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

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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 nephritic 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...
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
cased by an integral abnormality of the glomerulus, and there
is uncertainty as to how a corticosteroid or other immunosup-
presssive agent would affect these processes. Recently, a ste-
roid-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 be-
tween 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 inheri-
tance 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 in-
herited 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 ab-
ence 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, sever-
ity, 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 chromo-
some 19q (10). Although ACTN4 is expressed in a wide range
of tissues, it is highly expressed in podocytes. Alpha-actinin
 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 re-
lated in that they both are caused by mutations in the Wilms
tumor gene on chromosome 11p. Male pseudohermaphrodit-
ism, genitourinary tumors, and nephrotic syndrome are com-
ponents of these syndromes. Usually, Frasier syndrome is
associated with FSGS, and Denys-Drash causes diffuse me-
angial sclerosis (27). Congenital nephrotic syndrome has been
seen in CD2AP-deficient mice (8). CD2AP is an adapter pro-
tein that interacts with CD2. Renal pathology from CD2AP-
deficient mice revealed podocyte foot process effacement and
glomerulosclerosis.

Even though the aforementioned disease states are pheno-
typically heterogeneous, the causative genes all appear to af-
flect 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 charac-
terized by podocyte foot process abnormalities, including fu-
sion 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 in-
terference with the actin assembly mechanism, which distorts
the cytoskeleton.

Glomerular diseases cause enormous morbidity each year 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 touch-
stone of all that is nephrotic, and as new genes are discovered,
the inner mechanisms of this cell will continue to be eluci-
dated.

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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.