

Not All in the Family: Mutations of Podocin in Sporadic Steroid-Resistant Nephrotic Syndrome

MICHELLE P. WINN

Division of Nephrology, Duke University Medical Center, Durham, North Carolina.

The causes of familial nephrotic syndromes are varied and diverse. Although phenotypic differences are seen with distinct congenital and adult forms, renal pathology tends to be less well defined, with blurring and overlap of diagnoses. Clinically, symptoms of the familial nephrotic syndromes may appear from birth to late in life, which demonstrates the heterogeneity of these diseases. The disease may be mild or severe, such that there is variable progression to end-stage renal disease (ESRD) (1–3). Pathologic diagnoses associated with familial nephrotic syndromes include minimal change-type lesions, mesangial sclerosis, and focal segmental glomerulosclerosis (FSGS) (4,5). Treatment depends on the specific disease state, ranging from bilateral nephrectomy and transplantation directly after birth in Finnish nephropathy (6) to attempts at more traditional treatment with steroid therapy. Of particular interest is whether the disease recurs after transplantation, which would direct one to systemic pathogenetic mechanisms. The genetic bases for several forms of congenital nephrotic syndrome have been recently solved. The commonality among known causes of familial nephrotic syndromes is the underlying pathophysiology that is associated with increased glomerular permeability due to defects of some feature of podocyte biology (7–10).

Although the implications of these genetic discoveries in these rare inherited disorders to more common forms of nephrotic syndrome have been questioned, the article by Karle *et al.* in this issue suggests common genetic mechanisms and pathophysiology between inherited and sporadic forms of steroid-resistant nephrotic syndrome.

The classical syndrome of steroid-resistant congenital nephrotic syndrome (chromosome 1q) is inherited in an autosomal recessive fashion with an age of onset between 3 mo and 5 yr (11). Progression to ESRD is usually rapid, and pathology is characterized initially by minimal glomerular changes early and FSGS later in the course of disease. The disease does not recur after transplantation. The causative gene was recently identified by Boute *et al.* (9). The gene, named podocin or NPHS2, is solely expressed in podocytes and is an integral membrane protein that belongs to the stomatin protein family. Members of this family are known to interact with ion channels

and may be involved with protein trafficking (12). Recently an adult form of autosomal recessive FSGS has been linked to this region (13).

The article by Karle *et al.* (14) describes novel mutations of NPHS2 in steroid-resistant congenital nephrotic syndrome and provides first-time evidence for mutations in NPHS2 in sporadic disease. These findings bear out a frequently held assumption that genetic studies of rare familial diseases will provide insight into the pathogenesis of that disease and the mechanism of the more common sporadic forms of that same disease. The patients described by Karle *et al.* appear to differ phenotypically from the original description of families with steroid-resistant idiopathic nephrotic syndrome. For example, these individuals present much later in life (1 to 24 yr of age). They also exhibit a recurring theme that has emerged from studies of congenital nephropathies: phenotypic heterogeneity but genetic similarity. Although the original steroid-resistant idiopathic nephrotic syndrome was described as an autosomal recessive disease, mutations found in eight of the families were heterozygous, implying an autosomal dominant mode of inheritance. Nonetheless, three of the families appear to have an autosomal recessive pattern of inheritance even though they have heterozygous mutations. This might be explained if these patients were compound heterozygotes, as such, inheriting a different mutation from each parent.

This study also supports the hypothesis that minimal change disease and FSGS are different points on the same disease spectrum. In the study, patients with the same genetic defect exhibited a range of pathologies from minimal change to FSGS. This also highlights the issue of whether FSGS is just the generic result of a cascade of events or the primary event. For example, some have suggested that long-standing proteinuria may contribute to the transformation of minimal change disease to FSGS (15). In support of this view are studies showing that the administration of large amounts of albumin to rats causes glomerulosclerosis, tubular injury, and interstitial fibrosis (16). Similarly, in a study by Ahmad and Tejani (17) of 49 patients who over a 10-yr period had repeat renal biopsies, over 50% of the renal disease in these patients evolved into FSGS.

These findings raise additional issues that are related to the diagnosis and therapy of idiopathic nephrotic syndrome (INS). If genetic studies of patients with INS reveal NPHS2 mutations, should these patients be treated with corticosteroids or immunosuppressive therapy? To decide this issue, it must be shown that people with INS who are steroid-responsive do not have NPHS2 mutations. It is also reasonable to question

Correspondence to: Dr. Michelle P. Winn, Duke University Medical Center, Division of Nephrology, Box 2903, Durham, NC 27710. Phone: 919-660-0038; Fax: 919-970-5813; E-mail: mwinn@chg.mc.duke.edu

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whether to treat individuals with familial nephrotic syndromes. On the basis of our knowledge of the genetic pathogenesis of congenital nephropathies, most familial nephrotic disease is caused by an integral abnormality of the glomerulus, and there is uncertainty as to how a corticosteroid or other immunosuppressive agent would affect these processes. Recently, a steroid-responsive idiopathic nephrotic syndrome (SSINS) has been described (18). The apparent mode of inheritance of this disease is autosomal recessive, and renal pathology revealed minimal-change disease pathology. The patients presented between 7 mo and 14 yr of age. All patients were steroid-responsive, and the families were apparently not linked to the NPHS2 locus on chromosome 1q. Thus, although this disease is caused by a different genetic defect, the pattern of inheritance and pathology are similar to steroid-resistant congenital nephritic syndrome.

Identification of the genetic basis for other inherited forms of nephrotic syndrome has provided additional insights into pathogenesis. The locus for congenital nephrotic syndrome of the Finnish type or Finnish nephropathy (chromosome 19q) was published in 1994 and is the best described of all of the familial nephrotic syndromes (19). Finnish nephropathy is inherited as an autosomal recessive trait and begins *in utero*, with vast proteinuria and nephrotic syndrome directly after birth. The disorder is seen in populations other than the Finnish (20–22). Treatment consists of bilateral nephrectomy directly after birth, correction of protein deficiency, peritoneal dialysis, and early transplantation (6). The causative mutations are in the nephrin gene (NPHS1), where approximately 50 mutations have been described (23). The gene itself is a transmembrane protein with Ig-like motifs and localized to the slit diaphragm between podocytes (24,7). The location of nephrin concurs with expectations of pathogenesis in that the renal pathology of individuals with Finnish nephropathy reveals a complete absence of the slit diaphragm as well as foot process effacement.

Autosomal-dominant FSGS (chromosome 19q and 11q) is typically a disease of adults with variable age of onset, severity, and progression to ESRD (2). At present, there are two known loci for this inherited disease. Alpha-actinin 4 (ACTN4) was recently found to be the causative mutation in a subset of families with autosomal-dominant FSGS linked to chromosome 19q (10). Although ACTN4 is expressed in a wide range of tissues, it is highly expressed in podocytes. Alpha-actinins crosslink actin, and the mutated gene in these families appear to bind F-actin more tightly.

There are a number of other nephrotic syndromes that are associated with congenital malformations. Typically, FSGS is the predominant pathology seen in conjunction with these syndromes. Charcot-Marie-Tooth disease (25) and Laurence-Moon-Biedl syndrome (26) have both been associated with FSGS. Frasier syndrome and Denys-Drash frequently are related in that they both are caused by mutations in the Wilms tumor gene on chromosome 11p. Male pseudohermaphroditism, genitourinary tumors, and nephrotic syndrome are components of these syndromes. Usually, Frasier syndrome is associated with FSGS, and Denys-Drash causes diffuse mesangial sclerosis (27). Congenital nephrotic syndrome has been

seen in CD2AP-deficient mice (8). CD2AP is an adapter protein that interacts with CD2. Renal pathology from CD2AP-deficient mice revealed podocyte foot process effacement and glomerulosclerosis.

Even though the aforementioned disease states are phenotypically heterogeneous, the causative genes all appear to affect a single cell type: the podocyte. For these diseases, the theme of phenotypic heterogeneity and genetic similarity is once again raised. These nephrotic syndromes are all characterized by podocyte foot process abnormalities, including fusion and effacement. The most thoroughly studied of the known genes is nephrin. The exact pathogenetic mechanism is not yet identified; it has, however, been hypothesized that, as nephrin is a transmembrane protein that localizes to the slit diaphragm between podocyte foot processes, nephrin may form a zipper-like membrane structure, which is the glomerular filtration barrier ultrafilter (28). The function of ACTN4 is not fully understood. The mutated ACTN4 has been shown in cosedimentation studies to bind F-actin more tightly (10). Postulated mechanisms for podocyte dysfunction include interference with the actin assembly mechanism, which distorts the cytoskeleton.

Glomerular diseases cause enormous morbidity each year as well as costs and mortality from the eventual ESRD. As more is learned about the pathogenesis and molecular mechanisms that underlie this disease process, rational treatment guidelines can also be developed. The podocyte has become the touchstone of all that is nephrotic, and as new genes are discovered, the inner mechanisms of this cell will continue to be elucidated.

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See related article, “Novel Mutations in NPHS2 Detected in Both Familial and Sporadic Steroid-Resistant Nephrotic Syndrome,” on pages 388–393.