FEATURE

Single-Gene Defects Elucidate Mechanisms of CKD

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Focal segmental glomerulosclerosis (FSGS) in patients with steroid-resistant nephrotic syndrome (SRNS) may be caused by single-gene (monogenic) mutations in 1 of 30 genes. A monogenic mutation represents one of the strongest cause-and-effect relationships in clinical medicine, because a mutation in 1 of the 3.3 billion base pairs of the total genome is sufficient to cause FSGS. In his Homer W. Smith Award lecture, Friedhelm Hildebrandt, MD, Boston Children's Hospital, Boston, Massachusetts, USA, stated that FSGS is an example of the many monogenic diseases caused by a mutation in only 1 of the approximately 22 000 genes identified in the human genome.

A gene can be recessive, in which both parental copies of the gene are mutated and cause disease while the parents are heterozygous healthy carriers; recessive polycystic kidney disease (PKD) is an example. Alternatively, the gene can be dominant, as in dominant PKD, in which a mutation in 1 of the 2 parental genes is sufficient to cause disease. However, the term *monogenic* does not exclude the possibility that different genes in different patients can cause a similar disease—that is, genetic heterogeneity, as with the podocin or nephrin genes, which can both cause FSGS. Presently, >30 genes have been identified that will cause SRNS if mutated.

Gene analysis has uncovered the role of the glomerular podocyte in the pathogenesis of SRNS, and identification of single-gene causes of SRNS has elucidated essential components of glomerular function, including the integrin/laminin and actin-binding proteins.

The causative mutation (CM) has been identified in 29.5% of the 1783 families worldwide with SRNS that developed before 25 years of age [Sadowski CE et al. *J Am Soc Nephrol*. 2014]. Podocin, nephrin, WT1, and PLCE1 compose 24% of the CM in the 26 genes identified. A relation was found between younger age at SRNS onset and proportion of CM identified, ranging from about 60% in infants to about 10% in adolescents.

The North American Pediatric Renal Trials and Collaborative Studies list the disease categories that cause early-onset chronic kidney disease (CKD) [Smith JM et al. *Pediatr Transplant.* 2013]. When mutation analysis was performed in the monogenic genes known to cause these disorders, Dr Hildebrandt's laboratory identified CMs in a higher percentage of individuals (Table 1). Therefore, simple criteria were developed to guide the decision to perform a mutation analysis in persons that develop CKD before age 25 years (Table 2).

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Table 1. CKDs Caused by a Single-Gene Defect Before Age 25 Years

	Proportion Caused by Single-Gene Defect, %	No. of Genes Identified	Proportion of Monogenic Disease, %
CAKUT	50	30	>15
SRNS	15	30	>30
Chronic glomerulonephritis[a]	14	NA	NA
Cystic kidney disease[b]	6	95	>70
Tubulopathies	3	45	>20

CAKUT, congenital anomalies of kidneys and urinary tract; CKD, chronic kidney disease; NA, not available; SRNS, steroid-resistant nephrotic syndrome.
[a]Includes membranoproliferative nephropathy, systemic lupus erythematosus, immunoglobulin A nephropathy, and Wegener granulomatosis.
[b]Includes autorecessive polycystic kidney disease, autodominant polycystic kidney disease, nephronophthisis, and medullary cystic kidney disease.
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Table 2. Indications for Performing Mutation Analysis for Single-Gene Causes of CKD

	No. of Possible Genes	Proportion of Patients With Genes Detected, %
SRNS (proteinuria)	30	30
Cystic kidney disease[a]	95	> 70
CAKUT (identified on imaging)	30	> 15
Renal stones[b]	60	> 21
All CKD manifesting < 25 y	Approximately 215	> 20

CAKUT, congenital anomalies of kidneys and urinary tract; CKD, chronic kidney disease; SRNS, steroid-resistant nephrotic syndrome.

[a] ≥ 2 cysts or echogenicity on ultrasound.

[b] ≥ 1 stone or nephritis.

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According to Dr Hildebrandt, whole exome sequencing (WES) has made it possible to identify new monogenic disease genes and pathogenic pathways. One pathway that leads to SRNS has been identified in 2 siblings with FSGS whose parents were first-degree cousins, therefore representing a treatable cause of SRNS. Homozygosity mapping and WES determined that mutations in the *ADCK4* gene caused SRNS [Ashraf S et al. *J Clin Invest*. 2013]. The *ADCK4* gene has been shown to play a role in the biosynthesis of coenzyme Q10 (CoQ10), which has an important role in mitochondrial respiratory activity [DiMauro S et al. *J Clin Invest*. 2007]. Podocyte migration assays showed that an *ADCK4* mutation causes a loss of function and that the addition of CoQ10 restored function. One patient had a partial remission after CoQ10 treatment [Ashraf S et al. *J Clin Invest*. 2013]. Investigators also showed that CoQ10 reduced proteinuria in a 5-year-old patient with a CoQ6 mutation [Heeringa SF et al. *J Clin Invest*. 2011].

Another pathway implicated in the pathogenesis of SRNS involves the *ARHGDIA* homozygous truncated gene, which is a regulator of the GTPases RHOA, RAC, and CDC42 and in turn regulates podocyte cell migration and proliferation [Gee HY et al. *J Clin Invest*. 2013]. ARHGDIA does not bind to the GTPases when a mutation is present, leading to the development of SRNS. The mutation was identified via homozygosity mapping and WES in 2 siblings with infantile SRNS.

In the zebrafish model of nephrotic syndrome developed by the Hildebrandt laboratory, knockdown of ARHGDIA resulted in features seen in SRNS, including edema, periorbital edema, and proteinuria. Treatment with a RAC1 inhibitor, not a RHOA inhibitor, mitigated the disease process.

Currently, there is no effective treatment for SRNS. Dr Hildebrandt and colleagues will use podocyte migration assays and the zebrafish model to screen small molecules and to identify and develop new treatments for the disease. Some of these new drugs will likely target the genes implicated in the pathogenesis of SRNS.

Cystic kidney disease, often called *ciliopathies*, is another cause of kidney disease before age 25. Hildebrandt and colleagues have identified 35 of the 95 genes that cause ciliopathies [Hildebrandt F et al. *N Engl J Med*. 2014]. Many signaling pathways have been implicated in the pathogenesis of nephronophthisis-related ciliopathies, but it is likely that mutation analysis will identify, for individual patients, which of these pathogenic pathways is relevant, as a means of "personalized medicine."

In closing, Dr Hildebrandt stated that all patients who have a kidney disease known to be caused by a gene mutation should be given the opportunity to identify their gene mutation. It is now feasible to conduct the mutation analysis, which provides an unequivocal diagnosis. The analysis may reveal potential treatments; it allows for etiologic classification for therapeutic and clinical trials; and it provides additional information to elucidate the pathogenic pathways. Finally, it enables the generation of gene-specific animal models and screening for therapeutic molecules.