Familial FSGS

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Focal segmental glomerulosclerosis (FSGS) and nephrotic syndrome can be caused by rare highly penetrant mutations in number of genes. FSGS can follow both recessive and dominant inheritance patterns. In general, recessive forms present early, whereas the autosomal dominant forms present in adolescence or adulthood. Many of the genes found to be mutated in FSGS and nephrotic syndrome patients encode proteins essential for normal podocyte structure and/or function. An exception appears to be APOL1, which harbors common variants responsible for the high rate of FSGS and other nephropathies in people of recent African ancestry. Familial FSGS should be regarded as part of a spectrum of inherited glomerulopathies where the precise histologic presentation may depend on the age of onset, function of the responsible gene and gene products, and other factors.

Key Words: FSGS, Genetic

Focal segmental glomerulosclerosis (FSGS) is a pathologic rather than a diagnosis. In discussing "familial FSGS," it is easy to lose sight of this fact. A broad range of genetic and nongenetic factors can lead to kidney injury that manifests as focal and segmental scarring of the kidney's glomeruli. A common theme in these familial forms appears to be alterations in the glomerular podocyte's structure and/or function. It is commonplace to divide disease-altering genetic variants into 2 main groups: rare highly penetrant changes in DNA that cause Mendelian forms of disease and common genetic variation that underlies common disease-related phenotypes. There is increasing interest in the notion that rare variants may also help explain risk for more common diseases. We will focus here largely on the highly penetrant forms of FSGS and also the related "podocytopathies" that cause early-onset nephrotic syndrome (NS).

Inherited FSGS and NS can be broadly divided into early-onset recessive disorders and late-onset autosomal dominant disorders (Table 1). As a general rule, the recessive forms of FSGS and NS are caused by loss-of-function mutations and present in infancy or early childhood. In contrast, most of the dominant forms of FSGS are caused by gain-of-function mutations and are characterized by late-onset slowly progressive disease.

Autosomal Dominant FSGS

Point mutations in several genes lead to autosomal dominant kidney disease characterized by proteinuria, progressive CKD, and FSGS. Mutations in *INF2*, for Inverted Formin 2, appear to be the most common of these.[1-4] INF2 is a member of the formin family of actin polymerizing molecules. INF2 is unique in its ability to both accelerate actin polymerization and depolymerization. Formins are able to autoinhibit their activity by an intramolecular interaction between 2 domains, the N-terminal diaphanous inhibitory domain (DID) and the C-terminal diaphanous autoregulatory domain. For most formins studied, binding of a small GTPase to the N-terminus near the DID can relieve this autoinhibition. The DID also binds to the diaphanous autoregulatory domain regions of the diaphanous formins, downstream effectors of RhoA, inhibiting the activity of these actin regulators. All the 40 INF2 mutations reported to date localize to the DID, suggesting that loss of inhibition of INF2's own activity or the activity of other formins (or both) may be critical to the mechanism of this form of disease. Subsets of patients with INF2 mutants also have Charcot-Marie-Tooth disease, a peripheral demyelinating condition.[5] There does not appear to be a clear difference in the nature of the mutations associated with FSGS alone vs those with Charcot-Marie-Tooth disease.

By positional cloning efforts in large multiplex families, FSGS-causing mutations were identified in the alpha-actinin-4 gene *ACTN4* and in the *TRPC6* cation channel gene.[6,7] The ACTN4 and *TRPC6*-associated phenotypes are similar: proteinuria, typically in the non-nephrotic range, and progressive chronic kidney disease. *ACTN4* encodes an actin crosslinking protein alpha-actinin-4 that forms head-to-tail dimers with actin-binding domain at each end. FSGS-associated mutations localize to the N-terminal actin-binding domain of the protein. These point mutations cause an increase in actin-binding affinity of these rod-shaped dimers, likely causing changes in cytoskeletal biophysical properties and actin dynamics within cells.[8]

TRPC6 is a cation channel. Mutations in TRPC6 appear to be gain-of-function, leading to dominant disease through increased channel activity.[7,9] TRPC6-mediated calcium flux may activate RhoA signaling in cells.[10] This observation adds to the notion that altered small GTPase signaling is a common theme in podocyte dysfunction. Gain-of-function mutations in TRPC6 have also been shown to activate extracellular signal-regulated kinases 1/2 and cause constitutive activation of nuclear factor of activated T-cells (NFAT)-dependent transcription.[11,12]

Several FSGS genes have been identified by mutational analyses of candidate genes, chosen for examination based on known roles in glomerular biology. *ARHGAP24*, encoding the FilGAP protein, was examined for disease-associated variants because of its expression pattern in podocytes. *ARHGAP24* encodes a GTPase-activating protein that is

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activated by RhoA. Analysis of this gene in FSGS families identified 1 family in which a mutation interfered with the activity of FilGAP and segregated with disease.[13] Similarly, the *CD2AP* gene has been analyzed for disease-associated variation based on its role in podocyte and slit-diaphragm function.[14] Mutational analysis in DNA from FSGS patients identified 2 individuals with a mutation predicted to ablate expression of 1 *CD2AP* allele, consistent with the notion that haploinsufficiency of *CD2AP* can contribute to the development of FSGS under a dominant model of inheritance. In contrast, Lowik and colleagues[15] identified a homozygous mutation encoding a premature stop codon in the *CD2AP* gene, consistent with an autosomal recessive form of *CD2AP*-associated FSGS.

WT1, named for its role in Wilms tumor, plays a critical role in kidney development.[16] Mutations in *WT1* typically lead to the syndromic forms of kidney disease known as Frasier Syndrome and Denys-Drash Syndrome. *WT1* mutations can also rarely cause isolated NS after autosomal dominant inheritance.[17-21] Frasier syndrome is characterized by steroid-resistant NS in childhood with histologic findings of FSGS, progressive CKD, male pseudohermaphroditism, and a high rate of gonadoblastomas. Denys-Drash-affected individuals display steroid-resistant nephrosis in infancy with histologic findings of mesangial sclerosis. Denys-Drash patients progress to kidney failure and manifest ambiguous genitalia and nephroblastoma (Wilms tumor). Mutations altering the 3 amino acids KTS (lysine, threonine, and serine) in the splice site in intron 9 can cause isolated NS with the absence of Wilms tumor in 46, XX phenotypically concordant females.[19] Missense mutations in exons 8 and 9 of *WT1* have been detected in patients with isolated diffuse mesangial sclerosis.[22]

CLINICAL SUMMARY

- A large number of single-gene causes of focal segmental glomerulosclerosis and steroid resistant nephrotic syndrome have been identified.
- Even in the absence of a positive family history, a single gene form of kidney disease may be present.
- The high rate of FSGS in people of recent African ancestry is largely attributable to two variants in the *APOL1* gene.

Recessive Forms of FSGS

Inheritance of 2 mutant copies of several genes can cause recessive forms of FSGS/NS. In general, these recessive forms of disease present at earlier ages and are more aggressive than the autosomal dominant forms. Positional cloning studies in neonates with congenital NS of the Finnish type led to the identification of mutations in the gene *NPHS1*, encoding nephrin, as the genetic cause.[23] Nephrin is a transmembrane protein that serves structural and signaling functions.[24] Typically, inheritance of 2 pathogenic *NPHS2* mutations causes severe congenital nephrosis, with loss of podocyte foot process architecture and obliteration of a recognizable slit diaphragm.[23] Further studies suggest that the phenotypic spectrum of nephrin-associated disease is broader than originally observed, with some individuals presenting in childhood, or rarely, with FSGS in adulthood.[25,26] Close to 200 pathogenic *NPHS1* mutations have been identified to date.

Positional cloning efforts also identified the *NPHS2* gene, encoding podocin, as a relatively common cause of autosomal recessive steroid-resistant NS and FSGS in early childhood.[27] People with 2 pathogenic *NPHS2* mutations tend to present with NS between 3 months and 6 years of life, though some individuals present with congenital nephrosis and others with adult-onset FSGS.[28,29] Certain specific *NPHS2* variants appear more likely to cause disease at an earlier age, specifically frameshift, nonsense, and homozygous R138Q missense mutations.[30-35] *NPHS2*-associated disease is resistant to glucocorticoids and other immunosuppressive therapy. Patients with *NPHS2*-associated disease have a reduced risk for recurrence of FSGS after kidney transplantation compared with idiopathic FSGS.[27,32,36,37] Mutations in *NPHS2* have been found to be causal in 6% to 17% of sporadic cases and 28% to 39% of familial cases of steroid resistant nephrotic syndrome (SRNS). Late-onset FSGS is typically observed in individuals who carry the common R229Q *NPHS2* polymorphism together with a second mutation.[29,34] This R229Q variant has an allele frequency of about 3% in most populations. The podocin protein is a lipid raft component of the slit diaphragm.[38] Podocin interacts directly with nephrin and is required for nephrin localization and function.[39-41]

Homozygosity mapping in consanguineous families identified a locus for early-onset NS and diffuse mesangial sclerosis on chromosome 10, leading to the identification of the responsible gene, phospholipase C epsilon 1 (*PLCE1*). Both missense and truncating mutations have been identified in *PLCE1*. Late-onset *PLCE1*-associated disease may manifest as FSGS on biopsy.[42]

Other recent studies using high-throughput genotyping and next-generation sequencing in consanguineous families have led to the identification of additional autosomal recessive childhood nephrosis and/or proteinuria genes. These include the myosin 1E gene (*MYO1E*), the Nei endonuclease VIII-like 1 gene (NEIL1), the cubulin gene C, the *ADCK4* gene, and the RhoGDI alpha gene.[43-48] These forms of disease appear to be quite rare.

Data examining various therapies in genetic forms of FSGS and NS are very limited. Although there appears to be occasional patients who do respond to immunosuppression, this is rare. Most patients with *NPHS1* or *NPHS2* mutations do not respond to immunosuppression. Genetic testing may, therefore, guide the decision of how to treat an affected individual. Little information exists with regard to treatment response in autosomal dominant forms of FSGS caused by mutations in TRPC6, ACTN4, and INF2, but anecdotal information suggests that these forms of disease do not respond to immunosuppression.

APOL1 and FSGS in the African Diaspora

FSGS is particularly common in people of recent African ancestry. Genome-wide association studies using