

Inherited Podocytopathies: FSGS and Nephrotic Syndrome from a Genetic Viewpoint

MARTIN R. POLLAK

Renal Division, Brigham and Women's Hospital, Boston, Massachusetts.

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-

Correspondence to Dr. Martin R. Pollak, Renal Division, Brigham and Women's Hospital, 77 Ave Louis Pasteur, Boston, MA 02115. Phone: 617-525-5840; Fax: 617-525-5841; E-mail: mpollak@rics.bwh.harvard.edu

1046-6673/1312-3016

Journal of the American Society of Nephrology

Copyright © 2002 by the American Society of Nephrology

DOI: 10.1097/01.ASN.0000039569.34360.5E

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

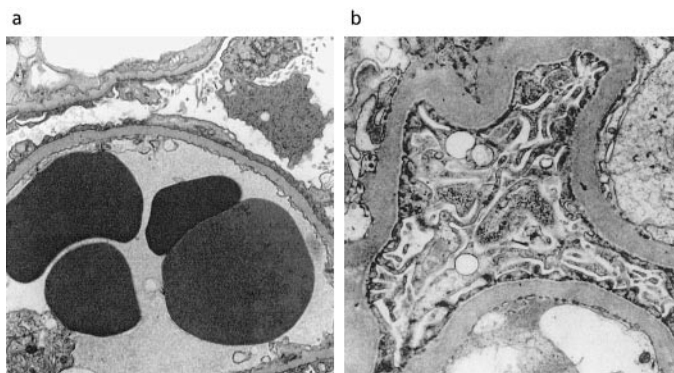


Figure 1. Electron micrographs from FSGS patients with (a) two mutant NPHS2 (podocin) alleles and (b) one mutant ACTN4 allele. EM (a) courtesy of Drs. Bernard Kaplan and Pierre Russo. EM (b) courtesy of Dr. Helmut Rennke.

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.

References

1. Ichikawa I, Fogo A: Focal segmental glomerulosclerosis. *Pediatr Nephrol* 10: 374–391, 1996
2. Werner M: *Handbuch der Erbbiologie*, Berlin, Springer, 1942
3. Vernier RL, Brunson J, Good RA: Studies on familial nephrosis. *Am J Dis Child* 93: 469, 1957
4. Fanconi G, Kousmine C, Frischknecht W: Die konstitutionelle bereitschaft zum nephrosesyndrome. *Helv Paediatr Acta* 6, 199–218, 1951
5. Tejani A, Nicastrì A, Phadke K, Sen D, Adamson O, Dunn I, Calderon P: Familial focal segmental glomerulosclerosis. *Int J Pediatr Nephrol* 4: 231–234, 1983
6. Conlon PJ, Butterly D, Albers F, Gunnels JC, Howell DN: Clinical and pathologic features of familial focal segmental glomerulosclerosis. *Am J Kidney Dis* 26: 34–40, 1995
7. Moncrieff MW, White RH, Glasgow EF, MH Winterborn, Cameron JS, Ogg CS: The familial nephrotic syndrome. II. A clinicopathological study. *Clin Nephrol* 1: 220–229, 1973
8. Mehls O, Scharer K: Familial nephrotic syndrome. *Monatsschr Kinderheilkd* 118: 328–330, 1970
9. Faubert PF, Porush JG, Familial focal segmental glomerulosclerosis: nine cases in four families and review of the literature. *Am J Kidney Dis* 30: 265–270, 1997
10. Rapola J, Congenital nephrotic syndrome. *Pediatr Nephrol* 1: 441–446, 1987
11. Srivastava T., Whiting JM, Garola RE, Dasouki MJ, Ruotsalainen V, Tryggvason K, Hamed R, Alon US: Podocyte proteins in Galloway-Mowat syndrome. *Pediatr Nephrol*. 16: 1022–1029, 2001
12. Kestila M, Mannikko M, Holmberg C, Gyapay G, Weissenbach J, Savolainen ER, Peltonen L, Tryggvason K: Congenital nephrotic syndrome of the Finnish type maps to the long arm of chromosome 19. *Am J Hum Genet* 54: 757–764, 1994
13. Mannikko M, Kestila M, Holmberg C, Norio R, Ryyanen M, Olsen A, Peltonen L, Tryggvason K: Fine mapping and haplotype analysis of the locus for congenital nephrotic syndrome on chromosome 19q13.1. *Am J Hum Genet* 57: 1377–1383, 1995
14. Kestila M, Lenkerri U, Mannikko M, Lamerdin J, McCreedy P, Putaala H, Ruotsalainen V, Morita T, Nissinan M, Herva R, Kashtan C, Peltonen L, Holmberg C, Olsen A, Tryggvason K: Positionally cloned gene for a novel glomerular protein - nephrin

- is mutated in congenital nephrotic syndrome. *Molecular Cell* 1:575–582, 1998
15. Lenkkeri U, Mannikko M, McCready P, Lamerdin J, Gribouval O, Niaudet PM, Antignac CK, Kashtan CE, Homborg C, Olsen A, Kestila M, Tryggvason K: Structure of the gene for congenital nephrotic syndrome of the Finnish type (NPHS 1) and characterization of mutations. *Am J Hum Genet* 64:51–61, 1999
 16. Holzman LB, St. John PL, Kovari IA, Verma R, Holthofer H, Abrahamson DR: Nephritin localizes to the slit pore of the glomerular epithelial cell. *Kidney Int* 56: 1481–1491, 1999
 17. Holthofer H, Ahola H, Solin ML, Wang S, Palmen T, Luimula P, Miettinen A, Kerjaschki D: Nephritin localizes at the podocyte filtration slit area and is characteristically spliced in the human kidney. *Am J Pathol* 155: 1681–1687, 1999
 18. Ruotsalainen V, Ljungberg P, Wartiovaara J, Lenkkeri U, Kestila M, Jalanko H, Holmberg C, Tryggvason K: Nephritin is specifically located at the slit diaphragm of glomerular podocytes. *Proc Natl Acad Sci USA* 96: 7962–7967, 1999
 19. Schwarz K, Simons M, Reiser J, Saleem MA, Faul C, Kriz W, Shaw AS, Holzman LB, Mundel P: Podocin, a raft-associated component of the glomerular slit diaphragm, interacts with CD 2AP and nephritin. *J Clin Invest* 108: 1621–1629, 2001
 20. Huber TB, Kottgen M, Schilling B, Walz G, Benzing T: Interaction with podocin facilitates nephritin signaling. *J Biol Chem* 276: 41543–41546, 2001
 21. Simons M, Schwarz K, Kriz W, Miettinen A, Reiser J, Mundel P, Holthofer H: Involvement of lipid rafts in nephritin phosphorylation and organization of the glomerular slit diaphragm. *Am J Pathol* 159: 1069–1077, 2001
 22. Patrakka J, Kestila M, Wartiovaara J, Ruotsalainen V, Tissari P, Lenkkeri U, Mannikko M, Visapaa I, Holmberg C, Rapola J, Tryggvason K, Jalanko H: Congenital nephrotic syndrome (NPHS 1): features resulting from different mutations in Finnish patients [In Process Citation]. *Kidney Int* 58: 972–980, 2000
 23. Belcheva O, Martin P, Lenkkeri U, Tryggvason K: Mutation spectrum in the nephritin gene (NPHS 1) in congenital nephrotic syndrome. *Hum Mutat* 17: 368–373, 2001
 24. Koziell A, Grech V, Hussain S, Lee G, Lenkkeri U, Tryggvason K, Scambler P: Genotype/phenotype correlations of NPHS 1 and NPHS2 mutations in nephrotic syndrome advocate a functional inter-relationship in glomerular filtration. *Hum Mol Genet* 11: 379–388, 2001
 25. Aya K, Tanaka H, Seino Y: Novel mutation in the nephritin gene of a Japanese patient with congenital nephrotic syndrome of the Finnish type. *Kidney Int* 57: 401–404, 2000
 26. Liu L, Done SC, Khoshnoodi J, Bertorello A, Wartiovaara J, Berggren PO, Tryggvason K: Defective nephritin trafficking caused by missense mutations in the NPHS 1 gene: Insight into the mechanisms of congenital nephrotic syndrome. *Hum Mol Genet* 10: 2637–2644, 2001
 27. Patrakka J, Martin P, Salonen R, Kestila M, Ruotsalainen V, Mannikko M, Ryyanen M, Rapola J, Holmberg C, Tryggvason K, Jalanko H: Proteinuria and prenatal diagnosis of congenital nephrosis in fetal carriers of nephritin gene mutations. *Lancet* 359:1575–1577, 2002
 28. Bolk S, Puffenberger EG, Hudson J, Morton DH, Chakravarti A: Elevated frequency and allelic heterogeneity of congenital nephrotic syndrome, Finnish type, in the old order Mennonites [letter]. *Am J Hum Genet* 65: 1785–1790, 1999
 29. Patrakka J, Ruotsalainen V, Reponen P, Qvist E, Laine J, Holmberg C, Tryggvason K, Jalanko H: Recurrence of nephrotic syndrome in kidney grafts of patients with congenital nephrotic syndrome of the Finnish type: role of nephritin. *Transplantation* 73: 394–403, 2002
 30. Wang SX, Ahola H, Palmen T, Solin ML, Luimula P, Holthofer H: Recurrence of nephrotic syndrome after transplantation in CNF is due to autoantibodies to nephritin. *Exp Nephrol* 9: 327–331, 2001
 31. Topham PS, Kawachi H, Haydar SA, Chugh S, Addona TA, Charron KB, Holzman LB, Shia M, Shimizu F, Salant DJ: Nephritogenic mAb 5–1–6 is directed at the extracellular domain of rat nephritin. *J Clin Invest* 104: 1559–1566, 1999
 32. Rantanen M, Palmen T, Patari A, Ahola H, Lehtonen S, Astrom E, Floss T, Vauti F, Wurst W, Ruiz P, Kerjaschki D, Holthofer H: Nephritin TRAP Mice Lack Slit Diaphragms and Show Fibrotic Glomeruli and Cystic Tubular Lesions. *J Am Soc Nephrol* 13: 1586–1594, 2002
 33. Putaala H, Soyninen R, Kilpelainen P, Wartiovaara J, Tryggvason K: The murine nephritin gene is specifically expressed in kidney, brain and pancreas: Inactivation of the gene leads to massive proteinuria and neonatal death. *Hum Mol Genet* 10: 1–8, 2001
 34. Hamano Y, Grunkemeyer JA, Sudhakar A, Zeisberg M, Cosgrove D, Morello R, Lee B, Sugimoto H, Kalluri R: Determinants of vascular permeability in the kidney glomerulus. *J Biol Chem* 2002, in press
 35. Fuchshuber A, Jean G, Gribouval O, Gubler MC, Broyer M, Beckmann JS, Niaudet P, Antignac C: Mapping a gene (SRN 1) to chromosome 1q25–q31 in idiopathic nephrotic syndrome confirms a distinct entity of autosomal recessive nephrosis. *Hum Mol Genet* 4: 2155–2158, 1995
 36. Boute N, Gribouval O, Roselli S, Benessy F, Lee H, Fuchshuber A, Dahan K, Gubler MC, Niaudet P, Antignac C: NPHS 2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 24: 349–354, 2000
 37. Huang M, Gu G, Ferguson EL, Chalfie M: A stomatin-like protein necessary for mechanosensation in *C. elegans*. *Nature* 378: 292–295, 1995
 38. Roselli S, Gribouval O, Boute N, Sich M, Benessy F, Attie T, Gubler MC, Antignac C: Podocin localizes in the kidney to the slit diaphragm area. *Am J Pathol* 160: 131–139, 2002
 39. Palmen T, Lehtonen S, Ora A, Kerjaschki D, Antignac C, Lehtonen E, Holthofer H: Interaction of endogenous nephritin and CD 2-associated protein in mouse epithelial M-1 cell line. *J Am Soc Nephrol* 13: 1766–1772, 2002
 40. Frishberg Y, Rinat C, Megged O, Shapira E, Feinstein S, Raas-Rothschild A: Mutations in NPHS2 encoding podocin are a prevalent cause of steroid-resistant nephrotic syndrome among Israeli-Arab children. *J Am Soc Nephrol* 13: 400–405, 2002
 41. Fuchshuber A, Gribouval O, Ronner V, Kroiss S, Karle S, Brandis M, Hildebrandt F: Clinical and genetic evaluation of familial steroid-responsive nephrotic syndrome in childhood. *J Am Soc Nephrol* 12: 374–378, 2001
 42. Wu MC, Wu JY, Lee CC, Tsai CH, Tsai FJ: A novel polymorphism (c288C>T) of the NPHS2 gene identified in a Taiwan Chinese family. *Hum Mutat* 17: 81–82, 2001
 43. Wu MC, Wu JY, Lee CC, Tsai CH, Tsai FJ: Two novel polymorphisms (c954T>C and c1038A>G) in exon8 of NPHS2 gene identified in Taiwan Chinese. *Hum Mutat* 17: 237, 2001
 44. Caridi G, Bertelli R, Carrea A, Di DM, Catarsi P, Artero M, Carraro M, Zennaro C, Candiano G, Musante L, Seri M, Ginevri F, Perfumo F, Ghiggeri GM: Prevalence, genetics, and clinical features of patients carrying podocin mutations in steroid-resis-

- tant nonfamilial focal segmental glomerulosclerosis. *J Am Soc Nephrol* 12: 2742–2746, 2001
45. Karle SM, Uetz B, Ronner V, Glaeser L, Hildebrandt F, Fuchshuber A: Novel mutations in NPHS2 detected in both familial and sporadic steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 13: 388–393, 2002
 46. Carraro M, Caridi G, Bruschi M, Artero M, Bertelli R, Zennaro C, Musante L, Candiano G, Perfumo F, Ghiggeri GM: Serum glomerular permeability activity in patients with podocin mutations (NPHS2) and steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 13: 1946–1952, 2002
 47. Conlon PJ, Lynn K, Winn MP, Quarles LD, Bembe ML, Pericak-Vance M, Speer M, Howell DN: Spectrum of disease in familial focal and segmental glomerulosclerosis. *Kidney Int* 56: 1863–1871, 1999
 48. Mathis BJ, Kim SH, Calabrese K, Haas M, Seidman JG, Seidman DE, Pollak MR: A locus for inherited focal segmental glomerulosclerosis maps to chromosome 19q13: Rapid Communication. *Kidney Int* 53: 282–286, 1998
 49. Vats A, Nayak A, Ellis D, Randhawa PS, Finegold DN, Levinson KL, Ferrell RE: Familial nephrotic syndrome: Clinical spectrum and linkage to chromosome 19q13. *Kidney Int* 57: 875–881, 2000
 50. Kaplan JM, Kim SH, North KN, Rennke H, Correia LA, Tong HQ, Mathis BJ, Rodriguez-Perez JC, Allen PG, Beggs AH, Pollak MR: Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. *Nat Genet* 24: 251–256, 2000
 51. Wachsstock DH, Schwartz WH, Pollard TD: Affinity of alpha-actinin for actin determines the structure and mechanical properties of actin filament gels. *Biophys J* 65: 205–14, 1993
 52. Winn MP, Conlon PJ, Lynn KL, Howell DN, Slotterbeck BD, Smith AH, Graham FL, Bembe M, Quarles LD, Pericak-Vance MA, Vence JM: Linkage of a gene causing familial focal segmental glomerulosclerosis to chromosome 11 and further evidence of genetic heterogeneity. *Genomics* 58: 113–120, 1999
 53. Haber DA, Buckler AJ, Glaser T, Call KM, Pelletier J, Sohn RL, Douglass EC, Housman DE: An internal deletion within an 11p13 zinc finger gene contributes to the development of Wilms' tumor. *Cell* 61: 1257–1269, 1990
 54. Gessler M, Poustka A, Cavenee W, Neve RL, Orkin SH, Bruns GA: Homozygous deletion in Wilms tumours of a zinc-finger gene identified by chromosome jumping. *Nature* 343: 774–778, 1990
 55. Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JE, Houghton DC, Junien C, Habib R, Fouser L: Germ-line mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. *Cell* 67: 437–447, 1999
 56. McTaggart SJ, Algar E, Chow CW, Powell HR, Jones CL: Clinical spectrum of Denys-Drash and Frasier syndrome. *Pediatr Nephrol* 16: 335–339, 2001
 57. Barbaux S, Niaudet P, Gubler MC, Grunfeld JP, Jaubert F, Kuttent F, Fekete CN, Souleyreau-Therville N: Donor splice-site mutations in WT1 are responsible for Frasier syndrome. *Nat Genet* 17: 467–470, 1997
 58. Klant B, Koziell A, Poulat F, Wieacker P, Scambler P, Berta P, Gessler M: Frasier syndrome is caused by defective alternative splicing of WT 1 leading to an altered ratio of WT1 +/-KTS splice isoforms. *Hum Mol Genet* 7: 709–714, 1998
 59. Demmer L, Primack W, Loik V, Brown R, Therville N, McElreavey K: Frasier syndrome: a cause of focal segmental glomerulosclerosis in a 46, XX female. *J Am Soc Nephrol* 10: 2215–2218, 1999
 60. Denamur E, Bocquet N, Mougnot B, Da Silva R, Martinat L, Loirat C, Elion J, Bensman A, Ronco PM: Mother-to-child transmitted WT 1 splice-site mutation is responsible for distinct glomerular diseases. *J Am Soc Nephrol* 10: 2219–2223, 1999
 61. Denamur E, Bocquet N, Baudouin V, Da Silva F, Veitia R, Peuchmaur M, Elion J, Gubler MC, Fellous M, Niaudet P, Loirat C: WT 1 splice-site mutations are rarely associated with primary steroid-resistant focal and segmental glomerulosclerosis. *Kidney Int* 57: 1868–1872, 2001
 62. Schumacher V., Scharer K, Wuhl E, Altrogge H, Bonzel KE, Guschmann M, Neuhaus TJ, Pollastro RM, Kuwertz-Broking E, Bulla M, Tondera AM, Mundel P, Helmchen U, Waldherr R, Weirich A, Royer-Pokora B: Spectrum of early onset nephrotic syndrome associated with WT1 missense mutations. *Kidney Int* 53: 1594–1600, 1998
 63. Simila S, Vesa L, Wasz-Hockert O: Hereditary onycho-osteodysplasia (the nail-patella syndrome) with nephrosis-like renal disease in a newborn boy. *Pediatrics* 46:61–65, 1970
 64. Dreyer SD, Zhou G, Baldini A, Winterpacht A, Zabel B, Cole W, Johnson RL, Lee B: Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. *Nat Genet* 19: 47–50, 1998
 65. Chen H, Lun Y, Ovchinnikov D, Kokubo H, Oberg KC, Pepicelli CV, Gan L, Lee B, Johnson RL: Limb and kidney defects in Lmx1b mutant mice suggest an involvement of LMX1B in human nail patella syndrome. *Nat Genet* 19: 51–55, 1998
 66. Morello R, Zhou G, Dreyer SD, Harvey SJ, Ninomiya Y, Thorner PS, Miner JH, Cole W, Winterpacht A, Zabel B, Oberg KC, Lee B: Regulation of glomerular basement membrane collagen expression by LMX 1B contributes to renal disease in nail patella syndrome. *Nat Genet* 27: 205–208, 2001
 67. Morello R, Lee B: Insight into podocyte differentiation from the study of human genetic disease: Nail-patella syndrome and transcriptional regulation in podocytes. *Pediatr Res* 51: 551–558, 2002
 68. Miner JH, Morello R, Andrews KL, Li C, Antignac C, Shaw AS, Lee B: Transcriptional induction of slit diaphragm genes by Lmx1b is required in podocyte differentiation. *J Clin Invest* 109: 1065–1072, 2002
 69. Rohr C, Prestel J, Heidet L, Hosser H, Kriz W, Johnson RL, Antignac C, Witzgall R: The LIM-homeodomain transcription factor Lmx 1b plays a crucial role in podocytes. *J Clin Invest* 109: 1073–1082, 2002
 70. Chance PF, Fishbeck KJ: Molecular genetics of Charcot-Marie-Tooth disease and related neuropathies. *Hum Mol Genet* 3 Spec. No: 1503–1507, 1994
 71. Cohen AH, Turner MC: Kidney in Galloway-Mowat syndrome: Clinical spectrum with description of pathology. *Kidney Int.* 45: 1407–1415, 1994
 72. Dustin ML, Olszowy MW, Holdorf AD, Li J, Bromley S, Desai N, Widder P, Rosenberger F, van der Merwe PA, Allen PN, Shaw AS: A novel adaptor protein orchestrates receptor patterning and cytoskeletal polarity in T-cell contacts. *Cell* 94: 667–677, 1998
 73. Shih NY, Li J, Karpitskii V, Nguyen A, Dustin ML, Kanagawa O, Miner JH, Shaw AS: Congenital nephrotic syndrome in mice lacking CD2-associated protein [see comments]. *Science* 286: 312–315, 1999

74. Shih NY, Li J, Cotran R, Mundel P, Miner JH, Shaw AS: CD2AP localizes to the slit diaphragm and binds to nephrin via a novel C-terminal domain. *Am J Pathol* 159: 2303–2308, 2001
75. Donoviel DB, Freed DD, Vogel H, Potter DG, Hawkins E, Barrish JP, Mathur BN, Turner CA, Geske R, Montgomery CA, Starbuck M, Brandt M, Gupta A, Ramirez-Solis R, Zambrowicz BP, Powell DR: Proteinuria and perinatal lethality in mice lacking NEPH1, a novel protein with homology to NEPHRIN. *Mol Cell Biol* 21: 4829–4836, 2001
76. Artero RD, Castanon I, Baylies MK: The immunoglobulin-like protein Hibris functions as a dose-dependent regulator of myoblast fusion and is differentially controlled by Ras and Notch signaling. *Development* 128: 4251–4264, 2001
77. Dworak HA, Charles MA, Pellerano LB, Sink H: Characterization of *Drosophila* hibris, a gene related to human nephrin. *Development* 128: 4265–4276, 2001
78. Togawa A, Miyoshi J, Ishizaki H, Tanaka M, Takakura A, Nishioka H, Yoshida H, Doi T, Mizoguchi A, Matsuura N, Niho Y, Nishimune Y, Nishikawa S, Takai Y: Progressive impairment of kidneys and reproductive organs in mice lacking Rho GDI α . *Oncogene* 18: 5373–5380, 1999
79. Yu CC, Yen TS, Lowell CA, DeFranco AL: Lupus-like kidney disease in mice deficient in the Src family tyrosine kinases Lyn and Fyn. *Curr Biol* 11:34–8, 2001
80. Weiher H, Noda T, Gray DA, Sharpe AH, Jaenisch R: Transgenic mouse model of kidney disease: insertional inactivation of ubiquitously expressed gene leads to nephrotic syndrome. *Cell* 62:425–34, 1990
81. Reuter A, Nestl A, Zwacka RM, Tuckermann J, Waldherr R, Wagner EM, Hoyhtya M, Meyer zum Gottesberge AM, Angel P, Weiher H: Expression of the recessive glomerulosclerosis gene Mpv 17 regulates MMP-2 expression in fibroblasts, the kidney, and the inner ear of mice. *Mol Biol Cell* 9: 1675–1682, 1998
82. Zwacka RM, Reuter A, Pfaff E, Moll J, Gorgas K, Karasawa M, Weiher H: The glomerulosclerosis gene Mpv 17 encodes a peroxisomal protein producing reactive oxygen species. *Embo J* 13: 5129–5134, 1994
83. Doyonnas R, Kershaw DB, Duhme C, Merckens H, Chelliah S, Graf T, McNagny KM: Anuria, omphalocele, and perinatal lethality in mice lacking the CD34-related protein podocalyxin. *J Exp Med* 194:13–27, 2001
84. Wharram BL, Goyal M, Gillespie PJ, Wiggins JE, Kershaw DB, Holzman LB, Dysko RC, Saunders TL, Samuelson LC, Wiggins RC: Altered podocyte structure in GLEPP1 (Ptp^{ro})-deficient mice associated with hypertension and low glomerular filtration rate. *J Clin Invest* 106: 1281–1290, 2000
85. Kopp JB, Factor VM, Mozes M, Nagy P, Sanderson N, Bottinger EP, Klotman PE, Thorgeirsson SS: Transgenic mice with increased plasma levels of TGF- β 1 develop progressive renal disease. *Lab Invest* 74: 991–1003, 1996
86. Schiffer M, Bitzer M, Roberts IS, Kopp JB, Ten BP, Mundel P, Bottinger EP: Apoptosis in podocytes induced by TGF- β and Smad7. *J Clin Invest* 108: 807–816, 2001
87. Le BL, Godfrin Y, Gunther E, Buzelin F, Perretto S, Smit H, Kerjaschki D, Usal C, Cuturi C, Soullillou JP, Dantal J: Extrarenal effects on the pathogenesis and relapse of idiopathic nephrotic syndrome in Buffalo/Mna rats. *J Clin Invest* 109: 491–498, 2002
88. Murayama S, Yagyu S, Higo K, Ye C, Mizuno T, Oyabu A, Ito M, Morita H, Maeda K, Serikawa T, Matsuyama M: A genetic locus susceptible to the overt proteinuria in BUF/Mna rat. *Mamm Genome* 9: 886–888, 1998
89. Savin VJ, Sharma R, Sharma M, McCarthy ET, Swan SK, Ellis E, Lovell H, Warady B, Gunwar S, Chonko AM, Artero M, Vincenti F: Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. *N Engl J Med* 334: 878–883, 1994
90. Sharma M, Sharma R, McCarthy ET, Savin VJ: “The FSGS factor:” enrichment and in vivo effect of activity from focal segmental glomerulosclerosis plasma. *J Am Soc Nephrol* 10: 552–561, 1999
91. Bolton LA, Munson L: Glomerulosclerosis in captive cheetahs (*Acinonyx jubatus*). *Vet Pathol* 36: 14–22, 1999
92. Luimula P, Ahola H, Wang SX, Solin ML, Aaltonen P, Tikkanen I, Kerjaschki D, Holthofer H: Nephrin in experimental glomerular disease. *Kidney Int* 58: 1461–1468, 2000
93. Luimula P, Sandstrom N, Novikov D, Holthofer H: Podocyte-associated molecules in puromycin aminonucleoside nephrosis of the rat. *Lab Invest* 82: 713–718, 2002
94. Yuan H, Takeuchi E, Taylor GA, McLaughlin M, Brown D, Salant DJ: Nephrin dissociates from actin, and its expression is reduced in early experimental membranous nephropathy. *J Am Soc Nephrol* 13: 946–956, 2002
95. Bonnet F, Tikellis C, Kawachi H, Burns WC, Wookey PJ, Cao Z, Cooper ME: Nephrin expression in the post-natal developing kidney in normotensive and hypertensive rats. *Clin Exp Hypertens* 24: 371–381, 2002
96. Bonnet F, Cooper ME, Kawachi H, Allen TJ, Boner G, Cao Z: Irbesartan normalises the deficiency in glomerular nephrin expression in a model of diabetes and hypertension. *Diabetologia* 44: 874–877, 2001
97. Patrakka J, Ruotsalainen V, Ketola I, Holmberg C, Heikinheimo M, Tryggvason K, Jalanko H: Expression of nephrin in pediatric kidney diseases. *J Am Soc Nephrol* 12: 289–296, 2001
98. Doublier S, Ruotsalainen V, Salvadio G, Lupia E, Biancone L, Conaldi PG, Reponen P, Tryggvason K, Camussi G: Nephrin redistribution on podocytes is a potential mechanism for proteinuria in patients with primary acquired nephrotic syndrome. *Am J Pathol* 158: 1723–1731, 2001
99. Tanawattanacharoen S, Falk RJ, Jennette JC, Kopp JB: Parvovirus B19 DNA in kidney tissue of patients with focal segmental glomerulosclerosis. *Am J Kidney Dis* 35: 1166–1174, 2000
100. Moudgil A, Nast CC, Bagga A, Wei L, Nurmamet A, Cohen AH, Jordan SC, Toyoda M: Association of parvovirus B 19 infection with idiopathic collapsing glomerulopathy. *Kidney Int* 59: 2126–2133, 2001
101. Ross MD, Klotman PE: Recent progress in HIV nephropathy. *J Am Soc Nephrol* 13: 2997–3004, 2002

**Access to UpToDate on-line is available for additional clinical information
at <http://www.jasn.org/>**