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Familial FSGS

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Abstract

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, while 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 age of onset, function of the responsible gene and gene products, as well as other factors.

Keywords

FSGS; Genetic

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 non-genetic 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 two main groups: rare highly penetrant changes in DNA that cause Mendelian forms of disease, and common genetic variation that underlie 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” which cause early onset nephrotic syndrome (NS).

Inherited FSGS and NS can be broadly divided into early onset recessive disorders and later onset autosomal dominant disorders. 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. By

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contrast, most of the dominant forms of FSGS are caused by gain-of-function mutations and are characterized by later 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 two domains, the N-terminal DID (diaphanous inhibitory domain) and the C-terminal DAD (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 DAD regions of the diaphanous formins, downstream effectors of RhoA, inhibiting the activity of these actin regulators. All of the 40 some INF2 mutations reported to date localize to the DID, suggesting that loss of inhibition of INF2 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 versus 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 (ERK1/2) and cause constitutive activation of 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 activated by RhoA. Analysis of this gene in FSGS families identified one 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 two

individuals with a mutation predicted to ablate expression of one CD2AP allele, consistent with the notion that haploinsufficiency of CD2AP can contribute to the development of FSGS under a dominant model of inheritance. By contrast, Lowik et al identified a homozygous mutation encoding a premature stop codon in the CD2AP gene, consistent with an autosomal recessive form of CD2AP associated FSGS¹⁵.

WT1, named for its role in Wilms' tumor, plays a critical role in kidney development¹⁶. 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 nephrotic syndrome following autosomal dominant inheritance^{17–21}. Frasier syndrome is characterized by steroid resistant nephrotic syndrome 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 three amino acids KTS (lysine, threonine, serine) in the splice site in intron 9 can cause isolated nephrotic syndrome with the absence of Wilms' tumor in 46, XX phenotypically concordant females¹⁹. Missense mutations in exons 8 and 9 of WT1 have been detected in patients with isolated diffuse mesangial sclerosis (DMS)²².

Recessive forms of FSGS

Inheritance of two 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 nephrotic syndrome of the Finnish type led to the identification of mutations in the gene NPHS1, encoding nephrin, as the genetic cause²³. Nephrin is a transmembrane protein that serves structural and signaling functions²⁴. Typically, inheritance of two pathogenic NPHS2 mutations causes severe congenital nephrosis, with loss of podocyte foot process architecture and obliteration of a recognizable slit diaphragm²³. 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 nephrotic syndrome and FSGS in early childhood²⁷. People with two pathogenic NPHS2 mutations tend to present with nephrotic syndrome 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 6–17% of sporadic cases and 28–39% of familial cases of SRNS. Later 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 diaphragm³⁸. 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 nephrotic syndrome and diffuse mesangial sclerosis on chromosome 10, leading to the identification of the responsible gene, *PLCE1* (phospholipase C epsilon 1). Both missense and truncating mutations have been identified in *PLCE1*. Later onset *PLCE1*-associated disease may manifest as FSGS on biopsy⁴².

Other recent studies utilizing 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 *CUBN*, 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 nephrotic syndrome is very limited. Although there appear 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 (GWAS) using mapping by admixture methods identified a genetic susceptibility locus on chromosome 22^{49,50}. Two coding variants in the *APOL1* drive this association^{51,52}. These variants, termed G1 and G2, in the *APOL1* gene confer increased risk of developing FSGS, hypertension-associated kidney disease, or HIV nephropathy (HIVAN)^{51,52}. G1 denotes the pair of missense variants encoding amino acid changes S342G and I384M that are almost always inherited together; G2 denotes a 6 base pair deletion leading to the in frame deletion of two amino acids near the C terminus of the protein. Individuals homozygous or compound heterozygous for these alleles have a 7–10 fold increased risk of developing FSGS or hypertension-associated ESRD. Those individuals with two *APOL1* risk alleles have an odds ratio as high as 30 for developing HIV-associated FSGS^{51,53,54}. These two risk alleles are common in people of recent African ancestry, with a combined allele frequency of approximately 35% in African Americans⁵⁴. The wild-type form of the *APOL1* protein provides a form of innate immunity against *trypanosoma b. brucei* but not *trypanosoma b. rhodesiense*. The G1 and G2 variants show enhanced lytic activity against the African Sleeping Sickness pathogen *trypanosoma b. rhodesiense*, perhaps leading to positive selective pressures on these alleles. The mechanisms by which these variants in *APOL1* cause kidney disease remains unknown. Because of the high

frequency of G1 and G2 as well as the large increased risk of FSGS associated with these variants, families in which multiple individuals have FSGS or ESRD may have APOL1-associated disease, rather than one of the rarer Mendelian forms of disease described above.

Conclusions

It is important for the clinician to remember that FSGS is a pathologically defined entity, rather than a specific disease. A broad range inherited syndromes may include FSGS as a component or a downstream effect of the primary biological lesion. Thus, individuals with, for example, various forms of nephronophthisis, glomerular basement membrane disorders, and mitochondrial diseases, may all exhibit proteinuria, chronic kidney disease, and FSGS. Thus, careful clinical phenotyping is a critical component in the accurate diagnosis of inherited forms of FSGS.

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Table

Gene	Locus	Inheritance	Protein	Phenotype
Slit diaphragm				
<i>NPHS1</i>	19q13.1	AR	Nephrin	Congenital nephrotic syndrome
<i>NPHS2</i>	1q25.2	AR	Podocin	Congenital, infant, childhood onset SRNS, FSGS.
<i>PLCE1</i>	10q23.33	AR	Phospholipase C epsilon 1	Early onset DMS. FSGS.
<i>CD2AP</i>	6p12	AD	CD2 associated protein	FSGS. CD2AP deficient mouse model develops severe proteinuria
<i>TRPC6</i>	11q22.1	AD	TRPC6	Adult onset FSGS
Actin cytoskeleton				
<i>ACTN4</i>	19q13	AD	Alpha-actinin 4	Adult onset FSGS
<i>INF2</i>	14q32.33	AD	Inverted formin 2	Adult onset FSGS
<i>MYO1E</i>	15q22.2	AR	Myosin 1E	Childhood onset SRNS
<i>ARHGAP24</i>	4q22.1	AD	Arhgap24 (RhoGAP)	Adolescent onset FSGS
<i>ARHGDIA</i>	17q25.3	AR	<u>Arhgdia</u>	Childhood onset SRNS
Nuclear				
<i>WT1</i>	11p13	AD	Wilms' tumor 1	Frasier or Denys Drash syndrome or isolated NS
Other				
<i>APOLI</i>	22q13.1	AR	Apolipoprotein 1	High risk of FSGS and ESKD in African Americans

Genetic causes of FSGS and steroid resistant nephrotic syndrome

AD = autosomal dominant

AR = autosomal recessive

DMS = diffuse mesangial sclerosis.