REVIEW ARTICLE

MEDICAL PROGRESS

Focal Segmental Glomerulosclerosis

Vivette D. D'Agati, M.D., Frederick J. Kaskel, M.D., Ph.D., and Ronald J. Falk, M.D.

From the Department of Pathology, Columbia University College of Physicians and Surgeons (V.D.D.); and the Division of Pediatric Nephrology, Albert Einstein College of Medicine (F.J.K.) — both in New York; and UNC Kidney Center and the Division of Nephrology and Hypertension, University of North Carolina, Chapel Hill (R.J.F.). Address reprint requests to Dr. D'Agati at Columbia University Medical Center, Division of Renal Pathology, Rm. VC14-224, 630 W. 168th St., New York, NY 10032, or at vdd1@columbia.edu.

N Engl J Med 2011;365:2398-411.

Focal segmental glomerulosclerosis accounts for approximately 20% of cases of the nephrotic syndrome in children and 40% of such cases in adults, with an estimated incidence of 7 per 1 million.[1] It is the most common primary glomerular disorder causing end-stage renal disease in the United States, with a prevalence of 4%.[2] The cardinal feature is progressive glomerular scarring. Early in the disease course, glomerulosclerosis is both focal, involving a minority of glomeruli, and segmental, affecting a portion of the glomerular globe. With progression, more widespread and global glomerulosclerosis develops. Since the first clinical–pathological studies of the disease in the 1970s,[3] there has been renewed interest because of the increasing incidence of the disease,[4] better understanding of causation, and identification of the podocyte as the major cellular target.[5] The discovery that mutations in podocyte genes are associated with genetic focal segmental glomerulosclerosis has advanced the field of podocyte biology and stimulated new approaches to diagnosis and management.[6]

CLINICAL FEATURES

Proteinuria is a defining feature of focal segmental glomerulosclerosis, typically accompanied by hypoalbuminemia, hypercholesterolemia, and peripheral edema. The nephrotic syndrome in children is defined as proteinuria (>1 g of urine protein per square meter of body-surface area per day), hypoalbuminemia (<2.5 g of albumin per deciliter), hypercholesterolemia (>200 mg of total cholesterol per deciliter), and edema. In adults, the nephrotic syndrome is defined as a urine protein level of more than 3.5 g per day and an albumin level of less than 3.5 g per deciliter. Approximately 75 to 90% of children and 50 to 60% of adults with focal segmental glomerulosclerosis have the nephrotic syndrome at presentation.

Once considered a single disease, focal segmental glomerulosclerosis is now viewed as a group of clinical–pathologic syndromes sharing a common glomerular lesion and mediated by diverse insults directed to or inherent within the podocyte (Table 1). Despite the identification of many factors that lead to focal segmental glomerulosclerosis, approximately 80% of cases are primary (idiopathic). Focal segmental glomerulosclerosis and a related disorder, minimal change disease, are quintessential podocyte diseases, or "podocytopathies."[7,8] In both conditions, podocyte injury leads to effacement of the podocyte foot processes, which is the major structural correlate of nephrotic proteinuria. This change in podocyte shape requires rearrangement of the actin cytoskeleton, a process that is typically reversible with glucocorticoid therapy in minimal change disease but irreversible and progressive in focal segmental glomerulosclerosis.

Table 1. Causes of Focal Segmental Glomerulosclerosis.

Type of Disease	Cause
Primary (idiopathic) form	Specific cause unknown; mediated by circulating permeability factors
Secondary forms	
Familial or genetic	Mutations in specific podocyte genes*
Virus-associated	Human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus, Epstein–Barr virus
Drug-induced	Heroin; interferons alfa, beta, and gamma; lithium; pamidronate; sirolimus; calcineurin-inhibitor nephrotoxicity; anabolic steroids
Adaptive†	Conditions with reduced renal mass: oligomeganephronia, very low birth weight, unilateral renal agenesis, renal dysplasia, reflux nephropathy, sequela to cortical necrosis, surgical renal ablation, renal allograft, aging kidney, any advanced renal disease with reduced functioning nephrons Conditions with initially normal renal mass: systemic hypertension, acute or chronic vaso-occlusive processes (atheroembolization, thrombotic microangiopathy, renal-artery stenosis), elevated body-mass index (obesity, increased lean body mass [e.g., bodybuilding]), cyanotic congenital heart disease, sickle cell anemia

* For details regarding genetic mutations associated with focal segmental glomerulosclerosis, see the table in the Supplementary Appendix.
† The adaptive form is mediated by adaptive structural–functional responses to glomerular hypertension caused by elevated glomerular capillary pressures and flows.

PATHOGENESIS

LOSS OF FILTRATION BARRIER

Nephrotic proteinuria results from loss of integrity of the glomerular filtration barrier, which regulates permselectivity through the intimate association of three layers: fenestrated glomerular endothelial cells at the inner blood interface, the glomerular basement membrane in the center, and podocytes (also known as visceral epithelial cells) at the outer urinary interface (Fig. 1). Podocytes are highly differentiated, polarized epithelial cells resembling neurons in their large cell body and elongated cellular extensions, stabilized by a central actin cytoskeleton core (Fig. 2). The foot processes interdigitate along the outer aspect of the glomerular capillary wall, linked to their neighbors by slit diaphragms, which are modified adherens junctions aligned in a zipperlike array.[9] Podocytes provide structural support to the glomerular capillaries and synthesize the proteins of the slit diaphragm and many extracellular matrix components of the glomerular basement membrane. These terminally differentiated cells cannot repair by means of cell division, making podocyte depletion through detachment, apoptosis, or necrosis a critical mediator of glomerulosclerosis.[8] In the past decade, new insights have derived both from animal models of podocyte depletion and genetic studies of human disease.

PODOCYTE DEPLETION IN EXPERIMENTAL TOXIN MODELS

Experimental models have addressed whether delivery of a lethal toxin specifically and exclusively to the podocyte is sufficient to cause focal segmental glomerulosclerosis. For example, the creation of a transgenic animal that expresses a toxin receptor under the control of a podocyte-specific promoter permits the targeting of a toxin exclusively to podocytes.[10,11] In such a model, internalization of diphtheria toxin or pseudomonas exotoxin A kills podocytes by the inhibition of protein synthesis. The degree of podocyte depletion after toxin exposure correlates closely with the severity of disease in these models.[11] Loss of more than 40% of podocytes leads to overt focal segmental glomerulosclerosis with high-grade proteinuria and renal insufficiency, indicating a disease threshold.[11] Podocytes are shed into the urine for months after a brief toxin exposure, suggesting a secondary autonomous phase of podocyte loss.[12] In a chimeric model in which only a subset of podocytes express toxin receptor, podocyte injury and dedifferentiation are observed to spread to neighboring toxin-resistant podocytes that escaped the initial insult.[13] This chimeric model suggests that injury can propagate locally from podocyte to podocyte by a domino-like effect, which may explain the segmental nature of the lesions. Although the mediators are unknown, a second-

ary wave of podocyte injury hypothetically might decrease podocyte survival factors that signal through nephrin and glutamate receptors[14] or might increase noxious factors, such as shear stress, angiotensin II, or transforming growth factor β (TGFβ).[13]

An experimental model of focal segmental glomerulosclerosis that is induced by the anthracycline doxorubicin (also called adriamycin) causes severe disease in BALB/c mice, whereas other mouse strains are protected. The strain dependence went unexplained until the recent discovery of the susceptibility gene as an ancestral mutation in *Prkdc* (protein kinase, DNA-activated, catalytic polypeptide), which encodes a component of the DNA double-strand break-repair machinery.[15] In BALB/c mice, there is no nonhomologous end-joining DNA repair after intercalation of doxorubicin into podocyte DNA, leading to mitochondrial DNA depletion.[15] This murine model illustrates the importance of protective mechanisms against genotoxic stress to enhance podocyte longevity.

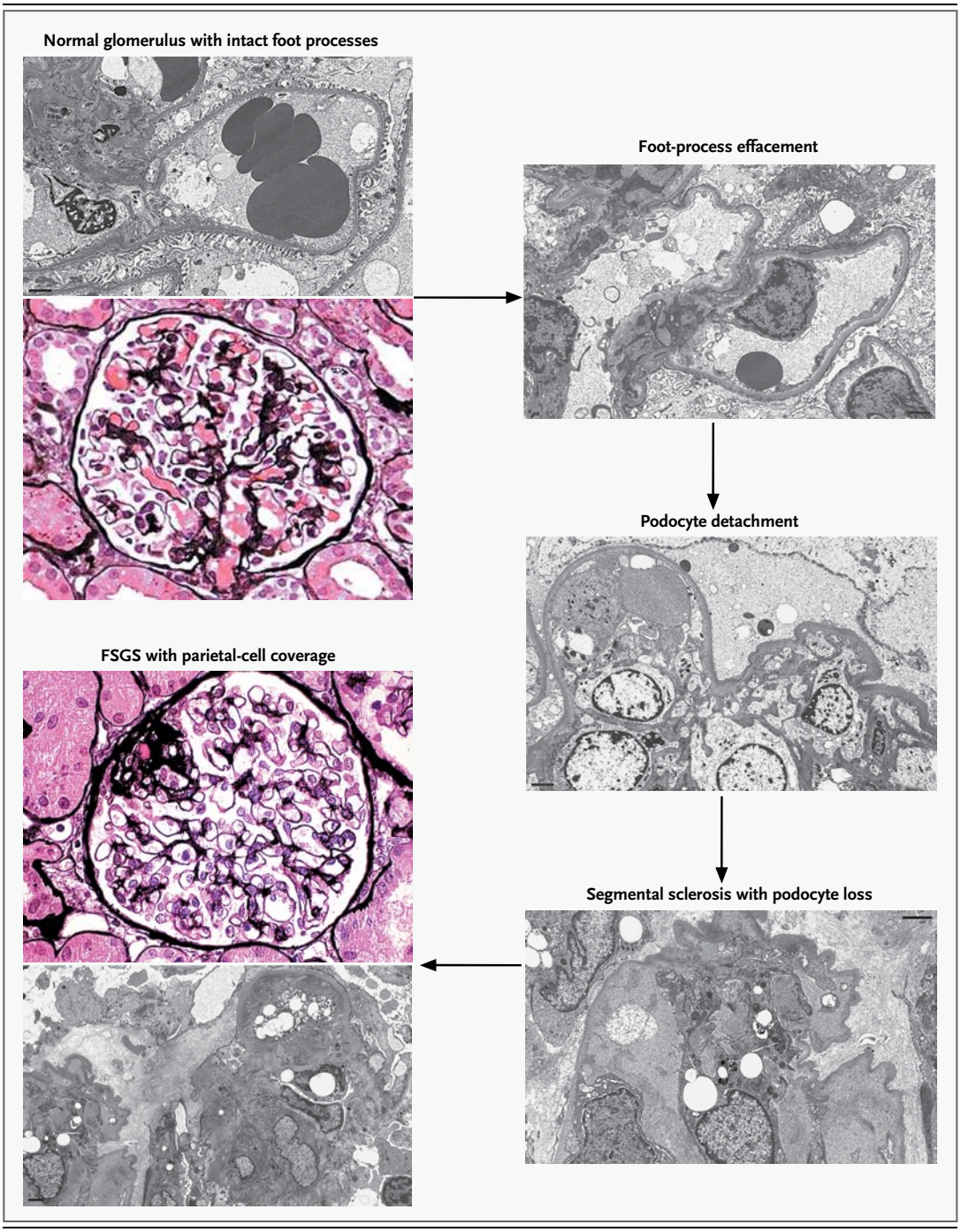
Figure 1 (facing page). Morphogenesis of Focal Segmental Glomerulosclerosis (FSGS).

The sequence of glomerular changes in the development of FSGS is illustrated by parallel light-microscopic and electron-microscopic images. The normal glomerular capillaries are widely patent and have intact foot processes (or pedicels) along their outer aspect. Podocytes that are targeted by cellular stresses, such as permeability factors (external causes) or disease-causing mutations (intrinsic defects), respond by the reorganization of their actin cytoskeleton, leading to foot-process effacement. This change in cell shape forms a sheet of undifferentiated cytoplasm over the surface of the glomerular basement membrane. If the inciting injurious factors are long-standing or the podocyte is exposed to second hits, a critical level of cell stress is reached and the injured or dying podocyte detaches from the glomerular basement membrane. Because podocytes are unable to repair by cell division, attrition of a finite number of podocytes leads to sclerosis of the underlying glomerular capillaries, which become obliterated by matrix. At these sites, adhesions to Bowman's capsule may form, and parietal cells often migrate onto the tuft, where they lay down loose matrix material. In the early stages, the sclerotic lesions are typically segmental, involving a portion of the glomerular tuft.

GENETIC SUSCEPTIBILITY

Since the discovery of nephrin as the major component of the slit diaphragm in 1998,[16] the number of identified podocyte mutations in familial and sporadic focal segmental glomerulosclerosis has grown (Fig. 2, and the table in the Supplementary Appendix, available with the full text of this article at NEJM.org). The genes encode diverse podocyte products located in the slit diaphragm,[16-19] cell membrane,[20-24] cytosol,[25] actin cytoskeleton,[26-29] nucleus,[30,31] mitochondria,[32-34] and lysosomes.[35] Mutations in nephrin and podocin are the most frequent.[36] Most mutations follow an autosomal recessive transmission and manifest early in life. Autosomal dominant forms (e.g., mutations in genes encoding α-actinin-4 and transient receptor potential cation channel 6) usually present in late adolescence or adulthood. Many of the genes that are involved were identified by positional cloning in affected families and later validated in global or podocyte-specific knockout models or in transgenic models that express the mutated genes. Genetic defects have been identified in up to two thirds of patients with focal segmental glomerulosclerosis who present in the first year of life, underscoring the importance of genetic testing in this age group.[37] Genetic testing is most likely to uncover a basis for focal segmental glomerulosclerosis in infants, young children, and patients with syndromic disease or a positive family history. A small but clinically important percentage of older children and adults with sporadic glucocorticoid-resistant disease may also harbor mutations.[36]

Podocyte genes encode diverse structural proteins or enzymes that participate in signaling events that regulate podocyte growth, differentiation, motility, and interactions between cells and between cells and matrix.[38] These gene products are coupled to the actin cytoskeleton directly or indirectly through intermediary proteins (Fig. 2). Disruption or dysregulation of signaling through these proteins leads to rearrangement of the actin cytoskeleton and the generalized response of foot-process effacement. The podocyte is a motile cell endowed with mechanosensors that respond to positional stimuli and shear stress.[39] Factors that promote the development of a cytoskeleton that is either too rigid or too dynamic pose potential threats to podocyte survival. For example, disease-causing mutations in α-actinin-4 produce a rigid cytoskeleton by exposing a buried actin-binding



site that is independent of calcium regulation, leading to a gain of function.[40] Once the actin cytoskeleton undergoes rearrangement, the loss of foot-process anchoring may weaken podocyte attachments to the glomerular basement membrane, rendering them more vulnerable to detachment in response to filtration pressures. It is likely that the wear and tear from shear stress, stretch tension, oxidative stress, and DNA damage that accrues over years may compound a genetic basis for this disease.[41] Such accumulated second hits might explain the late onset of genetic focal segmental glomerulosclerosis in adults with autosomal dominant mutations.

Figure 2 (facing page). Normal Glomerulus and Glomerular Filtration Barrier.

In Panel A, each kidney contains approximately 1 million glomeruli, which comprise the filtering units of the kidney. The normal glomerulus is composed of a specialized bundle of capillaries that originates from branchings of the afferent arteriole as it enters the hilus (or vascular pole). Between the afferent and efferent arterioles, bordered by the macula densa of the distal tubule, is the triangular juxtaglomerular apparatus, an endocrine organ involved in renin production and tubuloglomerular feedback. The glomerular capillaries are supported by the mesangial cells, which are invested in matrix and are continuous with the smooth-muscle cells of the hilar arterioles. The glomerular endothelial-cell bodies are oriented toward the mesangium, whereas their fenestrated cytoplasm lines the inner aspect of the peripheral glomerular basement membrane. The glomerular basement membrane forms a scaffold for the glomerular capillaries and reflects over the mesangium. Along their outer aspect, the glomerular capillaries are supported by the podocytes, which reside in the urinary space and have interdigitating foot processes. The glomerular ultrafiltrate enters the urinary space and passes into the tubular pole (the origin of the proximal tubule), which lies opposite the vascular pole. In Panel B, the glomerular capillary wall and selected components of the filtration barrier are shown. On the urinary side, the interdigitating podocyte foot processes are aligned in regular arrays separated by filtration slit diaphragms located above the glomerular basement membrane. The fenestrated glomerular endothelium is present at the blood interface. The inset diagrams show some of the molecules that make up the slit diaphragm (above) and the basal surface of the podocyte (below). Nephrin is the major component of the slit diaphragm. Pairs of nephrin molecules extending out into the center of the slit from adjacent podocyte foot processes form homophilic interactions as well as heterophilic interactions with NEPH. The slit diaphragm complex includes podocin, which forms a hairpin turn within the podocyte membrane. Through interaction with CD2-associated protein (CD2AP), the slit diaphragm molecules are linked to the actin cytoskeleton, which is regulated by α-actinin-4, inverted formin 2 (INF2), and myosin 1E (Myo1E). Calcium generated by phospholipase C epsilon 1 (PLCε1) through diacylglycerol (DAG) and inositol triphosphate (IP3) and entering the cell through transient receptor potential cation channel 6 (TRPC6) regulates actin polymerization. At the basal surface, adhesion molecules $\alpha_3\beta_1$ integrin and α-dystroglycan are linked to laminin. Integrin is coupled to the actin cytoskeleton through a complex of talin, vinculin, and paxillin, whereas adhesion molecule α-dystroglycan links to actin through utrophin. Negatively charged molecules podocalyxin and glomerular epithelial protein 1 (GLEPP-1) are arrayed on the apical-cell membrane.

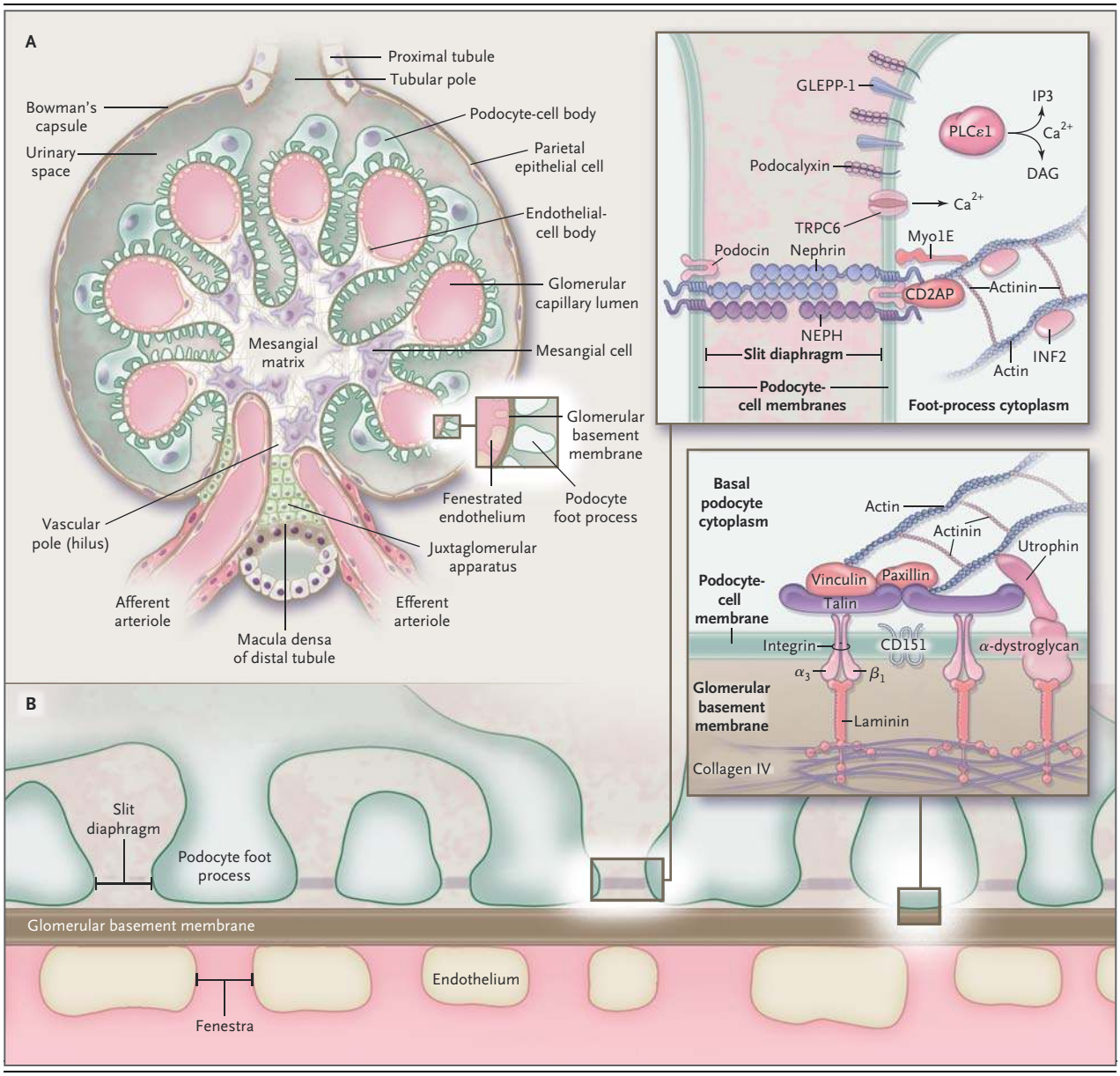
GENETIC BASIS IN PATIENTS OF AFRICAN DESCENT

Across age groups, the incidence of focal segmental glomerulosclerosis is higher and the rate of renal survival is worse among blacks than among whites. Mapping by means of admixture linkage disequilibrium in large populations identified genetic risk factors for focal segmental glomerulosclerosis and end-stage renal disease in blacks. Two genes in close linkage disequilibrium were identified on human chromosome 22. *MYH9*, encoding myosin heavy chain 9, a nonmuscle myosin IIA that is a component of the podocyte cytoskeleton, was identified first[42] and was an attractive candidate because *MYH9* mutations were known to cause a rare autosomal dominant form of focal segmental glomerulosclerosis in patients with Epstein–Fechtner syndromes (renal disease, sensorineural deafness, and macrothrombocytopenia).[27,43] Genomewide scans identified three single-nucleotide polymorphisms in intron 23 of the *MYH9* gene as conferring risk for primary focal segmental glomerulosclerosis and hypertensive end-stage renal disease among blacks in an autosomal recessive model.[42,44] However, further probing of the genetic interval found two independent sequence variants (called G1 and G2) in the last exon of the neighboring gene encoding apolipoprotein L1 (*APOL1*) that had a stronger association with focal segmental glomerulosclerosis, with a combined signal that was increased by a factor of 35 over that of *MYH9*. Thus, *APOL1* was implicated as the actual susceptibility gene.[45]

Selection tests in Europeans and Africans showed that the *APOL1* G1 and G2 haplotypes were under strong selection only in Africa.[45] Apolipoprotein L1 is a plasma factor that can lyse *Trypanosoma brucei brucei*, the parasite that causes sleeping sickness. Two subspecies of trypanosoma that are resistant to lysis by apolipoprotein L1, *T. brucei rhodesiense* and *T. brucei gambiense*, evolved in sub-Saharan Africa. The G1 and G2 variants of *APOL1* lyse *T. brucei rhodesiense*, but not *T. brucei gambiense*, a finding that explains how these variants could have risen to high frequency by natural selection. This scenario is analogous to sickle cell trait, in which a mutation in the hemoglobin A beta chain confers protection against malaria but at the risk of hemoglobinopathy. In both situations, the protection against parasitic infection is a dominant trait present in heterozygotes, whereas the development of host disease is a recessive trait, present in homozygotes. How the *APOL1* G1 and G2 variants act mechanistically on the podocyte to cause focal segmental glomerulosclerosis has not been delineated.

PATHOLOGICAL DEFINITION

The histologic definition of focal segmental glomerulosclerosis is a segmental obliteration of



glomerular capillaries by extracellular matrix.[7,46] Entrapment of plasma proteins as hyalinosis commonly accompanies the sclerosis. Because juxtamedullary nephrons are often affected first, adequate glomerular sampling is needed to identify the diagnostic lesions. Adhesions or synechiae may form between the sclerosing segment and Bowman's capsule. On electron microscopy, the major finding is extensive effacement of the foot processes without other abnormalities in the glomerular basement membrane. Detachment of podocytes from the glomerular basement membrane occurs in regions overlying the sclerotic lesions. At these sites, there is often accumulation of loose matrix material synthesized by parietal cells that migrate onto the tuft, producing a halolike effect. Granular immune-type electron-dense deposits are not present. Immunofluorescence typically reveals coarse segmental staining for IgM and C3 entrapped in areas of hyalinosis. As individual nephrons degenerate, tubular atrophy and interstitial fibrosis develop. Proximal tubular reabsorption droplets reflect heightened tubular trafficking of albumin and lipoproteins, a process that contributes to progressive tubulointerstitial injury.[47]

The pathologic diversity of glomerular lesions in focal segmental glomerulosclerosis is evident.[7,46,48] Lesions differ anatomically in their

location with respect to the glomerular hilus (vascular pole) and the tubular pole and qualitatively with respect to glomerular hypercellularity and capillary collapse.[46] A classification of histologic variants recognizes not-otherwise-specified (NOS),[46] perihilar,[46,49-53] cellular,[53,54] tip,[46,55,56] and collapsing disease[57-62] variants and is applicable to both primary and secondary focal segmental glomerulosclerosis (Fig. 3).

In the collapsing variant, podocytes have an

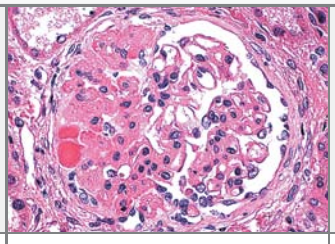
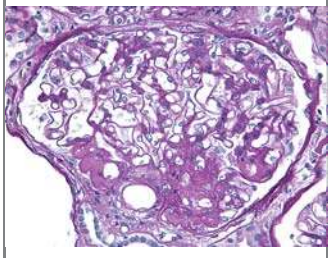
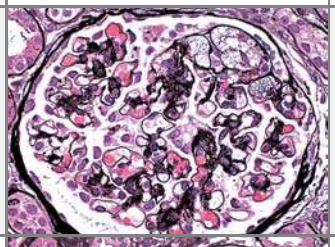
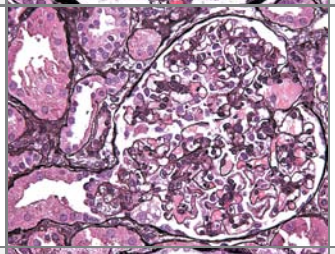
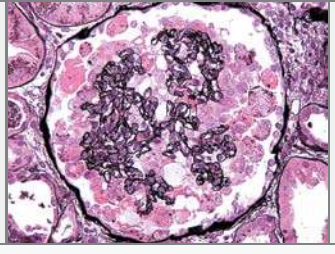
Histologic Subtype	Glomerular Lesion	Defining Features	Associations	Clinical Features
NOS		The usual generic form of FSGS. FSGS(NOS) does not meet defining criteria for any other variant. Foot-process effacement is variable.	Primary or secondary (including genetic forms and other diverse secondary causes). Cross-sectional studies suggest this is the most common subtype. Other variants can evolve into FSGS (NOS) over time.	May present with the nephrotic syndrome or subnephrotic proteinuria.
Perihilar		Perihilar hyalinosis and sclerosis involving the majority of glomeruli with segmental lesions. Perihilar lesions are located at the glomerular vascular pole. In adaptive FSGS, there is usually glomerular hypertrophy (glomerulomegaly). Foot-process effacement is relatively mild and focal, which probably reflects the heterogeneous adaptive responses of glomeruli.	Common in adaptive FSGS associated with obesity, elevated lean body mass, reflux nephropathy, hypertensive nephrosclerosis, sickle cell anemia, and renal agenesis. Predisposition for vascular pole is probably due to normally increased filtration pressures at the proximal afferent end of glomerular capillary bed, which are heightened under conditions of compensatory demand and vasodilatation of the afferent arteriole.	In adaptive FSGS, patients are more likely to present with subnephrotic proteinuria and normal serum albumin levels.
Cellular		Expansile segmental lesion with endocapillary hypercellularity, often including foam cells and infiltrating leukocytes, with variable glomerular epithelial-cell hyperplasia. There is usually severe foot-process effacement.	Usually primary, but also seen in a variety of secondary forms. This is the least common variant. It is thought to represent an early stage in the evolution of sclerotic lesions.	Usually presents with the nephrotic syndrome.
Tip		Segmental lesion involving the tubular pole, with either adhesion to tubular outlet or confluence of podocytes and tubular epithelial cells. Compared with other variants, it has the least tubular atrophy and interstitial fibrosis. There is usually severe foot-process effacement.	Usually primary. Probably mediated by physical stresses on the paratubular segment owing to the convergence of protein-rich filtrate on the tubular pole, causing shear stress and possible prolapse.	Usually presents with abrupt onset of the nephrotic syndrome. More common in white race. Best prognosis, with highest rate of responsivity to glucocorticoids and lowest risk of progression.
Collapse		Implosive glomerular-tuft collapse with hypertrophy and hyperplasia of the overlying visceral epithelial cells. Hyperplastic glomerular epithelial cells may fill the urinary space, resembling crescents. Severe tubular injury and tubular microcysts are common. There is usually severe foot-process effacement.	Primary or secondary to Viruses: HIV-1, parvovirus B19, SV40, EBV, CMV, hemophagocytic syndrome Drugs: pamidronate and interferon Vaso-occlusive disease: atheroemboli, calcineurin inhibitor nephrotoxicity, and chronic allograft nephropathy	Most aggressive variant of primary FSGS with black racial predominance and severe nephrotic syndrome. Worst prognosis, with poor responsivity to glucocorticoids and rapid course to renal failure.

Figure 3. Histologic Variants of Focal Segmental Glomerulosclerosis (FSGS).

CMV denotes cytomegalovirus, EBV Epstein–Barr virus, HIV-1 human immunodeficiency virus type 1, NOS not otherwise specified, and SV40 simian virus 40.

immature, dysregulated phenotype.[63,64] Because injured podocytes lose differentiation markers such as nephrin, the identity of the cells that proliferate in Bowman's space has been controversial. Recent studies using parietal-cell markers suggest that most of these cells actually originate from the parietal layer.[65-67] Moreover, progenitor cells bearing stem-cell markers CD133 and CD24 line Bowman's capsule, possibly serving as a reservoir to replenish lost podocytes.[68] Although progenitor cells may be recruited to sites of podocyte denudation, it is not known whether they can differentiate into the mature podocytes that are needed to reconstitute a normal filtration barrier.

PRIMARY (IDIOPATHIC) DISEASE

Primary focal segmental glomerulosclerosis has long been attributed to a putative circulating permeability factor. Indirect evidence for a circulating plasma factor includes the ability to modulate proteinuria by immunoadsorption, potential disease recurrence minutes after renal transplantation, and therapeutic reduction in proteinuria by plasmapheresis.[69] In addition, serum samples from patients with focal segmental glomerulosclerosis cause increased permeability to albumin in isolated glomeruli and induce foot-process effacement and proteinuria when injected into rats. Several candidate plasma factors have been proposed. For example, cardiotrophin-like cytokine 1, a member of the interleukin-6 family, has permeability activity in a plasma fraction with a molecular weight of less than 30 kD and can be enriched by means of galactose affinity chromatography.[69] Elevated serum levels of soluble urokinase receptor (>3000 pg per milliliter) have been identified in up to two thirds of patients with primary focal segmental glomerulosclerosis but not in those with minimal change disease.[70] Increased serum levels of soluble urokinase receptor before renal transplantation were associated with an increased risk of recurrent disease in the allograft.[70] Circulating soluble urokinase receptor induces foot-process effacement through the activation of podocyte β_3 integrin, and its effect can be blocked in animal models by neutralizing antibodies targeting soluble urokinase receptor.[70,71] The cellular source and stimulants of soluble urokinase receptor in patients with focal segmental glomerulosclerosis are unknown.

VIRUS-INDUCED DISEASE

Viruses can act on the podocyte either by direct infection or by the release of inflammatory cytokines that interact with podocyte receptors. The best studied of such viruses is human immunodeficiency virus type 1 (HIV-1), which directly infects podocytes and tubular epithelial cells.[72] Evidence supports HIV-1 entry by transfer from infected T cells to tubular epithelial cells through virologic synapses formed during cell adhesion, independent of CD4.[73] HIV-1 can persist in the kidney epithelium despite antiretroviral therapy and normalization of peripheral CD4 counts. HIV-1 gene expression by infected renal epithelium in turn induces dysregulation of host genes. The form of focal segmental glomerulosclerosis associated with untreated HIV-1, called HIV-associated nephropathy (HIVAN), typically progresses rapidly and is associated with glomerular collapse.[62] In vivo and in vitro models have identified viral genes *nef* and *vpr* as particularly important in HIVAN pathogenesis.[74,75] Nef, a virulence factor, contains a proline-rich motif that interacts with the SH3 domain of the Src family kinases. Through downstream activation of STAT3 and MAPK1/2, it promotes podocyte dedifferentiation and proliferation, whereas interaction with diaphanous interacting protein mediates the up-regulation of Rac1, reduction in RhoA, and dysregulation of actin cytoskeleton.[76] Vpr, which is required for nuclear entry of the HIV-1 preintegration complex, mediates tubular epithelial G2 cell-cycle arrest and apoptosis.[77,78] Parvovirus B19 is another virus that can infect podocytes and tubular cells, leading to collapsing focal segmental glomerulosclerosis.[60] Other viruses associated with this disease, such as simian virus 40, cytomegalovirus, and Epstein–Barr virus, are less well characterized.[57,61]

DRUG-INDUCED DISEASE

Historically, the first drug associated with focal segmental glomerulosclerosis was heroin, though the incidence of this drug-induced disease (known as heroin nephropathy) has fallen sharply in parallel with the increasing purity of modern street heroin.[79] The bisphosphonate pamidronate, an osteoclast inhibitor used to reduce bone resorption in patients with myeloma and metastatic cancers, has been linked to the development of focal segmental glomerulosclerosis.[58] Proteinuria and

renal failure associated with pamidronate typically improve after withdrawal of the drug. Pamidronate has direct toxic effects on osteoclasts, including disruption of the actin cytoskeleton, suggesting the possibility of a similar effect on the podocyte cytoskeleton.

All forms of interferon therapy, including interferon alfa (widely used to treat hepatitis C), interferon beta (indicated for multiple sclerosis), and interferon gamma (formerly used in idiopathic pulmonary fibrosis and indicated for chronic granulomatous disease and malignant osteopetrosis), have been reported to induce focal segmental glomerulosclerosis.[59] The podocyte has receptors for interferon alfa and interferon beta and expresses major histocompatibility complex class II antigen in response to interferon gamma, suggesting potential direct podocyte effects. In the transplanted kidney, toxic effects from calcineurin inhibitors are associated with collapsing focal segmental glomerulosclerosis and hyaline arteriolopathy, probably through acute ischemia from severe vasoconstriction.[80,81] In addition, the mammalian target of rapamycin (mTOR) inhibitor sirolimus (also known as rapamycin) can induce focal segmental glomerulosclerosis by reducing podocyte expression of critical proteins in the slit diaphragm and cytoskeleton, including nephrin.[82]

DISEASE SECONDARY TO HEMODYNAMIC ADAPTATIONS

Another form of focal segmental glomerulosclerosis, termed adaptive focal segmental glomerulosclerosis, is thought to result from structural and functional adaptations mediated by intrarenal vasodilatation, increased glomerular capillary pressures, and plasma flow rates.[52] Such maladaptive responses may arise through a reduction in the number of functioning nephrons (e.g., in unilateral renal agenesis, reflux nephropathy, or low nephron endowment owing to very low birth weight[50]) or through mechanisms that place hemodynamic stress on an initially normal nephron population (e.g., in morbid obesity, cyanotic congenital heart disease, and sickle cell anemia) (Table 1). Unlike primary focal segmental glomerulosclerosis, adaptive disease is often associated with normal serum albumin levels, despite nephrotic-range proteinuria, and biopsy samples obtained from such patients often show enlarged glomeruli, perihilar sclerosis, and relatively mild degrees of foot-process effacement.[7,46]

Animal models in which renal mass is markedly reduced have elucidated the mechanistic bases for adaptive focal segmental glomerulosclerosis.[83] Reflex vasodilatation of both the afferent and efferent arterioles follows a marked reduction in renal mass, causing elevation in the flow rate in the glomerular capillaries. Because the reduction in vascular resistance is greater in the afferent arteriole than in the efferent arteriole, glomerular hydrostatic pressure rises, producing glomerular hypertension. These responses cause an elevation in the single-nephron glomerular filtration rate in proportion to the amount of kidney excised.[52,83] Glomerular volume and surface area increase, placing mechanical strain on podocytes that stretch to cover the expanding tuft. Some hypertrophied podocytes detach, producing denuded patches of glomerular basement membrane. These sites become covered by parietal cells, leading to the formation of a synechia to Bowman's capsule and a nidus for the development of segmental sclerosis.[84]

Although this scenario is the initiating step in the adaptive forms of focal segmental glomerulosclerosis, it may supervene in the later stages of other forms of the disease. The loss of a critical number of nephrons promotes the activation of the renin–angiotensin system (RAS), exacerbating proteinuria and setting the stage for progressive glomerulosclerosis regardless of the initial cause. Angiotensin II also has direct proapoptotic effects on podocytes.[85] Excessive protein uptake by podocytes induces podocyte TGFβ,[86] which promotes apoptosis and leads to endoplasmic reticulum stress, cytoskeletal reorganization, and dedifferentiation.[87] Drugs that are aimed at the inhibition of RAS (such as angiotensin-converting–enzyme [ACE] inhibitors and angiotensin-receptor blockers) lower intraglomerular filtration pressures through the inhibition of angiotensin II–mediated vasoconstriction of the efferent arteriole. ACE inhibition also augments bradykinin, which contributes to efferent arteriolar dilatation. The resulting reduction in proteinuria exerts a protective effect on podocytes and tubular cells.

PROGNOSTIC FEATURES

A variety of clinical and pathologic features predict outcome. Black race, increased degrees of pro-

teinuria and renal insufficiency, and increased severity of interstitial fibrosis and tubular atrophy in biopsy specimens are associated with a worse outcome. Patients who have a partial or complete remission of proteinuria have better outcomes than those who do not.[88] The histologic variant also correlated with remission status and outcome in two large case series,[53,54] in which rates of complete and partial remission were highest for the tip variant, were intermediate for the cellular, perihilar, and NOS variants, and were lowest for the collapsing variant. Renal survival was inversely related to remission status, with the best rates of renal survival in the tip variant and the worst rates in the collapsing variant.[53,54] The prognosis in the adaptive form of the disease is typically much better than in the primary form, possibly as a consequence of an increased likelihood of complete or partial remission with RAS inhibition in this population.

THERAPY

The goal of therapy is to induce a complete or partial remission of proteinuria and preserve renal function. Even partial remission is associated with improved long-term survival.[89,90] The treatment of primary focal segmental glomerulosclerosis is empiric and based on the rationale that the permeability factor derives from a dysregulated immune response. In addition, these therapies have beneficial effects directly on podocytes.[91]

Children with the nephrotic syndrome are treated empirically with oral prednisone (60 mg per square meter of body surface per day) for 4 to 6 weeks, a regimen that is based on the statistical likelihood that most children (approximately 80%) will have glucocorticoid-responsive minimal change disease. In most centers, usually only children with glucocorticoid resistance are subjected to renal biopsy. In contrast, adults with the nephrotic syndrome usually undergo renal biopsy before the initiation of therapy, since the possible causes are far more varied.

Once a diagnosis is established on biopsy, potential secondary causes that require specific therapies should be ruled out before a patient is presumed to have primary focal segmental glomerulosclerosis. For example, the form of the disease that is caused by HIV-1 infection is treated with antiretroviral therapy, and drug-induced forms are managed by discontinuation of the inciting agent. Patients with focal segmental glomerulosclerosis receive RAS blockade and dietary sodium restriction as initial therapy. In the adaptive form of the disease, such therapy typically results in the diminution of proteinuria to less than 1 g per day. There is no evidence to support glucocorticoid therapy in adaptive or genetic forms of the disease. Some genetic forms may respond to empirical therapy with calcineurin inhibitors.

An algorithm for the treatment of primary focal segmental glomerulosclerosis is illustrated in Figure 4. High-dose glucocorticoid therapy can be given as 1 mg per kilogram of body weight daily or as 2 mg per kilogram on alternate days. In adults, a response to glucocorticoids may take up to 16 weeks,[92] after which the drugs can be slowly tapered over a period of 3 to 6 months. There is little evidence to recommend glucocorticoid therapy in patients with the primary form of the disease that is not accompanied by the nephrotic syndrome. Therapy for glucocorticoid-resistant focal segmental glomerulosclerosis is a calcineurin inhibitor, either cyclosporine[93] or tacrolimus. In some patients, such as those with diabetes, a psychiatric disorder, or severe osteoporosis, concern about the side effects of glucocorticoid therapy may prompt the selection of a calcineurin inhibitor alone as first-line therapy. Cyclosporine can be given in divided doses of 3 to 5 mg per kilogram per day for 4 to 6 months to induce remission. Patients are more likely to remain in remission if calcineurin inhibitor therapy is continued for at least 12 months before slowly tapering. In addition to the systemic immunosuppressive properties of glucocorticoids and calcineurin inhibitors, these drugs exert direct effects on the podocyte that enhance prosurvival pathways and stabilize the actin cytoskeleton.[91,94] The control of blood pressure and hyperlipidemia is also a critical element of supportive care.

A randomized trial was conducted in glucocorticoid-resistant children and adults up to 40 years of age comparing a 12-month course of cyclosporine therapy with a combination of oral pulse dexamethasone and mycophenolate mofetil.[95] Partial or complete remission occurred in 46% of the cyclosporine group versus 33% of the group receiving dexamethasone–mycophenolate mofetil, a difference that was not statistically significant. Although somewhat underpowered, this study suggests that these regimens have limited additional benefit in glucocorticoid-resistant patients

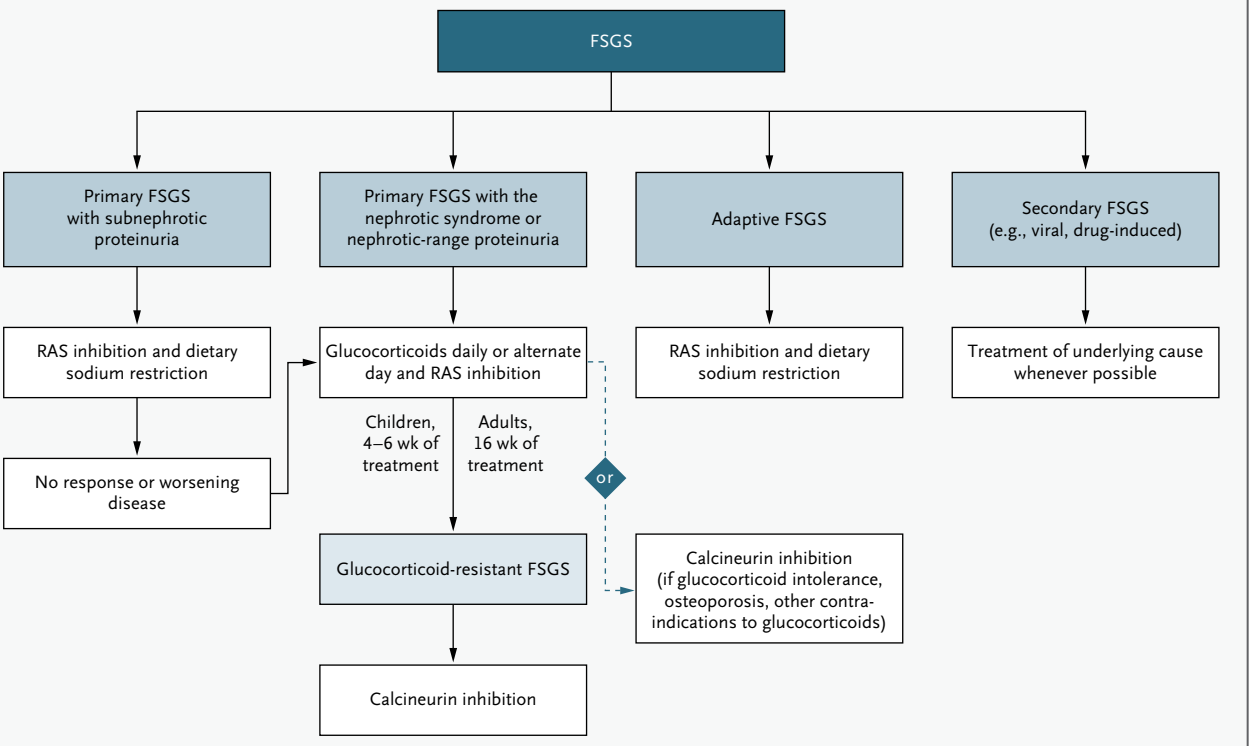


Figure 4. Treatment Algorithm for Focal Segmental Glomerulosclerosis (FSGS).
RAS denotes renin–angiotensin system.

and shows the potential for toxicity from large doses of glucocorticoids.

Glucocorticoid and calcineurin inhibitor therapies are successful in approximately 50% of patients. Other therapies have been tried, including alkylating agents, plasmapheresis, and even the anti–B-cell monoclonal antibody rituximab, which also stabilizes the podocyte actin cytoskeleton,[96] but none of these therapies have been shown to be effective. Sirolimus has been associated with adverse events, including acute renal failure.[97]

Most patients with progressive focal segmental glomerulosclerosis have persistent nephrotic-range proteinuria. Although patients with non-nephrotic proteinuria are at a reduced risk for progression to end-stage renal disease, sustained non-nephrotic proteinuria is associated with an increased risk of death and complications from cardiovascular causes.[98] Thus, the control of hypertension, hyperlipidemia, and edema is important in risk management.

RECURRENCE AFTER KIDNEY TRANSPLANTATION

In approximately 40% of patients with primary focal segmental glomerulosclerosis with end-stage renal disease who undergo kidney transplantation, recurrent disease develops in the allograft. Risk factors for recurrence include younger age (especially in children 6 to 15 years of age), nonblack race, a rapid course to end-stage renal disease (<3 years) in the native kidney, heavy proteinuria in the period before transplantation, and the loss of previous allografts to recurrence.[99] Early recurrent focal segmental glomerulosclerosis resembles minimal change disease with extensive foot-process effacement, but repeat biopsy samples show evolution to lesions associated with focal segmental glomerulosclerosis over time. In such cases, the histologic subtype is the same as that in the native kidney in approximately 80% of patients, supporting the persistence of a similar

pathogenesis.[100] Plasmapheresis to remove the putative permeability factor is most beneficial early in the course of recurrence and is reported to lead to remission after 8 to 12 treatments.[99]

CONCLUSIONS

Focal segmental glomerulosclerosis is a common pattern of glomerular disease comprising diverse clinical and pathologic syndromes. All forms of the disease share podocyte injury and depletion as central mediators of the pathology. Great progress has been made in unraveling the pathogenesis of genetic and secondary forms. Advances in identification of the permeability factors causing the common primary form hold promise for the design of more targeted therapies.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Kitiyakara C, Kopp JB, Eggers P. Trends in the epidemiology of focal segmental glomerulosclerosis. Semin Nephrol 2003;23:172-82.
2. Renal Data System. USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010.
3. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis: a report of the International Study of Kidney Disease in Children. Kidney Int 1978;13:159-65.
4. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. Am J Kidney Dis 1997;30:621-31.
5. Gbadegesin R, Lavin P, Foreman J, Winn M. Pathogenesis and therapy of focal segmental glomerulosclerosis: an update. Pediatr Nephrol 2011;26:1001-15.
6. Zenker M, Machuca E, Antignac C. Genetics of nephrotic syndrome: new insights into molecules acting at the glomerular filtration barrier. J Mol Med 2009; 87:849-57.
7. D'Agati VD. The spectrum of focal segmental glomerulosclerosis: new insights. Curr Opin Nephrol Hypertens 2008; 17:271-81.
8. Wiggins RC. The spectrum of podocytopathies: a unifying view of glomerular diseases. Kidney Int 2007;71:1205-14.
9. Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. N Engl J Med 2006;354:1387-401.
10. Matsusaka T, Xin J, Niwa S, et al. Genetic engineering of glomerular sclerosis in the mouse via control of onset and severity of podocyte-specific injury. J Am Soc Nephrol 2005;16:1013-23.
11. Wharram BL, Goyal M, Wiggins JE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. J Am Soc Nephrol 2005;16:2941-52.
12. Sato Y, Wharram BL, Lee SK, et al. Urine podocyte mRNAs mark progression of renal disease. J Am Soc Nephrol 2009;20:1041-52.
13. Matsusaka T, Sandgren E, Shintani A, et al. Podocyte injury damages other podocytes. J Am Soc Nephrol 2011;22:1275-85.
14. Puliti A, Rossi PI, Caridi G, et al. Albuminuria and glomerular damage in mice lacking the metabotropic glutamate receptor 1. Am J Pathol 2011;178:1257-69.
15. Papeta N, Zheng Z, Schon EA, et al. Prkdc participates in mitochondrial genome maintenance and prevents Adriamycin-induced nephropathy in mice. J Clin Invest 2010;120:4055-64.
16. Kestilä M, Lenkkeri U, Männikkö M, et al. Positionally cloned gene for a novel glomerular protein — nephrin — is mutated in congenital nephrotic syndrome. Mol Cell 1998;1:575-82.
17. Boute N, Gribouval O, Roselli S, et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. Nat Genet 2000;24:349-54.
18. Kim JM, Wu H, Green G, et al. CD2-associated protein haploinsufficiency is linked to glomerular disease susceptibility. Science 2003;300:1298-300.
19. Santín S, García-Maset R, Ruíz P, et al. Nephrin mutations cause childhood- and adult-onset focal segmental glomerulosclerosis. Kidney Int 2009;76:1268-76.
20. Kambham N, Tanji N, Seigle RL, et al. Congenital focal segmental glomerulosclerosis associated with beta4 integrin mutation and epidermolysis bullosa. Am J Kidney Dis 2000;36:190-6.
21. Karamatic Crew V, Burton N, Kagan A, et al. CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin. Blood 2004; 104:2217-23.
22. Ozaltin F, Ibsirlioglu T, Taskiran EZ, et al. Disruption of PTPRO causes childhood-onset nephrotic syndrome. Am J Hum Genet 2011;89:139-47.
23. Winn MP, Conlon PJ, Lynn KL, et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science 2005;308:1801-4.
24. Zenker M, Aigner T, Wendler O, et al. Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. Hum Mol Genet 2004;13:2625-32.
25. Hinkes B, Wiggins RC, Gbadegesin R, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nat Genet 2006;38:1397-405.
26. Brown EJ, Schlöndorff JS, Becker DJ, et al. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. Nat Genet 2010;42:72-6.
27. Ghiggeri GM, Caridi G, Magrini U, et al. Genetics, clinical and pathological features of glomerulonephritis associated with mutations of nonmuscle myosin IIA (Fechtner syndrome). Am J Kidney Dis 2003;41:95-104.
28. Kaplan JM, Kim SH, North KN, et al. Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. Nat Genet 2000;24: 251-6.
29. Mele C, Iatropoulos P, Donadelli R, et al. *MYO1E* mutations and childhood familial focal segmental glomerulosclerosis. N Engl J Med 2011;365:295-306.
30. Denamur E, Bocquet N, Mougenot B, et al. Mother-to-child transmitted WT1 splice-site mutation is responsible for distinct glomerular diseases. J Am Soc Nephrol 1999;10:2219-23.
31. Lücke T, Billing H, Sloan EA, et al. Schimke-immuno-osseous dysplasia: new mutation with weak genotype-phenotype correlation in siblings. Am J Med Genet A 2005;135:202-5.
32. Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, et al. COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. J Am Soc Nephrol 2007;18:2773-80.
33. Guéry B, Choukroun G, Noël LH, et

al. The spectrum of systemic involvement in adults presenting with renal lesion and mitochondrial tRNA(Leu) gene mutation. J Am Soc Nephrol 2003;14:2099-108.
34. Heeringa SF, Chernin G, Chaki M, et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest 2011;121:2013-24.
35. Berkovic SF, Dibbens LM, Oshlack A, et al. Array-based gene discovery with three unrelated subjects shows SCARB2/LIMP-2 deficiency causes myoclonus epilepsy and glomerulosclerosis. Am J Hum Genet 2008;82:673-84.
36. Santín S, Bullich G, Tazón-Vega B, et al. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol 2011;6:1139-48.
37. Hinkes BG, Mucha B, Vlangos CN, et al. Nephrotic syndrome in the first year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). Pediatrics 2007;119(4):e907-e919.
38. Löwik MM, Groenen PJ, Levtchenko EN, Monnens LA, van den Heuvel LP. Molecular genetic analysis of podocyte genes in focal segmental glomerulosclerosis — a review. Eur J Pediatr 2009;168:1291-304.
39. Peti-Peterdi J, Sipos A. A high-powered view of the filtration barrier. J Am Soc Nephrol 2010;21:1835-41.
40. Weins A, Schlondorff JS, Nakamura F, et al. Disease-associated mutant alpha-actinin-4 reveals a mechanism for regulating its F-actin-binding affinity. Proc Natl Acad Sci U S A 2007;104:16080-5.
41. Friedrich C, Endlich N, Kriz W, Endlich K. Podocytes are sensitive to fluid shear stress in vitro. Am J Physiol Renal Physiol 2006;291:F856-F865.
42. Kopp JB, Smith MW, Nelson GW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet 2008;40:1175-84.
43. Sekine T, Konno M, Sasaki S, et al. Patients with Epstein-Fechtner syndromes owing to MYH9 R702 mutations develop progressive proteinuric renal disease. Kidney Int 2010;78:207-14.
44. Kao WH, Klag MJ, Meoni LA, et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nat Genet 2008;40:1185-92.
45. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010;329:841-5.
46. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis 2004;43:368-82.
47. Eddy AA, Giachelli CM. Renal expression of genes that promote interstitial inflammation and fibrosis in rats with protein-overload proteinuria. Kidney Int 1995;47:1546-57.
48. Barisoni L, Schnaper HW, Kopp JB. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. Clin J Am Soc Nephrol 2007;2:529-42.
49. Herlitz LC, Markowitz GS, Farris AB, et al. Development of focal segmental glomerulosclerosis after anabolic steroid abuse. J Am Soc Nephrol 2010;21:163-72.
50. Hodgin JB, Rasoulpour M, Markowitz GS, D'Agati VD. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2009;4:71-6.
51. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 2001;59:1498-509.
52. Rennke HG, Klein PS. Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. Am J Kidney Dis 1989;13:443-56.
53. Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int 2006;69:920-6.
54. Stokes MB, Valeri AM, Markowitz GS, D'Agati VD. Cellular focal segmental glomerulosclerosis: clinical and pathologic features. Kidney Int 2006;70:1783-92.
55. Howie AJ, Pankhurst T, Sarioglu S, Turhan N, Adu D. Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion. Kidney Int 2005;67:987-1001.
56. Stokes MB, Markowitz GS, Lin J, Valeri AM, D'Agati VD. Glomerular tip lesion: a distinct entity within the minimal change disease/focal segmental glomerulosclerosis spectrum. Kidney Int 2004;65:1690-702.
57. Li RM, Branton MH, Tanawattanacharoen S, Falk RA, Jennette JC, Kopp JB. Molecular identification of SV40 infection in human subjects and possible association with kidney disease. J Am Soc Nephrol 2002;13:2320-30.
58. Markowitz GS, Appel GB, Fine PL, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001;12:1164-72.
59. Markowitz GS, Nasr SH, Stokes MB, D'Agati VD. Treatment with IFN-α, -β, or -γ is associated with collapsing focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2010;5:607-15. [Erratum, Clin J Am Soc Nephrol 2010;5:1353.]
60. Moudgil A, Nast CC, Bagga A, et al. Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. Kidney Int 2001;59:2126-33.
61. Tomlinson L, Boriskin Y, McPhee I, Holwill S, Rice P. Acute cytomegalovirus infection complicated by collapsing glomerulopathy. Nephrol Dial Transplant 2003;18:187-9.
62. Wyatt CM, Klotman PE, D'Agati VD. HIV-associated nephropathy: clinical presentation, pathology, and epidemiology in the era of antiretroviral therapy. Semin Nephrol 2008;28:513-22.
63. Barisoni L, Kriz W, Mundel P, D'Agati V. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 1999;10:51-61.
64. Hodgin JB, Borczuk AC, Nasr SH, et al. A molecular profile of focal segmental glomerulosclerosis from formalin-fixed, paraffin-embedded tissue. Am J Pathol 2010;177:1674-86.
65. Appel D, Kershaw DB, Smeets B, et al. Recruitment of podocytes from glomerular parietal epithelial cells. J Am Soc Nephrol 2009;20:333-43.
66. Smeets B, Kuppe C, Sicking EM, et al. Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. J Am Soc Nephrol 2011;22:1262-74.
67. Smeets B, Uhlig S, Fuss A, et al. Tracing the origin of glomerular extracapillary lesions from parietal epithelial cells. J Am Soc Nephrol 2009;20:2604-15.
68. Ronconi E, Sagrinati C, Angelotti ML, et al. Regeneration of glomerular podocytes by human renal progenitors. J Am Soc Nephrol 2009;20:322-32.
69. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2010;5:2115-21.
70. Wei C, El Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med 2011;17:952-60.
71. Wei C, Möller CC, Altintas MM, et al. Modification of kidney barrier function by the urokinase receptor. Nat Med 2008;14:55-63.
72. Bruggeman LA, Ross MD, Tanji N, et al. Renal epithelium is a previously unrecognized site of HIV-1 infection. J Am Soc Nephrol 2000;11:2079-87.
73. Chen P, Chen BK, Mosoian A, et al. Virological synapses allow HIV-1 uptake and gene expression in renal tubular epithelial cells. J Am Soc Nephrol 2011;22:496-507.
74. Rosenstiel P, Gharavi A, D'Agati V, Klotman P. Transgenic and infectious animal models of HIV-associated nephropathy. J Am Soc Nephrol 2009;20:2296-304.
75. Zuo Y, Matsusaka T, Zhong J, et al. HIV-1 genes vpr and nef synergistically damage podocytes, leading to glomerulosclerosis. J Am Soc Nephrol 2006;17:2832-43.
76. He JC, Husain M, Sunamoto M, et al. Nef stimulates proliferation of glomerular podocytes through activation of Src-dependent Stat3 and MAPK1,2 pathways. J Clin Invest 2004;114:643-51.
77. Rosenstiel PE, Gruosso T, Letourneau AM, et al. HIV-1 Vpr inhibits cytokinesis in human proximal tubule cells. Kidney Int 2008;74:1049-58.

78. Snyder A, Alsauskas ZC, Leventhal JS, et al. HIV-1 viral protein r induces ERK and caspase-8-dependent apoptosis in renal tubular epithelial cells. AIDS 2010; 24:1107-19.
79. Friedman EA, Tao TK. Disappearance of uremia due to heroin-associated nephropathy. Am J Kidney Dis 1995;25:689-93.
80. Nadasdy T, Allen C, Zand MS. Zonal distribution of glomerular collapse in renal allografts: possible role of vascular changes. Hum Pathol 2002;33:437-41.
81. Stokes MB, Davis CL, Alpers CE. Collapsing glomerulopathy in renal allografts: a morphological pattern with diverse clinicopathologic associations. Am J Kidney Dis 1999;33:658-66.
82. Vollenbröker B, George B, Wolfgart M, Saleem MA, Pavenstädt H, Weide T. mTOR regulates expression of slit diaphragm proteins and cytoskeleton structure in podocytes. Am J Physiol Renal Physiol 2009;296:F418-F426.
83. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-9.
84. Nagata M, Kriz W. Glomerular damage after uninephrectomy in young rats. II. Mechanical stress on podocytes as a pathway to sclerosis. Kidney Int 1992;42: 148-60.
85. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int 2006;69:2131-47.
86. Abbate M, Zoja C, Morigi M, et al. Transforming growth factor-beta1 is upregulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. Am J Pathol 2002;161: 2179-93.
87. Inagi R, Nangaku M, Onogi H, et al. Involvement of endoplasmic reticulum (ER) stress in podocyte injury induced by excessive protein accumulation. Kidney Int 2005;68:2639-50.
88. Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol 2004;15:2169-77.
89. Korbet SM. Primary focal segmental glomerulosclerosis. J Am Soc Nephrol 1998;9:1333-40.
90. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol 2005;16:1061-8.
91. Schönenberger E, Ehrich JH, Haller H, Schiffer M. The podocyte as a direct target of immunosuppressive agents. Nephrol Dial Transplant 2011;26:18-24.
92. Banfi G, Moriggi M, Sabadini E, Fellin G, D'Amico G, Ponticelli C. The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults: a collaborative retrospective study. Clin Nephrol 1991;36:53-9.
93. Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. Kidney Int 1999;56:2220-6.
94. Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med 2008;14:931-8.
95. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int 2011;80:868-78.
96. Fornoni A, Sageshima J, Wei C, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med 2011;3:85ra46.
97. Fervenza FC, Fitzpatrick PM, Mertz J, et al. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies. Nephrol Dial Transplant 2004;19:1288-92.
98. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-6.
99. Vinai M, Waber P, Seikaly MG. Recurrence of focal segmental glomerulosclerosis in renal allograft: an in-depth review. Pediatr Transplant 2010;14:314-25.
100. IJpelaar DH, Farris AB, Goemaere N, et al. Fidelity and evolution of recurrent FSGS in renal allografts. J Am Soc Nephrol 2008;19:2219-24.