the absence of kidney transplantation [11]. In 1994, Kestila *et al.* [12] mapped CNF to chromosome 19q13. In 1995, Fuchshuber *et al.* [13] mapped a form of childhood onset and steroid-resistant autosomal recessive nephrosis to

chromosome 1q25–31. The renal histopathology in most of the affected children showed FSGS. Subsequently, loci harboring genes for later onset, dominant forms of FSGS were identified on chromosomes 19q [5] and 11q [14*].

Nephrin

NPHS1, the gene defective in CNF, was identified by positional cloning methods. After fine mapping narrowed the CNF locus to chromosome 19q13.1 [15], mutational and expression analysis of positionally identified candidates identified *NPHS1*, encoding a protein product termed nephrin, as the mutant gene [16]. The nephrin sequence predicts a 180 000 M_r protein containing eight immunoglobulin C2 motifs, a fibronectin type III-like domain, and a single transmembrane segment. It is expressed predominantly in the podocyte, and is localized exclusively to the glomerular slit diaphragm [17*,18*]. It is hypothesized that nephrin molecules from neighboring foot processes form homoduplexes to create the slit diaphragm structure, which is absent or abnormal in patients with mutations in both nephrin alleles [19*]. Two mutations, termed Fin-major (deletion of nucleotides 121–122 causing a frameshift) and Fin-minor (a C–T substitution at the nucleotide causing protein truncation at amino acid 1109) account for over 90% of the *NPHS1* mutations found in the Finnish population [16,20]. A large number of mutations has now been described in both Finnish and non-Finnish patients [21*,22,23], which include missense as well as nonsense and splicing mutations. Rarely, affected infants with *NPHS1* mutations have a less severe form of disease [20,21*]. The genomic structure, as well as the cloning of the mouse and rat *NPHS1* homologs, has been reported [21*,24–26]. The absence of kidney disease in the parents of CNF patients, obligate heterozygotes for *NPHS1* mutations, indicates that two mutant alleles are required for phenotypic expression, and mutations generally cause disease by a loss-of-function mechanism.

Podocin

The gene for steroid-resistant nephrotic syndrome, *NPHS2*, previously mapped to chromosome 1q25–31 [13], shows podocyte-specific expression. The encoded protein, termed podocin, is predicted to be a 42 000 M_r integral membrane protein with moderate homology to human stomatin and *Caenorhabditis elegans MEC-2* [27**]. The function of podocin is unknown, but by analogy with *MEC-2*, it may serve to link ion channels to the cytoskeleton [28,29]. The 10 reported *NPHS2* mutations, missense, frameshift, and nonsense, are associated with disease onset between 3 months and 5 years of age. Later onset disease genetically linked to this region has also been reported, and may also be caused by mutations in *NPHS2* [30*]. Affected individuals show histological evidence of glomerular

epithelial cell foot process effacement and, in most cases, FSGS [13].

α-Actinin-4

Heterozygous missense mutations in *ACTN4*, encoding α-actinin-4, cause a dominant form of familial FSGS [31**,32]. This autosomal dominant disease is characterized by adult onset, non-nephrotic proteinuria and slowly progressive renal insufficiency in a significant fraction of patients. α-Actinin-4, a widely expressed protein, is the only one of the four α-actinin isoforms significantly expressed in the podocyte. *ACTN4* is located on chromosome 19q13. α-Actinin contains an N-terminal actinin binding domain, followed by four spectrin-like repeats. α-Actinin forms a head-to-tail homodimer that crosslinks and bundles actin filaments, and also interacts with a large number of cytoskeletal, cell-surface, and signalling molecules [33]. The disease-associated mutations occur in close proximity to each other in an evolutionarily conserved region of the encoded protein. The mutant proteins shown increased affinity for actinin filaments *in vitro* [31**]. By contributing to the organization of the actin cytoskeleton and anchoring it to the plasma membrane, α-actinin is thought to be important in the maintenance of cell shape, adhesion, and movement. The FSGS-associated *ACTN4* mutations may alter podocyte foot process function by altering its mechanical properties. The penetrance of this form of disease is high, but is less than 100%, indicating that factors in addition to *ACTN4* mutations must be required for disease expression.

Genetic heterogeneity

Not all cases of non-syndromic familial FSGS result from mutations in the above-mentioned genes (Table 1). Families with autosomal recessive steroid-resistant nephrotic syndrome unlinked to chromosome 1q25–31 (the *NPHS2* locus) have been reported [27**,30*]. In one large family with autosomal dominant FSGS, disease maps to chromosome 11q [14*]. The gene responsible has not been reported. Families with dominant inheritance of FSGS unlinked to both of these families have been identified [14*,31**].

Table 1. Inherited podocyte disorders

Disease	Locus	Inheritance	Gene	Protein
Congenital nephrotic syndrome	19q13	Recessive	<i>NPHS1</i>	nephrin
Steroid-resistant nephrotic syndrome	1q25–31	Recessive	<i>NPHS2</i>	podocin
Familial FSGS	19q13	Dominant	<i>ACTN4</i>	alpha-actinin-4
Neonatal nephrosis (in mice)		Recessive	<i>CD2AP</i>	CD2-associated protein

FSGS, Focal segmental glomerulosclerosis.

Syndromic focal segmental glomerulosclerosis

Familial FSGS can also be seen as a component of non-renal-limited familial syndromes. In familial cases of unilateral renal agenesis, the FSGS is probably secondary to the reduced functional renal mass [34]. FSGS has been reported in association with Charcot–Marie–Tooth disease, a genetically heterogeneous inherited neuropathy [35,36]. Mutations in the Wilms' tumor suppressor gene *WT1*, a zinc finger transcription factor, cause a group of diseases characterized by glomerulopathy and urogenital developmental abnormalities. Denys–Drash syndrome, the triad of progressive glomerular disease, Wilms' tumor, and male pseudohermaphroditism, is typically associated with mutations in exon 9 of *WT1* [37]. Mutations in the *WT1* intron 9 splice donor site cause Frasier syndrome, defined by male pseudohermaphroditism, gonadoblastoma, and FSGS [38,39]. These mutations alter the ratio of the *WT1* +KTS:–KTS isoforms (referring to the presence or absence of amino acids lysine–threonine–serine). The +KTS *WT1* isoform is thought to be involved in RNA splicing, whereas –KTS *WT1* is involved in transcription regulation [40]. Chromosomally normal (XX) females with isolated FSGS and *WT1* splice mutations have recently been described [41,42]. Presumably, alterations in this podocyte transcription factor cause FSGS by disrupting normal glomerular development. Recently, homozygosity for a mutation in $\beta 4$ -integrin was reported in an infant with epidermolysis bullosa and congenital FSGS with nephrotic proteinuria [43]. Integrin $\beta 4$ expression in the podocyte was demonstrated, suggesting that in this patient, the abnormal $\beta 4$ integrin may alter the normal integrin-mediated anchoring of the cytoskeleton to the glomerular basement membrane.

Animal studies

Mice homozygous for targeted deletions in the CD2-associated protein *CD2AP* develop nephrotic syndrome, renal failure, and, on histological examination, show podocyte foot process effacement [44••]. *CD2AP* encodes an 80 000 M_r protein that interacts with the cytoplasmic domain of nephrin [44••]. *CD2AP* is thought to stabilize cell–cell contacts between T cells and antigen-presenting cells [45,46•]. Although widely expressed, the principal site of *CD2AP* expression in the kidney is the podocyte. The possible role of *CD2AP* in human disease is not known. *CD2AP* defects appear to cause proteinuria in a mechanism similar to that seen in the human disorders mentioned above, by disrupting podocyte structure. However, alterations in the variety of other genes have been shown to cause nephrotic syndrome or glomerulosclerosis in animal studies. For example, mice with an insertional inactivation the *Mpv17* gene develop FSGS, hypertension, and inner

ear abnormalities [47,48]. The gene product of *Mpv17* is involved in the metabolism of reactive oxygen products [49]. Mice with a targeted deletion in Rho GDI- α , which regulates G protein activity, develop FSGS [50]. Transgenic mice overexpressing *Frat1*, a protooncogene that may inhibit GSK3 kinase, develop FSGS [51]. Mice overexpressing bovine growth hormone or transforming growth factor beta 1 (TGF- β 1) each develop FSGS-like lesions [52,53]. By contrast, mice failing to express p21, a cyclin-dependent kinase inhibitor involved in preventing progression of the cell cycle, are protected from developing secondary FSGS after 5/6 nephrectomy [54].

Conclusion

Disruption in several genes has recently been identified which cause kidney disease by altering normal podocyte function: *NPHS1* (encoding nephrin), *NPHS2* (encoding podocin), *ACTN4* (encoding α -actinin-4), and *CD2AP* (in mice). Nephrin appears to be a major component of the glomerular slit diaphragm [17•–19•]. Similar to its role in T lymphocytes, *CD2AP* may function in the podocyte to stabilize cell–cell contacts, perhaps via an interaction with nephrin. The function of podocin, a podocyte-specific cell surface protein, is unclear but may function similarly to *MEC-2*, linking ion channels to the cytoskeleton [28,29]. α -Actinin-4 cross-links and bundles actin filaments, and also interacts with other proteins important to podocyte structure, including integrins and components of the cadherin/catenin complex [55–58]. α -Actinin appears to be involved in regulating the mechanical deformability of the actin cytoskeleton [59–61]. The mutant forms of α -actinin may cause a slowly progressive form of glomerular disease by altering the mechanical properties of the podocyte.

All of the human FSGS and nephrotic syndrome genes identified to date appear to cause disease by altering podocyte function. In animal models, however, some of the genes with proteinuria-associated defects do not appear to be involved in the creation or maintenance of the filtration barrier created by the podocyte, but rather in the modulation of cell growth. The clearest example is in the mouse model lacking p21WAF1/CIP1, which is a potent inhibitor of cell cycling and proliferation [62]. Mice lacking this gene which undergo 5/6 nephrectomy develop significantly less proteinuria and pathological signs of FSGS than do normal mice receiving the same renal ablation [54]. This suggests that by tipping the balance between a hypertrophic and a hyperplastic response to injury, the degree of secondary FSGS can be diminished. Several other mouse models developing primary FSGS, including *Frat1*, TGF- β 1, and growth hormone overexpression, may develop FSGS by alteration of cell growth or the cellular response to minor injury [51–53].

FSGS is a common glomerular histopathological phenotype, not just in primary glomerular disease but also in secondary forms. Genes involved in the development of FSGS in humans and animals may define pathways important in the development of common forms of secondary glomerulosclerosis, such as that seen in diabetes. This hypothesis awaits further investigation.

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