Kidney Medicine

A Review of Focal Segmental Glomerulosclerosis Classification With a Focus on Genetic Associations

Marco Bonilla, Orhan Efe, Haresh Selvaskandan, Edgar V. Lerma, and Nasim Wiegley

Focal segmental glomerulosclerosis (FSGS) defines a distinct histologic pattern observed in kidney tissue that is linked to several distinct underlying causes, all converging on the common factor of podocyte injury. It presents a considerable challenge in terms of classification because of its varied underlying causes and the limited correlation between histopathology and clinical outcomes. Critically, precise nomenclature is key to describe and delineate the pathogenesis, subsequently guiding the selection of suitable and precision therapies. A proposed pathomechanism-based approach has been suggested for FSGS classification. This approach differentiates among primary, secondary, genetic, and undetermined causes, aiming to provide clarity. Genetic FSGS from monogenic mutations can emerge during childhood or adulthood, and it is advisable to conduct genetic testing in cases in which there is a family history of chronic kidney disease, nephrotic syndrome, or resistance to treatment. Genome-wide association studies have identified several genetic risk variants, such as those in apolipoprotein L1 (*APOL1*), that play a role in the development of FSGS. Currently, no specific treatments have been approved to treat genetic FSGS; however, interventions targeting underlying cofactor deficiencies have shown potential in some cases. Furthermore, encouraging results have emerged from a phase 2 trial investigating inaxaplin, a novel small molecule APOL1 channel inhibitor, in *APOL1*-associated FSGS.

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CLINICOPATHOLOGIC CLASSIFICATION OF FSGS

Focal segmental glomerulosclerosis (FSGS) is a pattern of injury driven by varying etiologies. The clinical classification of patients with FSGS lesions is challenging because of a broad spectrum of etiologies, a limited understanding of pathophysiology, and poor correlation between histopathology and treatment response and clinical outcomes. A morphologic classification was previously proposed based on the Columbia classification,[1] which defines 5 variants: collapsing, tip, cellular, perihilar, and not otherwise specified. However, treatment decisions solely based on this approach risked misguiding treatment and missing genetic cues or syndromic presentations. A clinicopathologic approach over a morphologic approach to FSGS classification, which is holistic and multifaceted, has since been advocated, classifying FSGS into primary, secondary, genetic, and undetermined forms.

Primary FSGS is associated with the presence of an unknown circulating factor, with no evidence of other underlying etiology.[2] To date, the hypothesized molecules are serum urine-type plasminogen activator receptor (suPAR), apA1b (ApoA1 isoform), cardiotrophin-like cytokine factor, and anti-CD40 antibody.[3-6] Primary FSGS is common in adolescents and young adults, although it may occur at any age. Clinically, it is typically associated with nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia.[7] The biopsy findings are characterized by diffuse foot process effacement visible by electron microscopy.[8]

Secondary FSGS, in contrast, arises as a consequence of various systemic conditions or external factors impacting kidney health.[7,9,10] For instance, viral infections, toxins, medications, and glomerular hyperfiltration (from obesity, kidney anomalies, solitary kidney, reflux nephropathy, viral infections, medications, toxins.) can lead to a secondary form of FSGS.[11] This condition leads to podocyte hypertrophy, stress, and glomerular hypertrophy.[12] Clinically, patients present with a normal limit of serum albumin levels with subnephrotic or nephrotic-range proteinuria. Kidney biopsy features that support the diagnosis of secondary FSGS include the appearance of large glomeruli, perihilar scars, and segmental (<80%) foot process effacement on electron microscopy.[8]

Genetic FSGS is associated with mutations in genes encoding proteins implicated in podocyte function or structure. Two important variations are patients who bear susceptibility genes (ie, *APOL1*) and patients with mutations with a high level of penetrance and will manifest maternal or Mendelian inheritance.[7,13] Clinical presentation is variable; some genes are associated with extrarenal manifestations, providing a clinical clue.[14,15] It usually presents in young patients and does not respond to immunosuppression.[16] The kidney biopsy findings are variable and may appear as primary or adaptive FSGS.[8]

This intricate interplay of primary, secondary, and genetic causes of FSGS results in diverse histologic patterns. Differentiating and classifying FSGS based purely on histologic appearance is challenging, though the degree of foot process effacement might help the busy clinician to make more accurate assessments. A

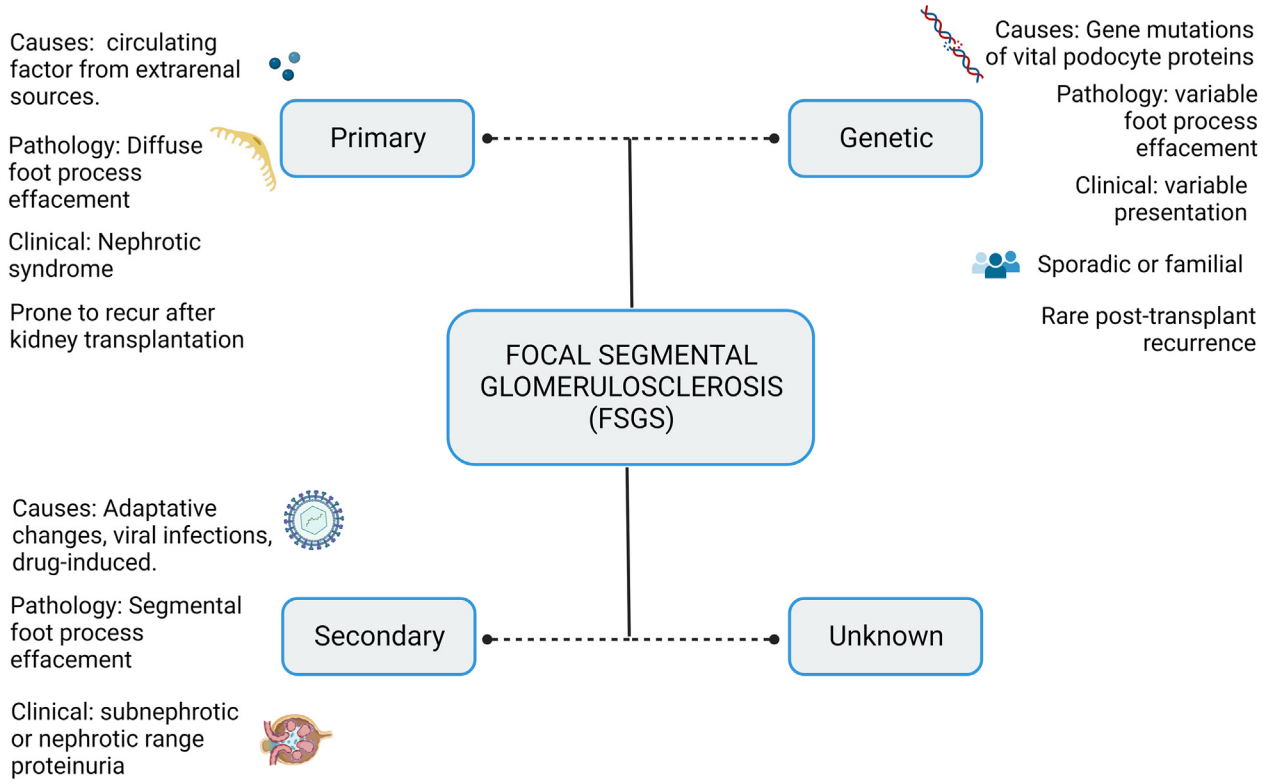

Figure 1. Summary of clinicopathological classification of focal segmental glomerulosclerosis (FSGS) based on the underlying cause. Created using biorender.com.

Japanese study[17] analyzed the degree of foot process effacement and foot process width in kidney biopsies of patients with FSGS. The patients with genetic FSGS had segmental foot process effacement and foot process width <2,000 nm; in contrast, patients with primary FSGS had diffuse foot process effacement and foot process width >3,000 nm. These findings shed light on the potential significance of the degree of foot process effacement in distinguishing between different FSGS subtypes.

The importance of a clinicopathologic classification is based on the different clinical presentations, management, and prognostic implications of the various disorders, all presenting as FSGS on histopathology. In a comprehensive review, De Vriese et al.[8] emphasized that a clinicopathologic classification would enhance clinical management and provide further guidance on the design and implementation of clinical trials. The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines adopted a pathomechanism-based approach to FSGS classification, differentiating among primary (immune-mediated), genetic, secondary or adaptative, and undetermined causes.[18] Figure 1 summarizes this classification.

CLINICAL MANIFESTATION AND ASSOCIATED GENES IN GENETIC FSGS

Genetic FSGS can present in either childhood or adulthood, depending on the affected gene, and can manifest with variable proteinuria and foot process effacement. In some cases of genetic susceptibility (eg, *APOL1* mutation), clinical manifestation only occurs after exposure to a second hit such as chemical toxicity, inflammation, or infection. Monogenic causes of genetic FSGS can be categorized as renal-limited and syndromic, the latter being associated with extrarenal manifestations such as hearing loss and vision impairment. The genes associated with nonsyndromic steroid-resistant nephrotic syndrome (SRNS) and/or FSGS are mainly expressed in the podocyte and are involved in the organization of the slit diaphragm and the actin cytoskeleton.[13] Mutations in *NPHS1*, *NPHS2*, *PLCε1*, *CD2AP*, and *MYO1E* possess an autosomal recessive inheritance pattern,[19-22] whereas mutations in *TRPC6*, *ACTN4*, and *INF2* cause autosomal dominant FSGS.[23-25] Syndromic FSGS results from mutations in genes encoding proteins expressed in tissues beyond the podocytes, such as *WT1*, *LAMB2*, *ITGB4*, *CD151*, *SCARB*, and *LMX1b*.[26-30] In these cases, extrarenal manifestations aid clinicians in making a diagnosis. Table 1 summarizes the genes and presentations involved.

The effect of collagen IV mutations on genetic FSGS and/or SRNS is significant. Deltas et al[31] initially investigated 12 families who were initially believed to have primary autosomal dominant FSGS; however, no causative gene mutations were detected. A shift to focus on a shared trait among all the families—microscopic

Table 1. Genes Involved in Nonsyndromic and Syndromic SRNS and/or FSGS

Gene	Protein	Clinical Manifestation
Nonsyndromic SRNS and/or FSGS—Autosomal recessive pattern of inheritance		
NPHS1	Nephrin	Congenital nephrotic syndrome
NPHS2	Podocin	Congenital and childhood nephrotic syndrome
PLCε1	Phospholipase Cε1	Familial and adult-onset nephrotic syndrome. Diffuse mesangial sclerosis
CD2AP	CD2 associated protein	Childhood-onset FSGS
MYO1E	Non muscle class I myosin 1E	Familial childhood-onset FSGS
Nonsyndromic SRNS and/or FSGS—Autosomal dominant pattern of inheritance		
TRPC6	Transient receptor potential cation channel 6	Familial or sporadic onset FSGS
ACTN4	alpha–Actinin-4	Familial or sporadic adult-onset FSGS
INF2	Inverted formin 2	Familial or sporadic adolescence and adult-onset FSGS
LAMA5	Laminin alpha 5	Adult-onset FSGS
Syndromic SRNS and/or FSGS—Autosomal recessive pattern of inheritance		
LAMB2	Laminin-beta2	Pierson syndrome
ITGB4	Integrin-beta-4	Epidermolysis bullosa, atresia of pylorus. Early-onset FSGS
SCARB2	Scavenger receptor class B member2	Action myoclonus-renal failure syndrome
COL4A3	Alpha 3 type 4 collagen	Alport syndrome
CUBN	Cubilin	Childhood-onset nephrotic syndrome and megaloblastic anemia
Syndromic SRNS and/or FSGS—Autosomal dominant pattern of inheritance		
MYH9	Myosin heavy chain 9	Epstein–Fechtner syndrome
WT1	Wilms tumor 1	Frasier syndrome, Denys–Drash syndrome
LMNA	Lamin A/C	Familial partial lipodystrophy with adult-FSGS

Abbreviations: FSGS, focal segmental glomerulosclerosis; SRNS, steroid-resistant nephrotic syndrome.

hematuria—led to a revelation. DNA linkage analysis pointed toward a genetic association of the *COL4A3* and *COL4A4* genes. A dual diagnosis of FSGS and thin basement membrane nephropathy was unveiled within these families, suggesting the possibility that thin basement membrane nephropathy might predispose certain patients to a more adverse kidney outcome.

In a separate study by Gast et al,[32] researchers delved into the distribution of gene mutations in adult patients with primary FSGS and/or SRNS by targeted next-generation sequencing covering 39 genes, including *COL4A3*-5. On examining 76 families, they discovered mutations in *COL4A3*-5 were present in 8 patients from 6 families, representing 56% of definitely pathogenic mutations. Collagen mutations were identified in 38% of families with familial FSGS and 3% with sporadic FSGS. Patients harboring collagen mutations presented at a younger age and were more likely to have family history, hematuria, and glomerular basement membrane abnormalities.

Variants in the *CUBN* gene have been linked to FSGS. However, in Imerslund-Gräsbeck syndrome, in which *CUBN* variants are often implicated, proteinuria appears to be tubular in nature.[33] Imerslund-Gräsbeck syndrome[34] is a rare genetic disorder involving defects in the absorption of vitamin B12 because of mutations in the *CUBN* or *AMN* genes, which results in various symptoms including megaloblastic anemia and proteinuria. The distinction here is crucial; while *CUBN* variants are associated with both FSGS and Imerslund-Gräsbeck Syndrome, the proteinuria seen in the latter arises from impaired tubular reabsorption of proteins rather than FSGS-related glomerular dysfunction.[35] This clarification underscores the variability in how *CUBN* mutations can manifest, leading to different renal manifestations.[34]

Genome-wide association studies are used to identify genotype–phenotype associations within the genomes of many individuals. In addition to monogenic causes, genome-wide association studies have shown genetic risk variants contributing to the development of FSGS. Most importantly, *APOL1* susceptibility variants on chromosome 22 (G1 and G2) confer a higher risk for FSGS, especially in patients of recent African ancestry.[36] Initially, another risk variant thought to increase the risk of kidney disease was linked to the *MYH9* gene.[37] However, despite exhaustive efforts, including resequencing of the *MYH9* gene, no definitive functional mutation has been identified in this gene.[38,39] Subsequent research led to a pivotal discovery that the *MYH9* gene itself was not the primary contributor to this heightened risk but rather the nearby *APOL1* gene, which often covariates with *MYH9* variants.[40] This clarification is crucial as further investigation identified a stronger association with specific *APOL1* variants, emphasizing their stronger association with the increased risk of kidney disease, including FSGS.[36,40,41] The increased prevalence of high-risk alleles helped

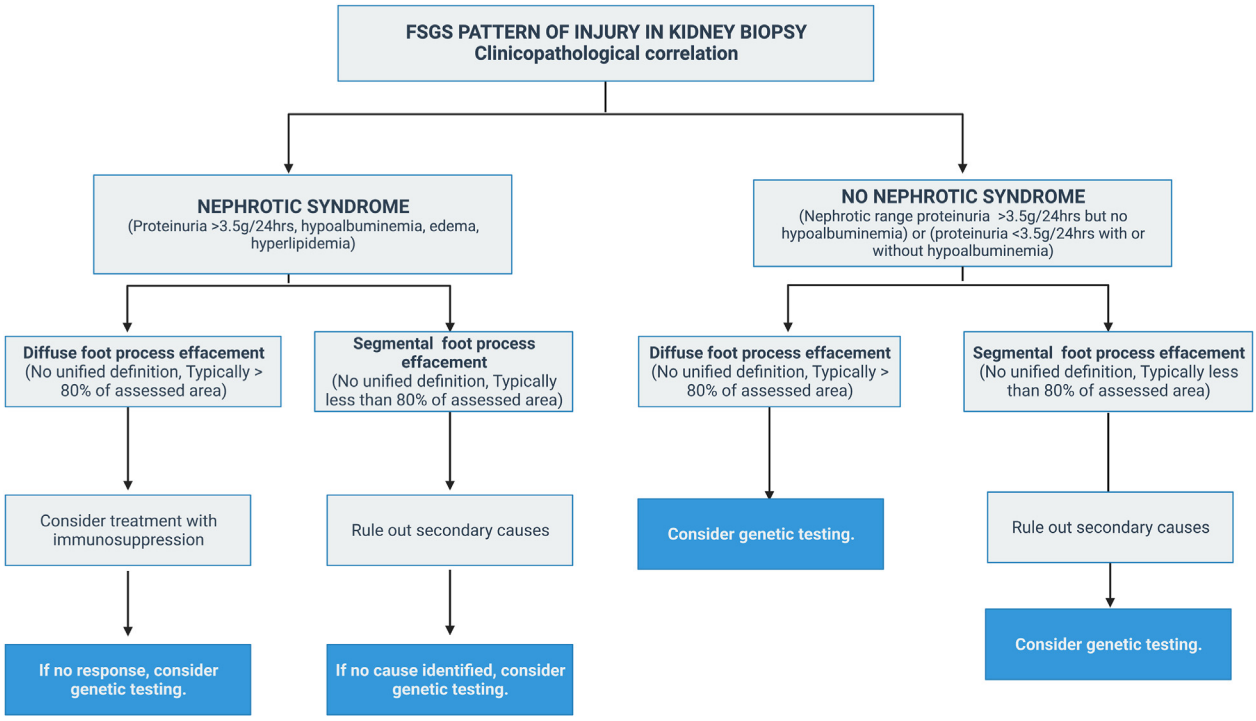

Figure 2. An algorithmic approach to genetic testing in patients with focal segmental glomerulosclerosis (FSGS). Created using biorender.com.

explain the increased risk of FSGS and kidney disease in African-descendant patients.

PREVALENCE OF THE VARIANTS OF GENETIC MUTATIONS IN FSGS

In congenital nephrotic syndrome, the most frequent gene mutation is found in nephrin (*NPHS1*),[19,42] with a prevalence varying from 40%-80% of cases. The second most common is in podocin (*NPHS2*), followed by *WT1* and Laminin β2 (*LAMB2*). A large cohort study of familial and sporadic cases of SRNS by Sadowski et al[43] found a single-gene cause in 29.5% of families with SRNS that manifested before 25 years' age. Regarding the distribution of causative genes, within the first 3 months' life, mutations in *NPHS1* were found in 40% of cases, followed by 10.6% for *NPHS2*, 8.5% for *WT1*, and 5.5% for *LAMB2*. *NPHS2* was the most common gene mutated in patients with noncongenital nephrotic syndrome (onset of SRNS between 1-18 years).

Adult-onset FSGS has been associated with a limited genetic mutation. Sadowski et al[43] found a causative monogenetic cause in 21.4% of the cases with onset between 19-25 years' age. The most common autosomal dominant gene mutation, occurring in up to 17% of familial cases with onset in early adulthood, is in *INF2*, which encodes a member of the diaphanous-related formin family involved in remodeling the actin and microtubule cytoskeletons,[44,45] followed by mutations in *TRPC6* (encodes a calcium-permeable cation channel), reported to account for ∼6% of familial FSGS and ∼2% of sporadic FSGS.[43,46-48] In autosomal recessive inheritance patterns, *NPHS2* is the gene most frequently mutated, with a reported prevalence that ranges from 4%-30% in familial cases.[49-51]

GENETIC TESTING

Establishing a molecular genetic diagnosis of FSGS can help in management decisions and prognostication, such as predicting posttransplant recurrence. Nevertheless, it is challenging for clinicians to select the best candidates for testing. In a cohort of patients with SRNS, underlying genetic mutations were identified in 24% of patients with early childhood-onset (4-12 months' age), 36% of patients with late childhood-onset (13 months' to 5 years' age), 25% of patients with adolescence-onset (6-12 years' age), and up to 14% of patients with adult-onset FSGS.[52] With the rapid advancements in identifying numerous genetic causes of podocytopathies and glomerular diseases that present with an FSGS pattern of injury, it is becoming clear that genetics plays an important role in the differential diagnosis and work-up of FSGS. Although routine genetic screening is not recommended, it should be considered in particular cases. Figure 2 is a proposed algorithmic approach to genetic testing in FSGS adopted from De Vriese et al.[8] In addition, a family history of chronic kidney disease or nephrotic syndrome should alert physicians to a possible genetic cause. Determining

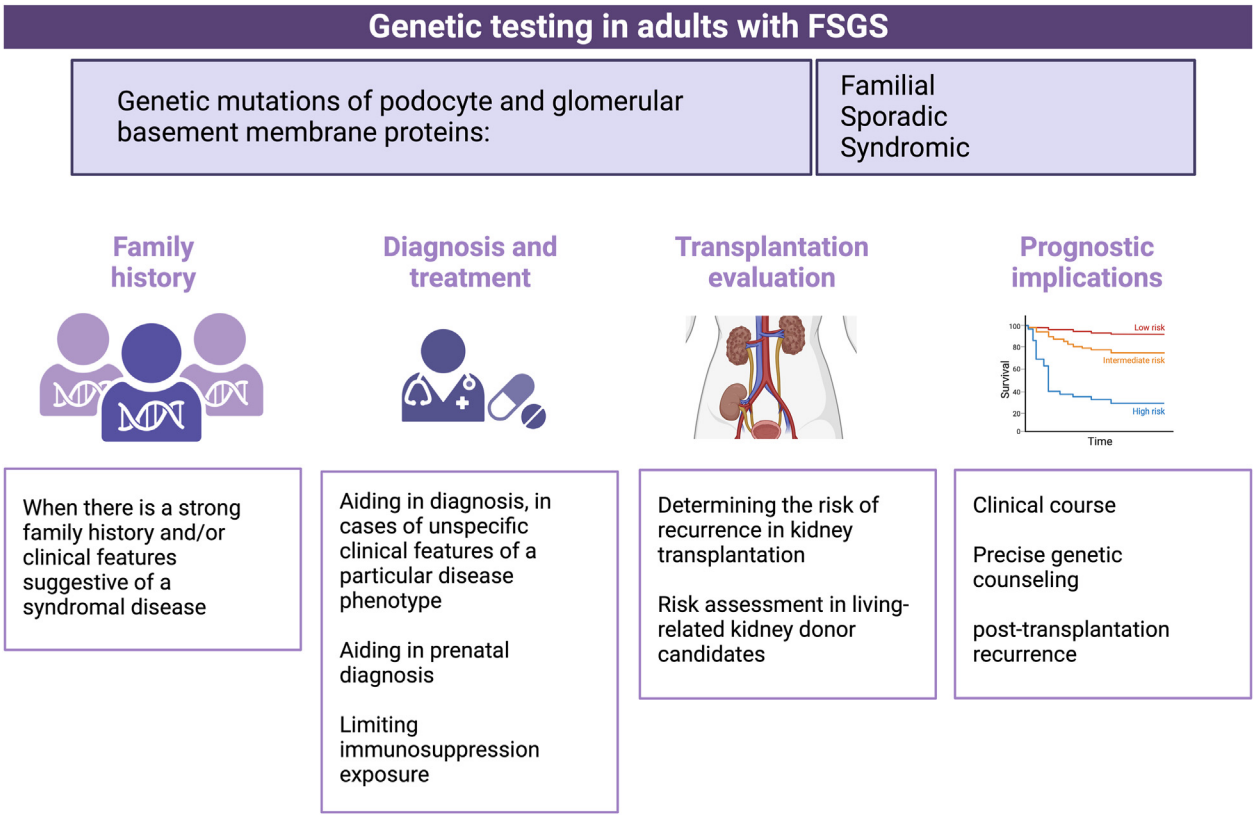

Figure 3. Implications of genetic testing in adults with focal segmental glomerulosclerosis (FSGS). Created using biorender.com.

a genetic cause of FSGS could avoid unnecessary treatments in pre- and posttransplant patients.

Advancements in genetic testing technologies, including next-generation sequencing, allow multiple genes to be screened simultaneously in patients with FSGS.[53,54] Several genetic tests are available for evaluating genetic factors associated with FSGS. With its ability to target thousands of base pairs, next-generation sequencing has been replacing Sanger sequencing, which targets a smaller portion of genes. Panel testing sequences multiple genes related to kidney disease, including FSGS, and can accommodate hundreds of genes of interest. Targeted gene testing[55] focuses on analyzing specific genes known to be associated with FSGS and is used when there is suspicion of a particular genetic mutation. Whole exome sequencing involves sequencing the protein-coding regions of an individual's genome, known as the exome.[56] Whole exome sequencing is useful in cases in which the underlying genetic cause is uncertain or multiple genes might be implicated in the disease. Whole genome sequencing[57] involves sequencing an individual's entire genome, including both protein-coding and noncoding regions. It provides a comprehensive view of an individual's genetic makeup. Whole genome sequencing is more extensive and expensive than other tests and is typically reserved for complex cases. It is important to note that the availability and scope of genetic testing may vary depending on the region, health care facility, and specific testing laboratory. Genetic counseling is often recommended before and after genetic testing to discuss the test results' potential benefits, limitations, and implications. Figure 3 summarizes the use of genetic testing.

TREATMENT FOR GENETIC FSGS

The majority of the genetic mutations are identified in cases of SRNS, and unfortunately, for the vast majority of these mutations, there are currently no specific therapies. However, in certain subgroups of genetic FSGS, treatments targeting the underlying cofactor deficiencies can improve clinical outcomes. For instance, early replacement of CoQ10 can reduce proteinuria in patients with a genetic mutation of CoQ6 monooxygenase.[58] Another underlying gene mutation that could be treated with vitamin replacement is in the *CUBN* gene, which encodes Cubilin. These patients have a hereditary form of megaloblastic anemia due to vitamin B12 deficiency and childhood-onset SRNS and may benefit from vitamin B12 replacement.[35]

A phase 2a trial investigating inaxaplin (VX-147), a small molecule inhibitor of *APOL1* channel function, in

patients with FSGS and proteinuria carrying 2 *APOL1* risk variants has shown positive results. The addition of inaxaplin to the standard of care (angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker + immunosuppressant or low-dose corticosteroids) for 13 weeks showed a substantial reduction in proteinuria of approximately 47.6% compared with baseline. The treatment response was brisk, with a decrease in proteinuria seen as early as day 15 and mild to moderate adverse events with no treatment discontinuation reported.[59]

Another novel therapy in the pipeline is targeting TRPC6. A phase 2 study of BI 764198, a potent, selective oral TRPC6 inhibitor, is being conducted in patients with FSGS. This new drug is expected to improve podocyte function and survival in these patients.[60]

Innovative and promising, gene therapy stands as a potential alternative treatment on the horizon. In a study conducted by Ding et al,[61] the investigators demonstrated the efficacy of adeno-associated virus LK03 at transducing human podocytes in vitro in patients with *NPHS2* mutation. This study used an adeno-associated virus-based gene therapy in human and mouse models with this genetic variant. They found that adeno-associated virus LK03 was a highly effective transducer of human podocytes in laboratory studies, and adeno-associated virus 2/9-mediated gene transfer in both the inducible podocin knockout and knockin mouse models resulted in positive outcomes—alleviation of kidney disease, improvements in markers such as albuminuria, creatinine, and urea, and even in long-term survival when the therapy was administered before disease onset. Additionally, they tested the therapy in mice after disease onset and noted improvements in urinary albumin and serum albumin levels, signifying therapeutic benefits even postdisease induction and providing proof-of-concept that gene therapy might be a viable treatment strategy for patients with monogenic causes of nephrotic syndrome.

RISK OF RECURRENCE POSTTRANSPLANT

In patients with primary or immune-related FSGS, the risk of recurrence posttransplant is high.[62,63] The posttransplant glomerular disease project found this risk to be as high as 32%, with up to 39% of patients losing their graft over a median of 5 years.[62] In contrast, the recurrence rate in patients with genetic FSGS is generally low.[64-66] One exception to this is podocin (*NHPS2*) mutation, which can lead to early recurrence of FSGS.[67,68] Patients with known *APOL1*-related FSGS have a low risk of recurrence because of kidney-specific podocyte injury.[69] The 5-year graft survival of recipients with a detected high-risk *APOL1* allele variant was similar to patients with no detected mutations.[70] On the contrary, Reeves-Daniel et al[66] found substantially decreased graft survival in patients who received a kidney from a donor with 2 *APOL1* risk allele variants. However, recipients of kidneys from donors with 1 *APOL1* risk variant had comparable graft survivals as those with no risk variants.

Patients with genetic causes of FSGS who have a specific mutation in the nephrin gene are at high risk of a recurrence posttransplant. In patients with *NPHS1* mutation, the risk of recurrence is up to 34%, driven predominantly by developing antinephrin antibodies against the donor nephrin.[71] In patients with negative genetic testing, the rate of recurrence is as high as 73% posttransplant.[72]

CONCLUSION

With the advances in genetic testing and the discovery of many more genes associated with FSGS, a correct differential diagnosis requires a clinicopathologic approach, prompting physicians to pursue a thorough evaluation of each patient to adequately identify and determine the underlying cause of an FSGS pattern of injury. Identifying the correct etiology of an FSGS pattern of injury is essential to guide the treatment approach and to design new clinical trials in developing targeted therapies for our patients.

ARTICLE INFORMATION

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