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Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach

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ABSTRACT

FSGS describes a renal histologic lesion with diverse causes and pathogenicities that are linked by podocyte injury and depletion. Subclasses of FSGS include primary, genetic, and secondary forms, the latter comprising maladaptive, viral, and drug-induced FSGS. Despite sharing certain clinical and histologic features, these subclasses differ noticeably in management and prognosis. Without an accepted nongenetic biomarker that discriminates among these FSGS types, classification of patients is often challenging. This review summarizes the clinical and histologic features, including the onset and severity of proteinuria as well as the presence of nephrotic syndrome, that may aid in identifying the specific FSGS subtype. The FSGS lesion is characterized by segmental sclerosis and must be differentiated from nonspecific focal global glomerulosclerosis. No light microscopic features are pathognomonic for a particular FSGS subcategory. The characteristics of podocyte foot process effacement on electron microscopy, while helpful in discriminating between primary and maladaptive FSGS, may be of little utility in detecting genetic forms of FSGS. When FSGS cannot be classified by clinicopathologic assessment, genetic analysis should be offered. Next generation DNA sequencing enables cost-effective screening of multiple genes simultaneously, but determining the pathogenicity of a detected genetic variant may be challenging. A more systematic evaluation of patients, as suggested herein, will likely improve therapeutic outcomes and the design of future trials in FSGS.

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The lesion of FSGS represents a segmental increase in glomerular matrix with obliteration of the capillary lumina in at least one glomerulus in the entire kidney biopsy.[1] This histologic lesion is caused by diverse etiologies and pathogenic mechanisms (Table 1), sharing the initiating and defining feature of podocyte alterations and depletion (podocytopathy). The lesion of FSGS can be broadly subdivided into primary ("idiopathic"), genetic, and secondary forms.

Primary FSGS is presumably caused by a circulating factor, possibly a cytokine elaborated from extrarenal sources, which causes generalized injury to podocytes.[2] Primary FSGS may respond to corticosteroids, immunomodulatory agents, plasmapheresis, or immunoadsorption[3] and is prone to recur posttransplantation. Maladaptive forms of secondary FSGS ensue from a reduction in the number of functioning nephrons or from a normal nephron population subjected to abnormal stress, and should primarily be treated with renin-angiotensin-aldosteron system inhibition.[4] Other forms of secondary FSGS include virus-associated FSGS[5] and drug-induced FSGS,[6] which typically improve on resolution of the infection or cessation of the drug. The genetic causes of FSGS may present as sporadic or familial disease, with autosomal dominant, autosomal recessive, X-linked, or mitochondrial (matrilineal) inheritance patterns. The age of onset of genetic FSGS is usually early childhood, but as additional mutations associated with FSGS are identified, adult-onset genetic FSGS assumes increasing significance. Genetic FSGS may be either limited to the kidney (Table 2) or part of a broader syndrome with extrarenal involvement (Table 3). Genetic FSGS is typically resistant to corticosteroids. Calcineurin inhibitors may be effective in few patients,[7] possibly reflecting direct stabilization of the podocyte actin cytoskeleton rather than an immunosuppressive effect.[8] A number of susceptibility genes may confer an increased risk of FSGS, the latter only overtly manifested after the imposition of genetic or environmental "second hits."[9] The best known of these are the G1 and G2 polymorphisms in the *apo L1* (*APOL1*) gene in patients of African ancestry, which

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Table 1. Causes of FSGS

Primary	Circulating podocyte-toxic factor
Secondary: Maladaptive	Reduced number of functioning nephrons (*e.g.*, unilateral renal agenesis, renal dysplasia, oligomeganephronia, glycogen storage disease, low birth weight)
	Abnormal stress on an initially normal nephron population (*e.g.*, morbid obesity, surgical reduction of renal mass [usually >75%], reflux nephropathy, high-protein diet, sickle cell disease, any advanced kidney disease with substantial loss of nephrons)
	Other causes: sleep apnea, cyanotic congenital heart disease, renal artery stenosis, malignant hypertension, cholesterol emboli
Secondary: Viral	HIV (established), CMV (probably), parvovirus B19 (possibly), EBV (possibly), HCV (possibly), hemophagocytic syndrome (possibly)
Secondary: Drug induced	Direct-acting antiviral therapy (ledipasvir, sofosbuvir), mTOR inhibitors, calcineurin inhibitors, anthracyclines, heroin(adulterants), lithium, IFN, anabolic steroids
Genetic	Renal limited (Table 2)
	Syndromic (Table 3)
Unknown	

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, Hepatitis C virus; mTOR, mammalian target of rapamycin. IFN, interferon

impart a greatly increased risk of adult-onset FSGS; these polymorphisms also impose a higher risk of other kidney diseases, in particular hypertensive nephropathy and HIV-associated nephropathy.[10,11] The presence of one or two high-risk APOL1 alleles is associated with more rapid disease progression and worse prognosis, but preliminary data suggest that the APOL1 high-risk alleles do not influence the sensitivity to corticosteroids or immunosuppressive treatment.[11,12] Many patients with FSGS cannot be readily classified, because an underlying cause or genetic mutation is not identified (the "unknown" forms of FSGS). At least some of these are likely genetic in origin.

Despite the heterogeneous etiology and pathogenesis of FSGS, the clinical and pathologic presentations may be similar (Figure 1). In the absence of a serum or urine nongenetic biomarker that reliably discriminates primary from secondary and genetic forms, correctly classifying the type of FSGS is often challenging.[13] Importantly, a misclassification may lead to inappropriate and potentially harmful therapy. As an example, primary FSGS can occur in a morbidly obese individual, and physicians may be reluctant to prescribe corticosteroids, because the lesion may be considered to be obesity-related FSGS. Conversely, an adult patient with a sporadic and unrecognized genetic form of FSGS and without a family history or clinical evidence of secondary FSGS may be exposed to a long course of steroids and/or calcineurin inhibitors in the belief that the underlying lesion is primary FSGS. This review discusses the clinical and pathologic characteristics of the FSGS lesion and offers clues in differentiating primary, maladaptive, and genetic forms, in particular in adult-onset FSGS. Viral- and drug-associated forms of FSGS are not the focus of this review, because they are often identified by viral serology and exposure context.

WHAT IS FSGS?

Glomerulosclerosis

The glomerular visceral epithelial cells (podocytes) are anchored to the underlying glomerular basement membrane (GBM) by their foot processes. This limited attachment to the GBM, along with their continuous exposure to the flow of the primary filtrate, render podocytes prone to detachment and loss in the urine. Podocytes are terminally differentiated, postmitotic cells unable to proliferate to compensate for lost cells. The ability of neighboring podocytes to hypertrophy and cover denuded areas of the GBM is limited. The stress caused by the process of hypertrophy and extending over bare areas of the GBM weakens the attachment to the GBM in the remaining podocytes that, in turn, detach. In this way, podocyte detachment and GBM denudation become self-perpetuating processes. The GBM tends to bulge outward in these bare areas, because the intraglomerular capillary hydrostatic pressure is no longer opposed by the podocytes, and synechial attachments with the parietal epithelial cells and Bowman's capsule occur. After podocyte loss has reached a critical point, the capillary loop collapses, and extracellular matrix accumulates, thus creating the characteristic segmental obliteration of the glomerular capillary tuft. In an animal model, glomerular growth exceeding the capacity of podocytes to adapt and adequately cover the filtration surface also resulted in a FSGS lesion, without a detectable reduction in average podocyte number per glomerulus.[14]

Focal

The term "focal" denotes a heterogeneous involvement of the glomerular population in the renal cortex. However, the segmental sclerotic lesion has only a small volume (on average, 12% of the entire glomerular volume)[15] and can thus be easily missed on a single section. Serial morphologic analysis in the various forms of FSGS shows that the sclerotic lesions involve the great majority of the glomeruli,[15–17] revealing that FSGS is not as focal as the name implies.

Segmental

The segmental pattern (affecting only a portion of the glomerular tuft) characteristic of the lesion of FSGS

Table 2. Genetic causes of FSGS: Renal-limited FSGS

Gene Locus Inheritance	Protein	Protein Function	Phenotype	Response to Therapy
Slit diaphragm–associated proteins				
NPHS1 19q13.1 AR	Nephrin	Essential component of the slit diaphragm	Finnish type congenital nephrotic syndrome, sporadic childhood FSGS, rarely adult-onset FSGS	Resistant to immunosuppression, reported patients with response to immunosuppression in heterozygous mutations or variants
NPHS2 1q25.2 AR	Podocin	Transmembrane protein involved in recruitment of nephrin to the slit diaphragm	Familial or sporadic FSGS or DMS in early childhood–, adolescence- or adult-onset FSGS in particular in compound heterozygotes for one pathogenic NPHS2 mutation and p.R229Q polymorphism	Resistant to immunosuppression, reported patients with response to immunosuppression in heterozygous mutations or variants
CD2AP 6p12 AD, rarely AR	CD2-associated protein	Scaffolding molecule between slit diaphragm and actin cytoskeleton	Childhood-onset FSGS	Resistant to immunosuppression
PLCE1 10q23.33 AR	Phospholipase Cε1	Signaling protein, interacts with nephrin	Isolated DMS, sporadic and familial early childhood–onset FSGS	Reported patients with (partial) response to immunosuppression
TRPC6 11q22.1 AD	Transient receptor potential cation channel 6	Receptor-activated calcium channel localized at the foot process membrane, interacts with nephrin and podocin	Familial or sporadic adult-onset FSGS, childhood-onset FSGS has also been described	Reported patients with (partial) response to cyclosporin
MAGI2 7q11.23-q21.11 AR	Membrane-Associated Guanylate Kinase, WW, and PDZ domain–containing 2	Scaffolding molecule between slit diaphragm and actin cytoskeleton	Familial and sporadic congenital nephrotic syndrome	Resistant to immunosuppression
Actin cytoskeleton and regulation				
ACTN4 19q13 AD	α–Actinin-4	Member of the spectrin gene superfamily, cytoskeletal protein	Familial or sporadic adult-onset FSGS	Resistant to immunosuppression
MYO1E 15q22.2 AR	Nonmuscle myosin 1e	Involved in intracellular movement and membrane trafficking	Familial childhood-onset FSGS	Reported patients with (partial) response to cyclosporin
ANLN 7p15-p14 AD	Anillin	F-actin binding protein, involved in slit diaphragm-cytoskeleton binding	Familial adult-onset FSGS	Resistant to immunosuppression
ARHGDIA 17q25.3 AR	Rho GDP dissociation inhibitor α	Regulation of podocyte migratory phenotype and shape	Congenital or early childhood-onset nephrotic syndrome	Resistant to immunosuppression, may respond to RAC1 inhibitors (eplerenone)
ARHGAP24 4q22.1 AD	RhoGTPase activating protein 24	Regulation of podocyte migratory phenotype and shape	Adolescence-onset FSGS	Resistant to immunosuppression
TTC21B 2q24.3 AR	Tetratricopeptide repeat domain 21B	Intraflagellar transport-A component, regulation cytoskeleton adult podocytes	Adolescence- or adult-onset FSGS associated with atrophic tubules	Resistant to immunosuppression
KANK 2 19p13.2 AR	Kidney ankyrin repeat-containing protein 2	Regulation Rho GTPase activity in podocytes (cell migration and shape)	Familial early-onset SRNS	Resistant to immunosuppression

Table 2. Continued

Gene Locus Inheritance	Protein	Protein Function	Phenotype	Response to Therapy
Nuclear pore complex proteins				
NUP93 16q13 AR	Nucleoporine 93 kD	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
NUP205 7q33 AR	Nucleoporine 205 kD	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
XPO5 6p21.1 AR	Exportin 5	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
NUP107 12q15 AR	Nucleoporine 107 kD	Component of the nuclear pore complex	Childhood-onset FSGS	Resistant to immunosuppression
Cell membrane–associated proteins				
PTPRO 12p13-p12 AR	Protein tyrosine phosphatase, receptor type O	Member of the R3 subtype family of protein tyrosine phosphatases at the apical surface of polarized cells	Childhood-onset FSGS	Resistant to immunosuppression, reported patients with partial response to immunosuppression
EMP2 16p13.2 AR	Epithelial membrane protein 2	Regulation of the amount of CAVEOLIN-1, EMP2 depletion causes decreased cell proliferation	Childhood-onset FSGS	Reported patients with response to steroids
PODXL 7q32.3 AD	Podocalyxin	Component of glycocalyx	Familial childhood- and adult-onset FSGS	Resistant to immunosuppression
GBM protein				
LAMA5 20q13.2-q13.3 AD (?)	Laminin α-5	Member of the α-subfamily of laminin chains, major component of basement membranes	Adult-onset FSGS	Likely resistant to immunosuppression

AR, autosomal recessive; DMS, diffuse mesangial sclerosis; AD, autosomal dominant; SRNS, steroid-resistant nephrotic syndrome.

must be distinguished from nonspecific focal global glomerulosclerosis (FGGS; affecting the entire glomerular tuft) observed in aging and hypertensive nephropathy (Figure 1). FGGS seen in the aging kidney usually occurs without FSGS. The likely driving process for age-related FGGS is arteriosclerosis and glomerular ischemia, resulting in podocyte stress and depletion.[18] An alternative and more podocyte-centered viewpoint suggests that progressive podocyte loss with aging is the primary event, resulting in an ever-increasing hypertrophic stress on remaining podocytes.[19] Whatever the initiating event, after a critical number of podocytes are lost, catastrophic podocyte detachment leads to glomerular tuft collapse and rapid obsolescence of the entire glomerulus. Global glomerulosclerosis exceeding the threshold expected for a given age[20] is indicative of CKD as a consequence of hypertensive damage. This insight may be of particular clinical relevance in patients of African descent with hypertension, in whom FGGS and not FSGS was found to be the dominant lesion on kidney biopsy.[21]

Not Nonspecific Scarring

FSGS should also be differentiated from focal segmental scarring that develops in immune-mediated GN (*e.g.*, IgA nephropathy, ANCA-associated GN, and lupus nephritis) as a result of postinflammatory scarring of necrotizing or proliferative lesions. In addition to nonspecific scarring, a significant proportion of segmental sclerotic lesions in IgA nephropathy may represent podocyte injury with mechanisms similar to those seen in FSGS.[22]

THE CLINICAL AND PATHOLOGIC HALLMARKS OF FSGS

Segmental versus Diffuse Foot Process Effacement

Podocytes play a cardinal role in glomerular barrier function because of their specialized architecture. Neighboring podocytes form meandering cell-cell contacts through the formation of foot processes that are arranged in an interdigitating pattern. The slit diaphragm between adjacent interdigitating podocyte foot processes consists of a complex membrane-like structure that acts as a sieve and represents the major barrier

Table 3. Genetic causes of FSGS: Syndromic FSGS

Gene, Locus, Inheritance	Protein	Protein Function	Syndromic Association	Response to Therapy
MYH9 22q12.3 AD	Myosin heavy chain 9	Protein with several important functions, including cytokinesis, cell motility, and maintenance of cell shape	Epstein–Fechtner syndrome (FSGS, sensorineural deafness, cataracts, macrothrombocytopenia, leukocyte inclusions)	Resistant to immunosuppression
KANK 1 9p24.3 AR	Kidney ankyrin repeat-containing protein 1	Regulation Rho GTPase activity in podocytes (cell migration and shape)	Familial early-onset SRNS and intellectual disability	Resistant to immunosuppression
KANK 4 1p31.3 AR	Kidney ankyrin repeat-containing protein 4	Regulation Rho GTPase activity in podocytes (cell migration and shape)	Familial early-onset FSGS, intellectual disability, facial dysmorphism, and atrial septal defect	Resistant to immunosuppression
ITGA3 17q21.33 AR	Integrin-α3	Component of integrin-α3 β4 involved in podocyte-GBM interaction	NEP syndrome (early-onset FSGS, epidermolysis bullosa, and interstitial lung disease)	Resistant to immunosuppression
ITGB4 17q11 AR	Integrin-β4	Component of integrin-α3 β4 involved in podocyte-GBM interaction	Early-onset FSGS, epidermolysis bullosa, and pyloric atresia	Resistant to immunosuppression
LAMB2 3p21 AR	Laminin-β2	Extracellular matrix glycoprotein implicated in cell adhesion, differentiation, migration, signaling	Pierson Syndrome (microcoria, neuromuscular junction defects, early-onset DMS or FSGS), isolated congenital or childhood-onset SRNS	Resistant to immunosuppression
LMX1B 9q34 AD	LIM homeobox transcription factor 1β	Nuclear transcription factor	Sporadic FSGS, Nail–Patella syndrome (hypoplastic or absent patella, dysplasia of elbows, dystrophic nails, frequently glaucoma)	Resistant to immunosuppression
PAX2 10q24 AD	Paired box 2	Nuclear transcription factor	Renal coloboma syndrome (childhood-onset FSGS, optic nerve colobomas, and renal hypoplasia), isolated adult-onset FSGS	Resistant to immunosuppression
WT1 11p13 AD	Wilms tumor 1	Nuclear transcription factor	Frasier syndrome (FSGS, gonadoblastoma, male pseudohermaphroditism), Denys–Drash syndrome (DMS, Wilms' tumor, male pseudohermaphroditism), isolated congenital or childhood-onset DMS or FSGS	Reported patients with (partial) response to cyclosporin
NUP107 12q15 AR	Nucleoporine 107 kD	Component of the nuclear pore complex	Childhood-onset FSGS and microcephaly	Resistant to immunosuppression
SMARCAL1 2q34–36 AR	SMARCA-like protein	Protein with helicase and ATPase activities	Schimke immuno-osseous dysplasia (immunodeficiency, skeletal dysplasia, childhood-onset FSGS)	Resistant to immunosuppression
NXF5 Xq22 X-linked	Nuclear RNA export factor 5	Member of family of nuclear RNA export factor genes	Adult-onset FSGS and cardiac conduction disorders	Resistant to immunosuppression
COQ2 4q21.23 AR	Coenzyme Q2 4-hydroxybenzoate polyprenyl transferase	Enzyme involved in the biosynthesis of CoQ10	Childhood-onset collapsing FSGS, encephalopathy	May respond to coenzyme Q10

Table 3. Continued

Gene, Locus, Inheritance	Protein	Protein Function	Syndromic Association	Response to Therapy
COQ6 14q24.3 AR	Coenzyme Q6 monooxygenase	Enzyme involved in the biosynthesis of CoQ10	Early childhood-onset FSGS/DMS, sensorineural deafness	May respond to coenzyme Q10
PDSS2 6q21 AR	Prenyl diphosphate synthase subunit 2	Enzyme involved in the biosynthesis of CoQ10	Congenital SRNS and encephalomyopathy, Leigh syndrome	May respond to coenzyme Q10
ADCK4 19q13.2 AR	aarF domain containing kinase 4	Enzyme involved in the biosynthesis of CoQ10	Childhood and early adult–onset FSGS (neurologic manifestations in 20% of patients)	May respond to coenzyme Q10
MTTL1 mtDNA Maternal	Mitochondrially encoded tRNA leucine 1	Mitochondrial tRNA	MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), isolated adult-onset FSGS	Resistant to immunosuppression
MTTL2 mtDNA Maternal	Mitochondrially encoded tRNA leucine 2	Mitochondrial tRNA	MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), isolated adult-onset FSGS	Resistant to immunosuppression
MTTY mtDNA Maternal	Mitochondrially encoded tRNA tyrosine	Mitochondrial tRNA	MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), isolated adult-onset FSGS	Resistant to immunosuppression
EYA1 8q13.3 AD	Eyes absent homolog 1	Transcriptional activator involved in kidney, branchial arches, eye and ear development	Adult-onset FSGS and Branchio-Oto-Renal syndrome (abnormalities in branchial, ear and renal development)	Resistant to immunosuppression
LMNA 1q21.2-q21.3 AD	Lamin A/C	Component of the inner nuclear membrane	Familial partial lipodystrophy with adult-onset FSGS	Resistant to immunosuppression
SCARB2 4q13–21 AR	Scavenger receptor class B member 2	Type 3 glycoprotein located primarily in limiting membranes of lysosomes and endosomes	Action myoclonus-renal failure syndrome (ataxia, myoclonus, collapsing FSGS)	Resistant to immunosuppression
COL4A3 2q36–37 AR	α3 type 4 collagen	Subunit of type 4 collagen (main component of GBM)	Alport syndrome, familial/sporadic FSGS	Resistant to immunosuppression
COL4A4 2q35–37 AR	α4 type 4 collagen	Subunit of type 4 collagen (main component of GBM)	Alport syndrome, familial/sporadic FSGS	Resistant to immunosuppression
COL4A5 Xq22 X-linked	α5 type 4 collagen	Subunit of type 4 collagen (main component of GBM)	Alport syndrome, familial/sporadic FSGS	Resistant to immunosuppression

Table 3. Continued

Gene, Locus, Inheritance	Protein	Protein Function	Syndromic Association	Response to Therapy
CUBN 10p12.31 AR	Cubilin	Receptor for intrinsic factor-vitamin B12 complexes, role in reabsorption of albumin at renal tubular compartment	Childhood-onset SRNS and megaloblastic anemia, rarely associated with urinary tract malformation (Imerslund–Gräsbeck syndrome)	May respond to vitamin B12
WDR73 15q22 AR	WD repeat domain 73	Scaffold protein for the assembly of protein complexes	Childhood-onset SRNS and Galloway–Mowat syndrome (microcephaly and developmental delay)	Resistant to immunosuppression
ALG1 16p13.3 AR	Asparagine-linked glycosylation 1	Catalyzes the first mannosylation step in the biosynthesis of lipid-linked oligosaccharides	Congenital nephrotic syndrome in setting of disorder of glycosylation type 1-k	Resistant to immunosuppression
PMM2 16p13.3 AR	Phosphomannomutase 2	Synthesis of dolichol-*P*-oligosaccharides	Childhood-onset SRNS and deficient glycoprotein syndrome type 1	Resistant to immunosuppression
CD151 11p15.5 AR	Tetraspanin CD151	Member of the transmembrane 4 superfamily, cell-surface proteins	Childhood-onset FSGS and bullous skin lesions, sensorineural deafness, β-thalassemia	Resistant to immunosuppression
CRB2 9q33.4 AR	Crumbs Homolog 2	Regulation of podocyte cell polarity, differentiation and protein trafficking of slit diaphragm components	Familial childhood-onset FSGS, congenital nephrotic syndrome and cerebral ventriculomegaly	Resistant to immunosuppression
INF2 14q32.33 AD	Inverted formin 2	Member of the formin family, function in de- and polymerization of actin filaments	Familial or sporadic adolescence and adult-onset FSGS, association with Charcot–Marie–Tooth disease	Resistant to immunosuppression
SGPL1 10q22 AR	Sphingosine-1-phosphate lyase	Enzyme involved in sphingolipid catabolic pathway	Familial and sporadic congenital nephrotic syndrome or childhood-onset FSGS, association with adrenal insufficiency, ichthyosis, immunodeficiency, and neurologic defects	Resistant to immunosuppression
ZMPSTE24 1p34.2 AR	Zinc Metalloproteinase Ste 24	Enzyme involved in degradation of prelamin A	Young adult–onset sporadic FSGS, associated with mandibuloacral dysplasia	Likely resistant to immunosuppression

AD, autosomal dominant; AR, autosomal recessive; SRNS, steroid-resistant nephrotic syndrome; NEP, Nephrotic syndrome, epidermolysis bullosa and pulmonary disease; DMS, diffuse mesangial sclerosis; mtDNA, mitochondrial DNA; tRNA, transfer RNA; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

to protein leakage. Podocytes can be damaged by a spectrum of mechanisms that encompass nonmechanical insults (immunologic, toxic, viral), mechanical stress, and genetic mutations, which compromise specific cellular components. Whatever the type of stress, the podocyte initially responds with loss of the interdigitating foot process pattern, termed foot process effacement (FPE). FPE starts with sealing of the filtration slits between neighboring cells through replacement of the slit diaphragm with occluding junctions. It proceeds with retraction, shortening, and widening of the foot processes, ultimately resulting in a continuous and flattened cytoplasmic sheet covering the GBM. Whether FPE is merely a sign of derangement of a highly organized system or rather, a coordinated process to promote cell survival remains controversial.[23] However, substantive evidence supports the latter view, *i.e.* that FPE may be a protective response, whereby podocytes attempt to secure adhesion to the GBM and thus escape detachment. Indeed, FPE is potentially reversible. When local conditions improve, podocytes resume their original shape, and the functionality of the filtration barrier steadily improves. In contrast, the persistence of stress of whatever cause may overwhelm the capacity of FPE to enable podocyte adherence to the GBM, thereby leading to irreversible podocyte detachment. The

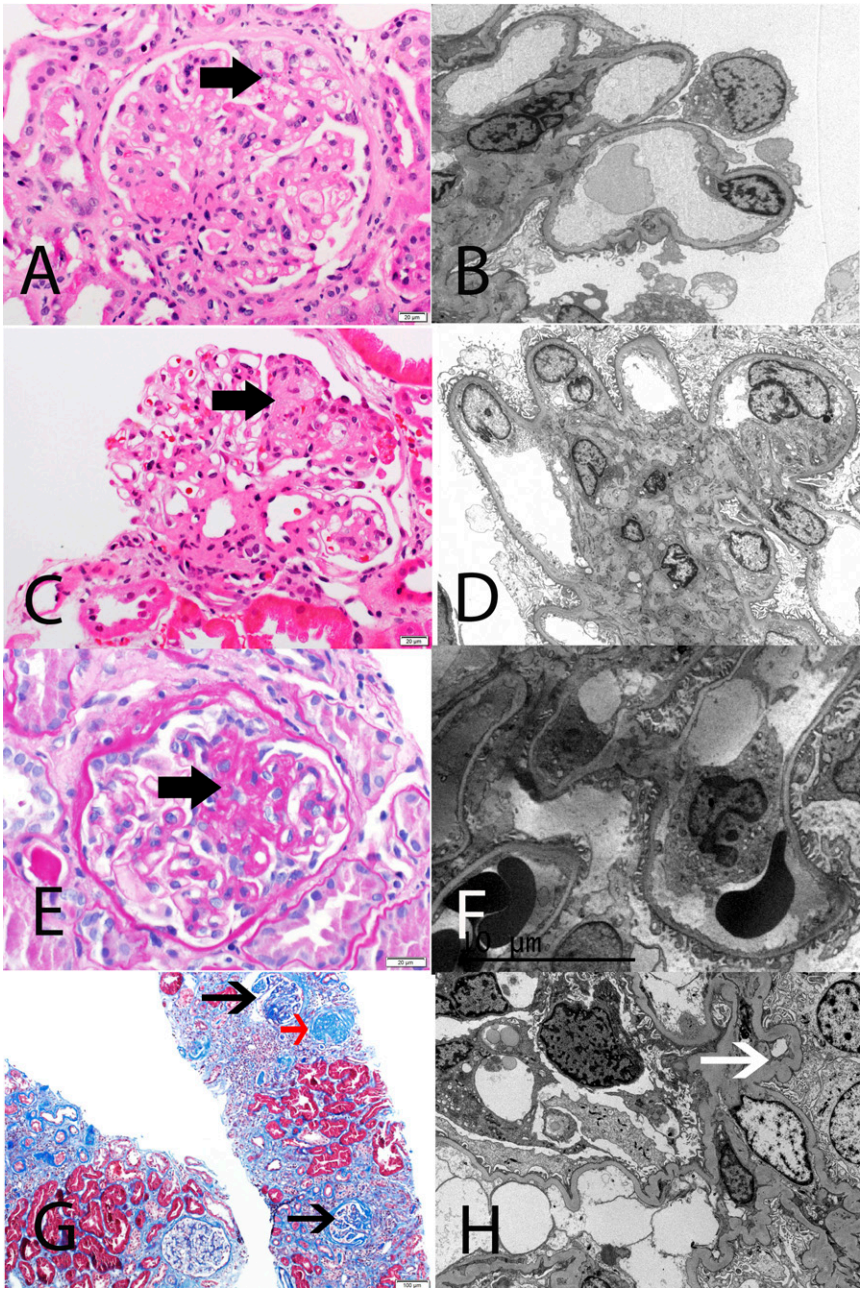

Figure 1. Representative LM and EM findings in FSGS and FGGS. (A and B) Primary FSGS in a 61-year-old white man with serum creatinine 1.5 mg/dl, proteinuria 14.2 g/24 h, and serum albumin 2.5 mg/dl. LM shows segmental sclerosis, and EM highlights diffuse FPE. (C and D) Maladaptive FSGS in a 53-year-old white man with serum creatinine 1.9 mg/dl, proteinuria 5.8 g/24 h, and serum albumin 4.1 mg/dl. LM shows segmental sclerosis, and EM reveals well preserved foot processes. (E and F) Genetic FSGS in a 39-year-old white man with familial history of *PLCE1* mutation, serum creatinine 1.3 mg/dl, proteinuria 2.0 g/24 h, and serum albumin 4 g/dl. LM shows segmental sclerosis, and EM features only minimal FPE. (G and H) FGGS in a 38-year-old black man with a long history of uncontrolled hypertension, serum creatinine 5.1 mg/dl, proteinuria 2.8 g/24 h, and serum albumin 4.3 g/dl. LM shows ischemic changes, as well as a globally sclerosed glomerulus (red arrow), and EM shows relatively well preserved foot processes. Note ischemic capillary loops (white arrow). (A, C, E) Thick black arrow points to segmental sclerosis, and (G) thin black arrow points to ischemic glomeruli. (A and C) Hematoxylin and eosin. (E) Periodic acid–Schiff. (G) Masson trichrome stain. Original magnification, ×40 in A, C, and E; ×2500 in B; ×3000 in D; ×3500 in F; ×10 in G; ×5000 in H.

type and severity of the stress and the adequacy of the response vary considerably, and this likely underlies the observed variability in extent, distribution, and speed of development of FPE in the different forms of FSGS.

Maladaptive FSGS results from a mismatch between glomerular load and glomerular capacity in conditions associated with hyperfiltration, glomerular capillary hypertension, and glomerular hypertrophy.[24] Hyperfiltration and glomerular capillary hypertension represent a major mechanical strain to the podocytes. Podocytes are extremely sensitive to shear stress generated by the increased filtrate flow through the filtration slits and over their apical surface.[25,26] Glomerular hypertrophy challenges the podocytes to cover an increased filtration surface. However, the ability of the foot processes to display hypertrophic growth is limited. The podocytes may be unable to maintain a normal foot process pattern, leading to a further increase in local shear stress. When the rheologic stress becomes untenable, the process of FPE is set in motion to redistribute the mechanical forces and decrease the local shear stress. Although glomerular capillary hypertension affects all capillaries to comparable degrees, shear stress is unevenly distributed along the glomerular capillaries, decreasing toward the end of the capillary network.[25] FPE as a response to increased fluid shear stress is, therefore, typically a segmental phenomenon, encountered only in the parts of the podocyte that are affected by the rheologic disturbances, whereas the other parts display an intact foot process pattern.[25] This crucial new insight explains why FPE develops slowly and has a heterogeneous distribution in maladaptive FSGS (Figure 1). The mean percentage of the glomerular surface area affected by FPE was reported to be 40% in obesity-related FSGS[27,28] and 25% in reflux nephropathy.[27] In a mixed cohort of patients with secondary FSGS (that also included some patients with genetic FSGS), the median degree of FPE was 30%.[29]

In primary FSGS, however, a putative circulating factor capable of crossing the GBM barrier causes generalized podocyte dysfunction, ensuing in sudden and widespread FPE (Figure 1). In a

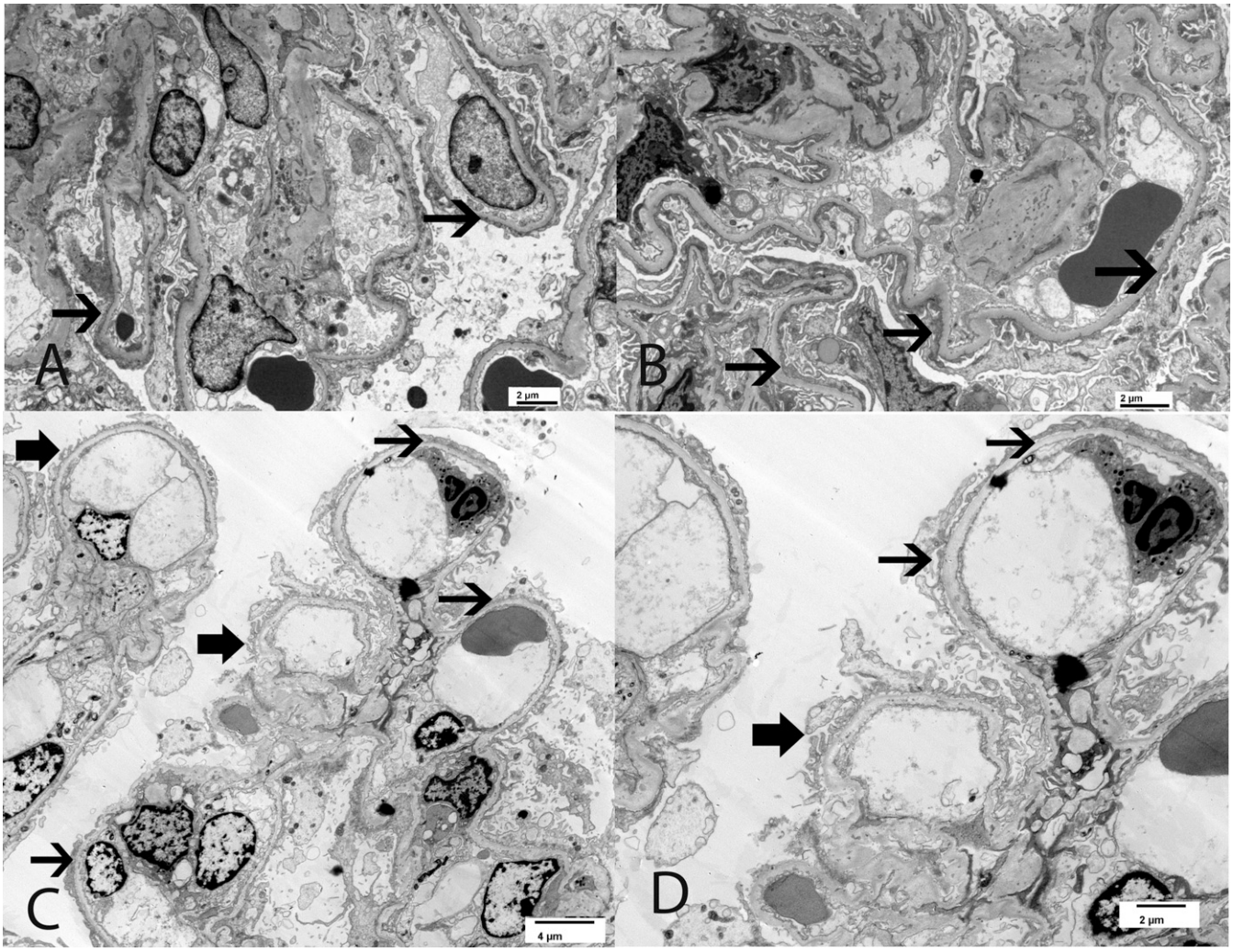

Figure 2. EM findings in two siblings who are both compound heterozygotes for the *NPHS2* mutation and the R286fs pathogenic variant along with a non-neutral polymorphism R229Q. (A and B) The 63-year-old brother with serum creatinine 1.1 mg/dl, proteinuria 6.6 g/24 h, and serum albumin 3.4 g/dl. EM shows diffuse FPE. (C and D) The 47-year-old sister with serum creatinine 0.9 mg/dl, proteinuria 2.5 g/24 h, and serum albumin 4 g/dl. EM shows segmental FPE. Thick black arrow points to preserved foot processes, and thin black arrow points to effaced foot processes. Original magnification, ×5000 in A and B; ×2900 in C; ×4800 in D.

series of adult and predominantly white patients with primary FSGS, median FPE was 100%.[29] In two older series, the mean degrees of FPE in primary FSGS were 75%[28] and 65%, with the greatest degrees in the collapsing (82%) and cellular (87%) forms.[27] There was considerable overlap with the degree of FPE observed in secondary FSGS, possibly related to the inclusion of unrecognized genetic FSGS under the primary FSGS designation. A morphometric analysis of foot process width, which excluded patients with heredofamilial forms of FSGS, found broader foot processes in patients with primary FSGS compared with those with secondary FSGS.[30] A foot process width >1500 nm adequately differentiated primary from secondary FSGS.[30] In patients with primary FSGS who develop recurrent disease in the allograft, FPE was observed within minutes after reperfusion,[31] further supporting the concept of sudden podocyte cytoskeletal dysregulation caused by an as yet elusive circulating factor.

The mechanism of virus-associated FSGS, epitomized by HIV-associated nephropathy, involves direct infection of the podocytes, resulting in dysregulation of the cellular phenotype and apoptosis.[32–34] In accordance, diffuse FPE (referring to the entire population of glomeruli) (mean, 89%) was reported in patients with HIV-associated nephropathy,[27] although in another cohort, only 57% of patients had FPE covering >80% of the glomerular capillary surface.[35] Direct podocyte toxicity resulting in dysregulation of the cytoskeleton has also been described in drug-induced FSGS. As an example, biopsies of patients with collapsing FSGS caused by high-dose pamidronate featured extensive FPE (mean, 84%; range, 60%–100%) associated with loss of expression of the cytoskeletal protein synaptopodin.[36]

Genetic FSGS results from a mutation in genes encoding vital podocyte proteins, including those involved in slit diaphragm structure and function, actin

Table 4. Differential diagnostic characteristics of primary FSGS, genetic FSGS, maladaptive FSGS, and FGGS

	Primary FSGS	Genetic FSGS	Maladaptive FSGS	FGGS
Clinical	NS	NS common in childhood, less common in adults	Nephrotic- or subnephrotic-range proteinuria without NS	Variable proteinuria, usually subnephrotic
LM	FSGS Often no other damage (unless late in disease course) Glomerulomegaly uncommon	FSGS FGGS common in adult-onset, uncommon in juvenile forms	FSGS Often perihilar Other signs of scarring FGGS in many glomeruli Glomerulomegaly common	FGGS No FSGS No glomerulomegaly Ischemic glomeruli[a] Associated with tubulointerstitial fibrosis, vascular sclerosis
EM	Diffuse FPE (>80%)	Variable (diffuse or segmental) FPE, characteristic features in some mutations	Segmental FPE	Minimal or no FPE in unaffected glomeruli

NS, nephrotic syndrome.
[a]Characterized by thickening and wrinkling of the GBM and distention of the Bowman space.

cytoskeleton, or cell signaling apparatus (Tables 2 and 3). No systematic evaluation of FPE in genetic FSGS has yet been performed, but from a pathophysiologic point of view, a broad variability can be expected. FPE is initiated by the intrinsic dysfunction of the podocyte rather than by a response to extrinsic injury. For example, in genetic FSGS caused by *NPHS1* mutations, the essential slit diaphragm component nephrin is absent, resulting in diffuse FPE with severe congenital nephrotic syndrome.[37] In contrast with these immediate pathophysiologic effects attendant on the loss of an indispensable slit diaphragm protein, other genetic mutations or polymorphisms may merely render the podocyte more vulnerable to stress, and thus require modifier genes or additional metabolic, hypertensive, or other stress to develop the fully expressed phenotype.[9] The plausibility of this scenario was supported by findings in patients with mutations in *ACTN4*, the gene encoding the actin binding protein α–actinin-4.[38] The mutant protein may cause a cytoskeletal disorganization that decreases the resistance of the podocyte to mechanical stress, explaining the phenotype of adult-onset FSGS with biopsy characteristics suggestive of a maladaptive FSGS.[38] The importance of environmental, genetic, or epigenetic modifiers is further illustrated by the development of distinct phenotypes in family members affected by the same mutation[39] (Figure 2).

Nephrotic Syndrome, Nephrotic-Range Proteinuria, and Subnephrotic Proteinuria

Proteinuria is the cardinal presenting clinical feature of FSGS. The distinction between nephrotic syndrome (defined as urinary protein excretion $\geq$3.5 g/24 h, serum albumin concentration of $\leq$3.5 g/dl, often but not necessarily accompanied by hyperlipidemia, lipiduria, and/or edema), nephrotic-range proteinuria (defined as urinary protein excretion $\geq$3.5 g/24 h in the absence of low serum albumin), and subnephrotic proteinuria (defined as urinary protein excretion $>$0.2 and $<$3.5 g/24 h)[40] is helpful in the differential diagnostic evaluation of patients with an FSGS lesion.

Patients with primary FSGS typically present with abrupt-onset marked proteinuria (sometimes as much as 20 g/24 h or greater) and severe nephrotic syndrome. The prevalence of nephrotic syndrome in primary FSGS has been reported to vary from 54%[28] to 58%[41] to 70%[42] to 90%.[43] Such variability may be due to the inclusion of unrecognized sporadic genetic FSGS, because primary FSGS has historically been defined as FSGS with absence of conditions typically associated with secondary FSGS. However, when primary FSGS was defined as FSGS with absence of conditions typically associated with secondary FSGS and with presence of diffuse FPE, the prevalence of nephrotic syndrome was 100%.[29]

More consistently, patients with well-defined forms of maladaptive FSGS (such as obesity, vesicoureteral reflux, and renal mass reduction) present with subnephrotic-range to nephrotic-range proteinuria and rarely, if ever, develop nephrotic syndrome,[28,29,43–45] despite often marked proteinuria well above 3.5 g/24 h.

Most patients with childhood-onset genetic FSGS have autosomal recessive mutations that almost always convey full penetrance and present with or progress to severe nephrotic syndrome.[46] However, adult-onset genetic FSGS is generally inherited as autosomal dominant disease with variable penetrance, and it exhibits proteinuria of usually $<$5 g/24 h and more slowly progressive CKD. It should be noted, however, that there is a dearth of detailed information on the clinical presentation of adult-onset genetic FSGS, and it is often unclear whether patients have nephrotic-range proteinuria or nephrotic syndrome.[47]

PROPOSAL FOR A CLINICOPATHOLOGIC APPROACH TO A LESION OF FSGS

Clinical Evaluation

Detailed documentation of the clinical phenotype remains of unassailable importance, even when a kidney biopsy is the next diagnostic step. Medical,

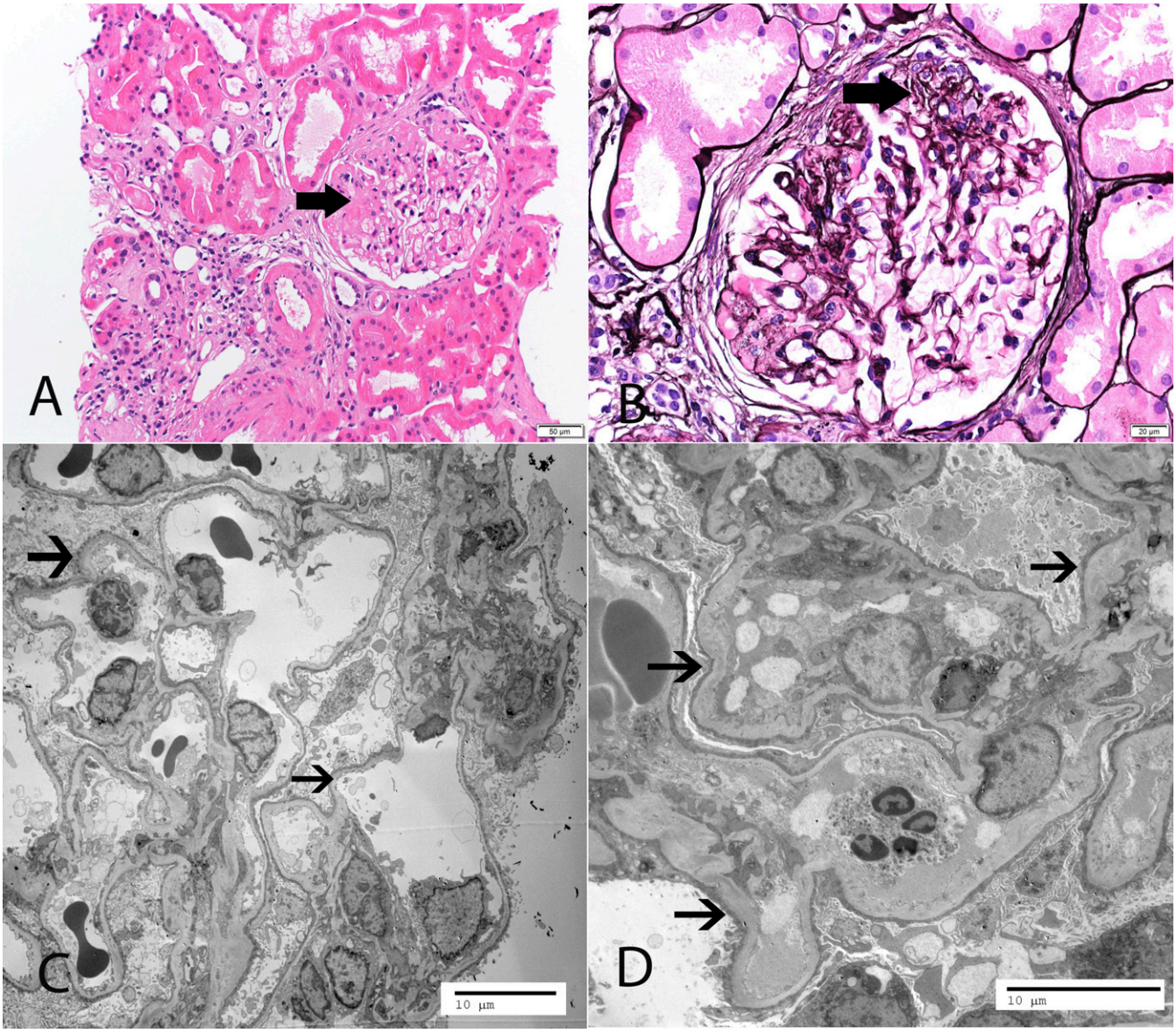

Figure 3. Representative LM and EM findings. A 46-year-old white woman, in whom the initial biopsy at age 18 years old was reported as minimal change disease, presented with serum creatinine 1.5 mg/dl, proteinuria 5.8 g/24 h, and serum albumin 3.4 g/dl. The patient was resistant to corticosteroids and calcineurin inhibitors. Mutation analysis with a next generation sequencing panel showed two mutations in *NPHS2* and a heterozygous variation in *WDR73*, which is known to cause the Galloway–Mowat syndrome. (A and B) LM shows segmental sclerosis (thick arrows point to segmental sclerosis). (C and D) EM reveals diffuse FPE (thin arrows point to effaced foot processes). (A) Hematoxylin and eosin. (B) Silver methenamine stain. Original magnification, ×20 in A; ×40 in B; ×1900 in C; ×2900 in D.

medication and family history, body mass index, birth weight, and viral serology should be documented. Clinical evidence of a syndromic presentation should also be sought (*e.g.*, hearing loss, skin or eye abnormalities, cardiac dysfunction or anatomic disturbances, hepatosplenomegaly, *etc.*). Measurement of serum albumin concentration and quantitation of urinary proteins are the required first steps in patient stratification (Table 4). It is also important to determine the identity of the urinary proteins. Initially, a urinary protein-to-creatinine ratio can be compared with a urinary albumin-to-creatinine ratio. If <50% of total proteinuria is due to albumin, then the possibility of tubular proteinuria or presence of light chains should be considered.[47,48]

Pathologic Evaluation

Light Microscopy

The Columbia classification subdivides the lesion of FSGS irrespective of underlying etiology or pathogenesis by its appearance on LM into collapsing, tip lesion, cellular, perihilar lesion, and not otherwise specified variants.[1,49] A detailed description of the histologic characteristics and prognostic implications of the different variants is beyond the scope of

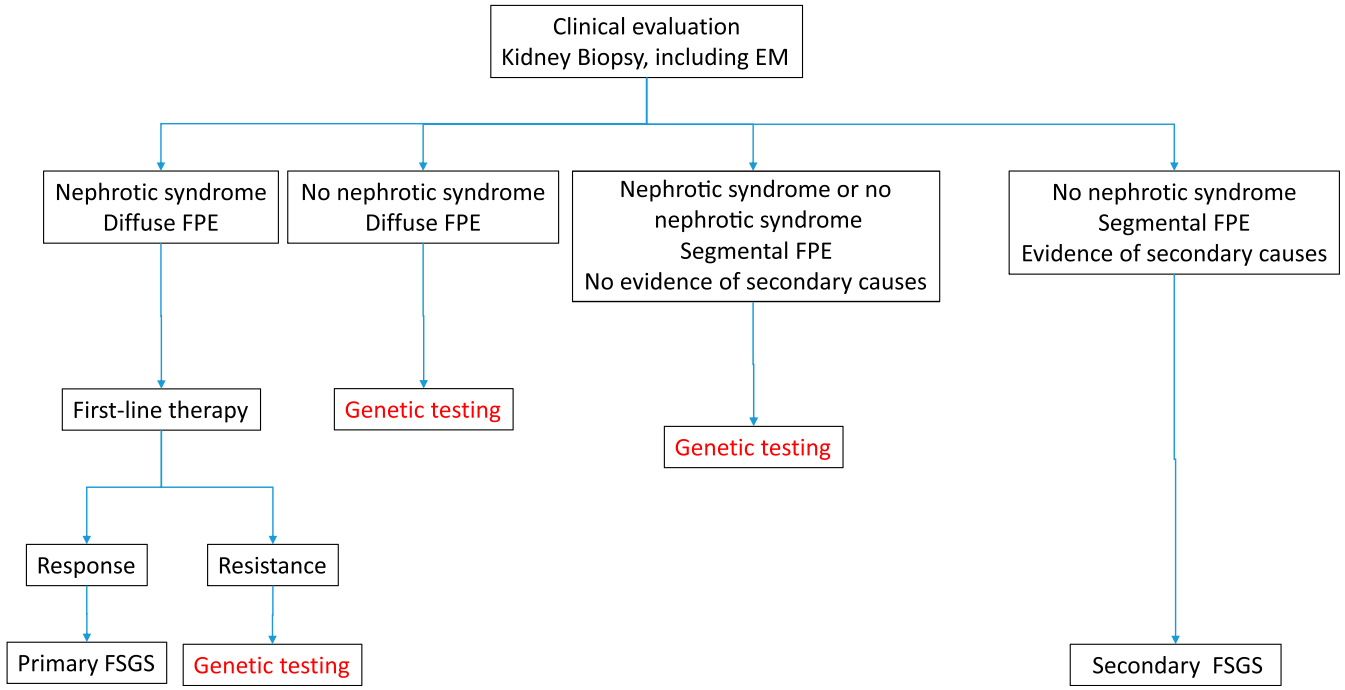

Figure 4. Opinion-based approach to genetic testing in adult-onset FSGS. Note that viral- and drug-associated forms of FSGS are usually excluded by clinical and serologic evaluation.

this review. Not otherwise specified is the most common variant, and it is equally distributed among primary and secondary forms.[29,50] Perihilar lesions are more usual in maladaptive FSGS, although they can also occur in primary FSGS[29,50,51] and genetic FSGS.[38] Tip lesion, cellular, and collapsing variants usually share the presenting features of heavy proteinuria and the nephrotic syndrome, but they may also present with subnephrotic-range proteinuria. Tip lesions tend to occur more frequently in white patients, are more likely to respond to therapy, and have overall the best prognosis.[49] Conversely, the collapsing variant affects predominantly patients from African heritage and is particularly malignant in its course. The clinical course and morphologic characteristics of the collapsing variant are different from the other FSGS variants, such that some believe that it is a different entity altogether. The collapsing pattern of injury occurs in patients with primary FSGS, but it is also the characteristic lesion seen in HIV-associated nephropathy, parvo B19 virus infection, and pamidronate toxicity. Individuals of African ancestry with high-risk APOL1 alleles are prone to this FSGS variant.

Glomerulomegaly is very common in FSGS caused by obesity, reflux nephropathy, or surgical- or disease-related reductions in nephron mass or in low-birth weight individuals,[27,28,43,44,50] but it is also observed in 10%–30% of patients with presumed primary FSGS.[28,50] A reliable determination of glomerulomegaly requires the measurement of maximal glomerular diameter on multiple sections in approximately 50 glomeruli. It is, therefore, neither a dependable nor a practical parameter to discriminate between primary and maladaptive FSGS.

Because primary FSGS presents with an abrupt onset of nephrotic syndrome, kidney biopsy is often done early in the course and generally shows a relatively well preserved parenchyma with few glomeruli featuring the characteristic FSGS lesion. In contrast, maladaptive FSGS often presents with progressive proteinuria, and the kidney biopsy is done later in the course. As such, varying degrees of parenchymal scarring are often associated with maladaptive FSGS. Advanced primary FSGS and maladaptive FSGS are indistinguishable on LM.

Taken together, none of the LM features are pathognomonic for a particular type of FSGS. Thus, the etiopathogenesis of FSGS cannot be reliably determined by LM alone.

Immunofluorescence Microscopy

Granular deposition of IgM and C3 with a distribution of the segmental sclerosis is frequently detected in FSGS and thought to represent nonspecific macromolecular trapping rather than specific deposition. More recently, it has been suggested that the exposure of glomerular neoepitopes by nonimmune injury may lead to secondary IgM deposition and complement activation.[52] Whatever the underlying molecular mechanism, the staining for IgM and C3 is clearly a secondary phenomenon and does not help to differentiate between the various forms of FSGS. The main purpose of immunofluorescence studies in FSGS is to rule out nonspecific segmental sclerosis as a consequence of postinflammatory scarring in immune-mediated GN, such as in IgA nephropathy.

Electron Microscopy

The major ultrastructural finding on electron microscopy (EM) is FPE. The speed of development and extent of FPE are determined by the underlying mechanism of podocyte injury as detailed above. As a consequence, the FPE characteristics can be used to help discriminate between primary and secondary forms of FSGS (Table 4). Directly overlying the lesions of segmental sclerosis, there usually is complete FPE. It is, therefore, essential to select at least two relatively intact glomeruli to evaluate the degree of foot process integrity. Diffuse FPE is not necessarily a defining signature of primary FSGS, but it eliminates maladaptive mechanisms as the cause of the FSGS lesion. Features such as podocyte vacuolization and microvillous transformation are related to the degree of proteinuria, and as such, they are more likely to be present in primary FSGS than in secondary FSGS; however, they are nonspecific. A genetic form of FSGS must be considered when either diffuse or segmental FPE is observed.

Some mutations have distinctive features on EM that are of diagnostic relevance. Mutations in *ACTN4*, encoding for α–actinin-4, are characterized by segmental FPE and irregularly aggregated electron-dense material in the podocyte cytoplasm, most likely composed of actin and mutant α–actinin-4.[38] Mutations in *INF2*, encoding a member of the formin family of actin-regulating proteins, feature segmental FPE and preserved foot processes that focally appear irregular and jagged, often with unusually prominent longitudinal actin bundles.[53] EM can also help to uncover FSGS as a manifestation of the expanding spectrum of collagen 4 nephropathies by revealing typical (alternating thinning and thickening with lamellation of the lamina densa) or more subtle (abnormal uniform thinning) GBM abnormalities.[54,55] EM can also identify other rare but important causes of secondary FSGS, such as Fabry disease and lecithin acyl cholesterol transferase deficiency.

Quality and Timing of the Biopsy

The probability of finding a segmental lesion critically depends on the number of glomeruli evaluated. In addition, the FSGS lesions preferentially affect the juxtamedullary cortex in the early stages of disease. Adequate sampling is thus essential in disclosing the lesion of FSGS and to avoid misdiagnosis as minimal change disease. Ideally, 12–15 serial sections each containing a minimum of eight glomeruli[15] should be evaluated.

The timing of the biopsy with respect to the disease course is also important. The initial changes (podocyte FPE) are only detectable by EM, because the characteristic sclerotic lesion takes time to develop.[56] It is, therefore, not uncommon that FSGS lesions are absent on the initial biopsy, and a diagnosis of minimal change disease is made, whereas a later biopsy reveals the true nature of the disease by showing clear FSGS lesions. This was typically illustrated by serial biopsy data in kidney transplant recipients with documented FSGS in the native kidneys.[51] Biopsy at the moment of proteinuria recurrence showed only minimal change disease (widespread FPE), whereas subsequent biopsies revealed FSGS lesions, except in those patients who achieved complete remission under treatment regimens for recurrence.[51] As FSGS progresses, more widespread and global glomerulosclerosis develops, and segmental and global sclerotic lesions can be concomitantly observed.[1] A correction for the degree of FGGS anticipated from normal aging alone must always be applied.[20] The timing of the renal biopsy also needs to be correlated with the use of immunosuppressive therapy, because a patient with primary FSGS recently treated with immunosuppression may be going into remission at the time of biopsy. In this scenario, EM examination will likely show segmental FPE as opposed to widespread FPE seen in untreated patients with primary FSGS.

Genetic Testing: Why, How, Whom, and When?

The vast majority of patients with monogenic forms of FSGS do not respond to corticosteroids (Tables 2 and 3) and have a very low risk of recurrence in the allograft. Establishing a genetic cause of disease thus avoids exposure to regimens used to treat primary FSGS and to prevent post-transplantation recurrence. Conversely, mutations with a potentially favorable response to cyclosporin, coenzyme Q10, or vitamin B12 may be identified. Genetic testing allows genetic counseling, preimplantation diagnosis and selection of living donors to ensure that they are not asymptomatic carriers. Finally, patients presenting with apparent secondary FSGS in the absence of defining disease characteristics may be unmasked as having atypical presentations of collagen 4 nephropathies, nephronophthisis,[54,55] or even Fabry disease.

The likelihood of identifying a monogenic cause of FSGS or steroid-resistant nephrotic syndrome correlates inversely with the age of disease onset. Pathogenic mutations are identified in 60%–100% during the first year of life, 40%–60% of young children, 25%–40% of older children, and 10%–25% of adolescents.[46,57–60] Not surprisingly, the yield is higher in patients with familial compared with sporadic cases and in those with syndromic compared with renal-limited disease cases. In patients with adult-onset FSGS, a genetic cause was established in only 8%–14%.[54,57,61]

On the basis of these observations, genetic screening has been recommended in early-onset disease resistant to immunosuppressive therapy, syndromic, and familial disease, but has not been recommended in sporadic adolescence or adult-onset FSGS that does not have clinical evidence of a genetic syndrome.[57] However, this restrictive approach may no longer be valid in the face of a continuously expanding library of genes implicated in the development of FSGS (currently >50) and rapid advances in DNA sequencing technology. Conventional Sanger sequencing allows screening of only the few most frequently mutated genes according to a stepwise algorithm on the basis of age of onset, mode of inheritance, and clinicopathologic presentation, at a high cost and long processing time.[46,57,59,61] However, next generation high-throughput sequencing enables the rapid analysis of vast amounts of DNA at a fraction of the cost. Whole-exome sequencing scans the entire subset of DNA that encodes proteins, known as the exome

(constituting about 1% of the genome), in search of protein-altering mutations.[62,63] An intermediate approach is targeted next generation sequencing of a large panel of genes known to be involved in FSGS.[54,58,60,64,65] With the broad implementation of this technology, the proportion of genetic causes of FSGS is expected to grow substantially (Figure 3). As an example, the yield of mutations in a cohort of patients with adult-onset FSGS increased to 20%.[54] However, the pathogenicity of some of the mutations is currently not established,[54] immediately revealing the Achilles heel of this technology. The pathogenicity of a novel mutation or sequence variant can be predicted by computer models that consider the structure of the protein, but validation ultimately requires difficult and time-consuming functional assays of the gene and gene products.[66] Some variants may not be directly pathogenic, but rather require the interaction with other mutations to render podocytes susceptible to injury,[66] adding another layer of complexity to the interpretation of the genetic results.

We propose that genetic testing be performed in all patients with adult-onset FSGS that cannot be readily categorized by clinicopathologic assessment (Figure 4). In genetic FSGS, response to immunosuppression is rare, and any such response is generally partial. Therefore, response to first-line corticosteroid treatment can be taken as a *prima facie* confirmation of the diagnosis of primary FSGS and precludes the need for genetic analysis. In addition, patients with conditions well known to be associated with secondary FSGS and a compatible clinicopathologic presentation should not be offered genetic analysis. Testing should be done by targeted sequencing of the most recent panel of genes associated with genetic podocytopathies (Tables 2 and 3). In patients of African descent, the G1 and G2 APOL1 alleles should be screened.

Biomarkers

An in-depth discussion of the candidate biomarkers for primary FSGS is presented elsewhere,[67] and it is beyond the scope of this review. To summarize briefly, currently, there are no reliable and clinically useful biomarkers that aid the diagnostic process of classifying FSGS lesions.

CONCLUSION

With the current state of knowledge, empirical treatment of FSGS with corticosteroids or immunosuppressive agents is no longer defensible: such treatment is often ineffective and may impose considerably toxicity. A central consideration in the management of patients with FSGS is the identification of those patients who would likely benefit from such therapies and the delineation of those patients for whom renin-angiotensin-aldosteron system blockade remains the prudent therapeutic approach.

FSGS should be differentiated from FGGS and nonspecific segmental scarring. When a typical FSGS lesion is identified on LM, careful interpretation of clinical and electron microscopic characteristics may point to one of the main subtypes. Patients with primary disease or high-penetrance mutations disruptive to podocyte function present with sudden onset of nephrotic syndrome and with diffuse FPE. Patients with maladaptive FSGS are characterized by slow development of subnephrotic- or nephrotic-range proteinuria without nephrotic syndrome and by segmental FPE. In contrast to these two phenotypes, there is a significant subset of patients lacking clear causative factors and exhibiting variable degrees of proteinuria and FPE. Many of these patients may have an undiagnosed genetic basis of FSGS.[68] New sequencing technologies have dramatically increased the sensitivity for disease-associated variants and mutations compared with the traditional Sanger sequencing. However, many of those genetic abnormalities require additional hits, such as other susceptibility genes or disease-related stressors, before FSGS ensues. The emerging picture is that, in the majority of adults, the lesion of FSGS may be the final common pathway of a complex interplay of factors, each contributing only a small amount of the risk. Although the identification of all etiologic factors may be difficult or even impossible at this stage, it should be clear that such patients should not be treated with immunosuppression or specific measures to prevent post-transplant recurrence.

DISCLOSURES

None.

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