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Spectrum of disease in familial focal and segmental glomerulosclerosis

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Spectrum of disease in familial focal and segmental glomerulosclerosis.

Background. Focal segmental glomerulosclerosis (FSGS) is the underlying pathologic entity in 5% of adults and 20% of children with end-stage renal disease (ESRD). FSGS is generally considered to be sporadic in origin.

Methods. Recently, we identified 60 families involving 190 individuals with familial FSGS, providing evidence for a subset of families in which a genetic form is segregating. Each family had at least one member with renal biopsy-confirmed FSGS and at least one other member with either renal biopsy-confirmed FSGS or ESRD.

Results. Twenty-six families had individuals affected in more than one generation [multigeneration (MG)], and the remaining 34 families had only a single generation (SG) affected. There was equal representation of males and females among affected individuals. Ten percent of MG families were African American, and 52% of SG families were African American. The mean age of presentation was significantly higher in the MG families (32.5 ± 14.6 years) compared with the SG families (20.1 ± 12.1 years, $P = 0.0001$). SG cases had higher levels of proteinuria at presentation (7.0 ± 5.6 g/24 hr, compared with 3.8 ± 3.4 g/24 hr, for the MG families, $P = 0.002$). On renal biopsy, tubulointerstitial damage was more severe in patients in the SG families than in the MG families; however, the level of glomerular damage did not differ between these groups. Fifty percent of the patients had progressed to ESRD by the age of 30 years. Variables measured at presentation that were independently associated with poor renal survival were decreased age, increased serum creatinine, and increased urinary protein excretion. Forty-one patients underwent successful renal transplantation, with a 10-year graft survival rate of 62%. One patient developed clinical and biopsy evidence of recurrence of FSGS in the allograft.

Conclusion. These data confirm the existence of a non-Alport's form of hereditary glomerulonephritis, which has a morphological pattern of FSGS.

Focal segmental glomerulosclerosis (FSGS) is a primary glomerular disease of unknown etiology with a population incidence of approximately two per million [1–3]. FSGS is a major cause of end-stage renal failure, particularly in young people [4], accounts for at least 2.5% of all cases of end-stage renal disease (ESRD), and it is refractory to treatment. It has been reported in patients of varied ethnic backgrounds, including American Caucasian, European, Hispanic, and African American [5, 6],

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although it appears to be more frequent among African Americans than among other ethnic groups [6, 7]. The etiology of FSGS is poorly understood: It is unclear whether FSGS is the result of a systemic disease or an intrinsic defect of the glomerulus [8–10].

Although it is well recognized that genetics plays an important role in the development of many forms of renal disease [11–13], FSGS has, until recently, been considered to be primarily a sporadic disorder. Recently, we reported a number of families in which FSGS affected multiple members within the same family (multiplex FSGS families) [14]. The occurrence of FSGS in multiple members of the same family has also been observed by a number of other authors [15–26]. The identification of large pedigrees with familial FSGS (FFSGS) may allow the application of positional cloning technology to identify the underlying molecular pathogenesis of FSGS. We have recently developed an international collaborative group to study this syndrome. Here we present our findings with respect to family history, clinical and associated pathological findings, and their relationship to the long-term prognosis in this large series of multiplex FSGS families.

METHODS

Patients

Families that contained at least two individuals who carried a diagnosis of FSGS, as defined later in this article, were ascertained. Sixty families were identified through a variety of sources and referral patterns. Advertisements were placed in the leading nephrology journals and on the "NEPHROL" e-mail nephrology discussion group. Cases were identified from the published literature. Information regarding additional patients was obtained from the clinics and medical personnel in the Division of Nephrology at Duke University Medical Center. In order to be included in this analysis, each family needed to have at least one member with biopsy-proven FSGS and either a second member with biopsy-confirmed FSGS or other family members with ESRD. Individuals were excluded if they had any secondary form of FSGS such as those associated with HIV infection, reflux nephropathy, sickle cell disease, or intravenous drug use.

A detailed family history was obtained from all participating families. Medical records and renal pathological material were obtained when available to confirm the diagnosis and family history reports. The medical records of all of these subjects were reviewed to identify factors pertaining to the clinical presentation of the disorder, associated syndromes, natural history, pattern of inheritance, and outcome following renal transplantation. Hypertension was considered to be present if at presentation the subject was taking antihypertensive medication or had a resting blood pressure of greater than 140/90 mm Hg. All family history and clinical data were recorded in a database using the Pedigene system. As many first-degree relatives as were available were studied for the presence of occult renal disease by the qualitative analysis of a freshly voided urine specimen for proteinuria. Subjects who were demonstrated to have 2+ or greater proteinuria were invited to have a more complete nephrological evaluation, including renal biopsy where appropriate.

Within these families, subjects were classified as definitely affected, probably affected, status unknown, and probably unaffected.

Definitely affected. Subjects who had a renal biopsy demonstrating FSGS in the absence of evidence for secondary FSGS were classified as definitely affected.

Probably affected. Family members with ESRD requiring renal replacement therapy, who had not undergone renal biopsy, or family members with 3 or 4+ proteinuria on a urine dipstick in the absence of other systemic disease likely to lead to proteinuria (such as diabetes or lupus) were classified as probably affected.

Status unknown. Family members with 1 or 2+ proteinuria or with 500 mg or less of proteinuria on a 24-hour collection were classified as status unknown.

Probably unaffected. Subjects within these families without evidence of proteinuria on dipstick urinalysis were classified as probably unaffected.

This report focuses on definitely affected or probably affected individuals.

Families were classified according to whether there was evidence that individuals from one or more generations were affected. Families with multiple generations (MG) affected had to have clear-cut evidence of vertical transmission of the trait, with individuals from two or more generations affected, based on the definitions given previously in this article. Families with single generation (SG) involvement had no more than one generation demonstrating any manifestation of disease. This classification (SG) was applied only where the parents of the individuals were available for examination and/or urinalysis and were demonstrated to be free of renal disease or the parent died at an advanced age and was known to have died of a nonrenal cause. Individuals whose parents were not available for examination or in whom the cause of death was not available were excluded.

Pathological data

The histological diagnosis of FSGS was based on the criteria of Churg, Habib, and White and required the presence of areas of glomerular sclerosis or tuft collapse that were both focal (involving only a subpopulation of glomeruli) and segmental [7]. Segmental hyalinosis was present in several cases, but was not considered a requirement for the diagnosis. Morphological features considered

ancillary factors supporting the diagnosis of FSGS included the detection of focal, segmental glomerular staining for immunoglobulin M and/or C3 by immunofluorescence microscopy and the presence of epithelial cell foot process effacement by electron microscopy.

Glomerular sclerotic lesions were further classified according to the presence or absence of "collapsing" features [27, 28]. Glomerular lesions were considered to be of the collapsing variety if they had wrinkling and "collapse" of the glomerular capillary walls with prominent hypertrophy and hyperplasia of the overlying visceral epithelial cells, often accompanied by intracytoplasmic protein resorption droplets.

In each case, possible underlying causes of segmental glomerulonephritis (for example, immune complex deposition, antiglomerular basement membrane antibodies, vasculitis) and other potential causes of segmental glomerular pathology (such as Alport's syndrome) were ruled out to the fullest extent possible on clinical and histological grounds.

Renal biopsies were performed and processed in a standard fashion, and each was reviewed by an experienced renal pathologist (D.H.) without regard to clinical information. Histological features were graded by calculating the percentage of glomeruli exhibiting a particular histological finding (global or segmental collapse or global or segmental glomerulosclerosis) and by semiquantitative analysis (using a scale of 0 to 3+) for the following features: visceral epithelial hypertrophy, mesangial hypercellularity, synechiae, hyalinosis, tubular microcysts, tubular epithelial degenerative and regenerative changes, tubular atrophy, interstitial edema, interstitial inflammation, interstitial fibrosis, and arteriolar sclerosis. These were recorded 0 for absent, 1 for $<20\%$, 2 for 20 to 50% and 3 for $>50\%$ of the biopsy surface affected.

Statistical analysis

Survival times were calculated as the time to initiation of dialysis, renal transplantation, or death, whichever came first. In subjects not reaching ESRD, the date of last follow-up was taken as the date of censoring. Kaplan–Meier product-limit survival times were calculated using SAS PROC LIFETEST (Cary, NC, USA). Risk ratios were calculated using the Cox proportional hazards model, which was also used to test for the influence of multiple risk factors on survival. The log rank test was used to compare survival curves. Differences between groups were assessed using the chi-square test and Student's *t*-test as appropriate. A P value of < 0.05 was considered significant.

RESULTS

Clinical presentation

Clinical and pathological data were available on 60 families involving 190 affected individuals. In addition, 260 family members were examined and had urinalysis. These families were living in the United States ($N = 33$), the United Kingdom ($N = 5$), Belgium ($N = 4$), New Zealand ($N = 4$), France ($N = 3$), Germany ($N = 1$), Turkey ($N = 1$), Peru ($N = 6$), and Canada ($N = 3$).

One hundred and four subjects were considered to be definitely affected, and 86 were considered probably affected (*vide supra*). A total of eight family members previously considered unaffected were identified as probably affected as a result of screening for proteinuria. Twenty-six families had individuals affected from MG. Figure 1 displays the pedigree of our largest family, involving 37 affected individuals. In the remaining 34 families, only individuals from an SG were affected. The transmission of the trait from both males and females to both male and female children was observed, thus excluding either a sex linkage or a mitochondrial DNA disorder.

Six families contained one set of twins each. Two of these sets were dizygotic twins, and in each of these families one member of the twin set was affected. Both members of the twin set were affected in three of the four sets of monozygotic twins. In the one discordant identical twin set, the affected was 11 years of age and had 5 g of protein excretion with normal renal function. Her father developed ESRD secondary to biopsy-proven FSGS. The apparently unaffected child had been followed for two years and had no protein excretion on dipstick.

In only one family, the development of FFSGS was associated with a dysmorphic syndrome. This was in two children ages 22 months and 9 months who developed FSGS with nephrotic syndrome. They were the children from the marriage of first cousins, and had congenital microcephaly, hypotonia, poor neurological development, and low-set ears in addition to nephrotic syndrome.

Clinical features at presentation were compared between SG and MG cases. SG subjects presented at a younger age (20.1 ± 12.1 vs. 32.5 ± 14.6 years, $P = 0.0001$; Fig. 2), had heavier proteinuria (7.0 ± 5.6 vs. 3.8 ± 3.4 g/24 hr, $P = 0.002$), and were more likely to be hypertensive (82 vs. 60%, $P = 0.01$) than individuals within MG families (Table 1). There was no difference in serum creatinine between SG and MG individuals.

Pathologic features

A total of 104 patients underwent renal biopsy, of which 68 had electron microscopy and immunofluorescence examinations in addition to light microscopy. Renal pathology slides were available for review by us from 88 biopsies performed on 75 patients, and the renal pathology reports were reviewed on the remainder. The number of renal biopsies per family ranged from 1 to 15. Thirteen patients had two or more renal biopsies.

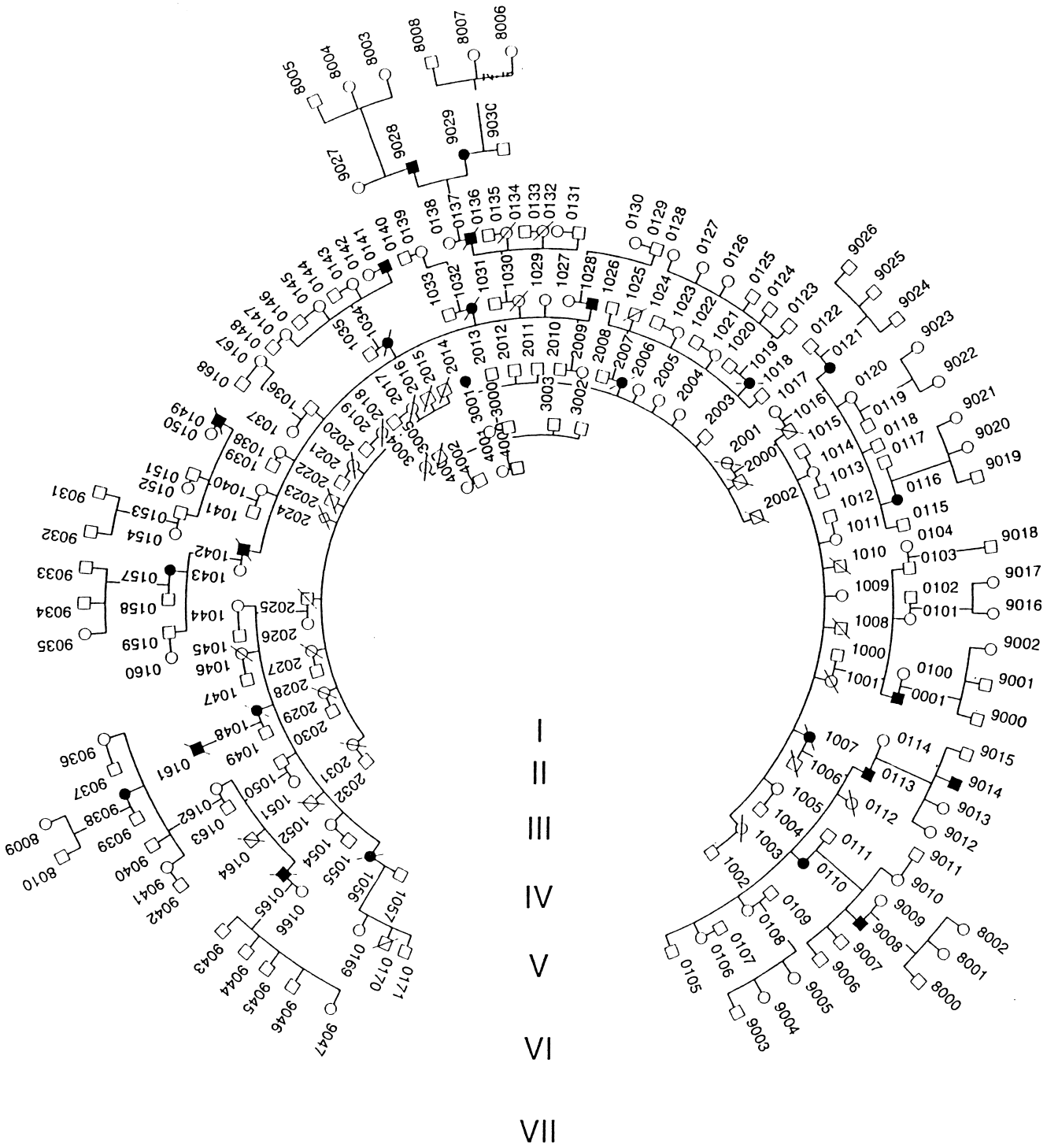

Fig. 1. Pedigree of largest multigeneration family in the series. Symbols are: (■) affected male; (●) affected female; (□) unaffected male; (○) unaffected female; (⍁) deceased.

Histological examination of biopsy tissue revealed a wide variety of glomerular and extraglomerular abnormalities. Segmental sclerosis was identified in biopsies from 52% of patients with FFSGS, and segmental or global collapse was seen in biopsies from 11%; both segmental sclerotic and collapsing lesions were seen in biopsies from 15% of the patients. In all, 78% of the patients had evidence of either segmental sclerosis or collapse. The mean percentages of segmentally sclerotic glomeruli and glomeruli with segmental and/or global

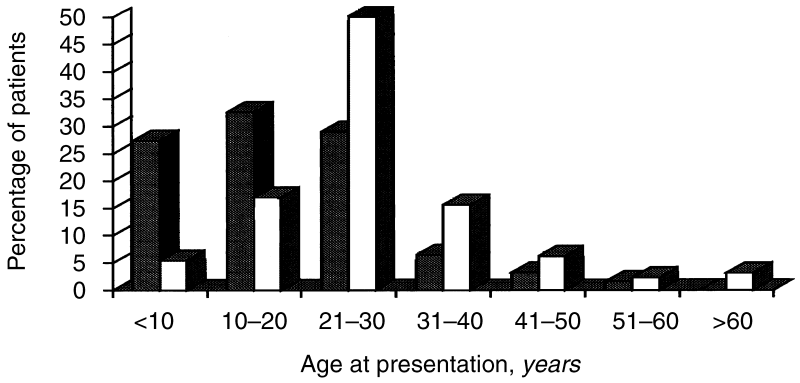

Fig. 2. Age at presentation of patients with familial focal segmental glomerulosclerosis (FFSGS). Symbols are: (■) single generation inheritance; (□) multigeneration inheritance.

Table 1. Clinical variables measured at presentation

	Multigeneration ($N = 125$)	Single generation ($N = 65$)	P
Race *% black*	10.1	52	0.001
Sex *% male*	44	43	0.5
Age at presentation *years*	32.5 ± 14.6	20.1 ± 12.1	0.0001
Serum Cr at presentation *mg/dl*	4.1 ± 5.7	3.0 ± 3.7	0.2
Proteinuria at presentation *g/24 hr*	3.8 ± 3.4	7.0 ± 5.6	0.002
Hypertension	60%	82%	0.01

Table 2. Histology of familial FSGS: Glomerular

	Multigeneration	Single generation	P
Of all glomeruli			
Global collapse %	2.5 ± 5.7	12 ± 22.1	0.07
Segmental collapse %	2.8 ± 6.3	5.2 ± 7.6	0.2
Global sclerosis %	19.7 ± 21.9	27.2 ± 33.4	0.4
Segmental sclerosis %	10.9 ± 10.5	9 ± 12.2	0.3
2+ or greater on semiquantitative analysis			
Visceral epithelial hypertrophy	9.3	5.8	0.1
Mesangial hypercellularity	0	0	NS

collapse did not differ significantly between SG and MG groups (Table 2). Globally sclerotic glomeruli were a common feature in both groups, constituting 19.7 ± 21.9% of the glomeruli in the MG biopsies and 27.2 ± 33.4% in the SG group ($P = 0.4$).

In biopsies from 9% of patients, global glomerular sclerosis was the only lesion identified. In half of these, all of the glomeruli were globally sclerotic. In an additional 5% of biopsies, no significant glomerular lesions were identified, possibly as a result of sampling early in the course of the disease. The remaining 8% of biopsies contained insufficient tissue for a definitive diagnosis.

A variety of tubulointerstitial changes was also noted in the biopsies (Table 3). Of particular note were tubular degeneration/regeneration, tubular atrophy, interstitial inflammation, and interstitial fibrosis, all of which were significantly more prevalent in biopsies from the SG group than those from the MG group. Prominent tubular microcyst formation and interstitial edema were noted in only a small fraction of the biopsies and did not differ significantly between the two groups. Extensive arteriolar sclerosis was seen in occasional biopsies, with approximately equal frequency in the two groups.

Renal survival

Ninety-three individuals developed ESRD. The median age for the development of ESRD was 30 years. Variables measured at the presentation that were significantly associated with worse renal survival (Table 4) included decreased age of presentation, single-generation involvement (Fig. 3), increased serum creatinine, increased urinary protein excretion (Fig. 4), and black race (Fig. 5). None of the pathological variables were significantly associated with prolonged renal survival. Using backward elimination from the Cox proportional hazards model (Table 5), the following variables were

Table 3. Histology of familial FSGS: Tubulointerstitial

	Multigeneration	Single generation	*P*
2+ or greater on semiquantitative analysis			
Tubular microcysts	0	2%	0.6
Tubular degeneration/regeneration	1%	9%	0.03
Tubular atrophy	3.6%	18%	0.002
Interstitial edema	0	5.3	0.9
Interstitial inflammation	3.1%	16.3%	0.004
Interstitial fibrosis	4.6%	17.8%	0.0039
Arteriolar sclerosis	6.1%	8.9%	0.3

Table 4. Clinical variables associated with progression to end-stage renal disease (ESRD)

	Risk ratio (95% CI)	*P*
Age[a]	0.66 (0.7–0.95)	0.0001
Creatinine	1.04 (1.02–1.07)	0.04
SG vs. MG	0.3 (0.2–0.4)	0.0001
Proteinuria	1.13 (1.1–1.16)	0.0001
Sex (male vs. female)	(0.9–1.4)	0.4
Race (white vs. other)	2.1 (1.7–2.7)	0.0005
Hypertension (present vs. absent)	(0.8–1.9)	0.4

Abbreviations are: SG, single generation; MG, multigeneration.
[a]Risk ratio expressed for 10 unit change.

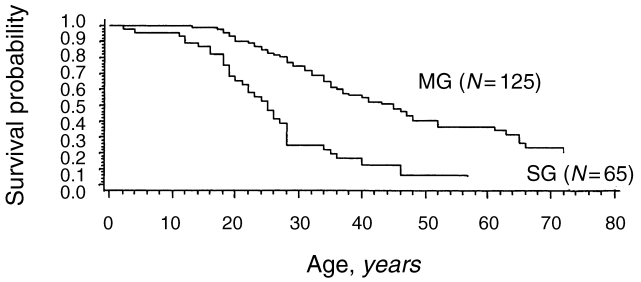

Fig. 3. Survival based on the pattern of inheritance. Renal survival was worse in patients with single generation involvement ($N = 65$) compared with families with multigeneration involvement ($N = 125$).

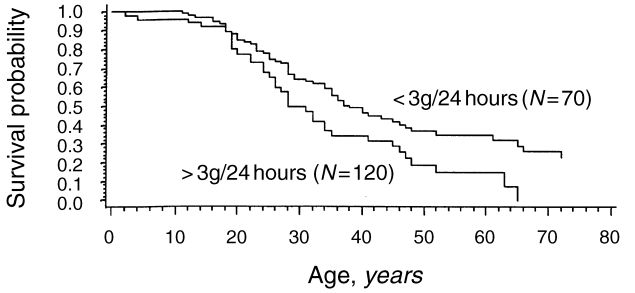

Fig. 4. Survival based on proteinuria at presentation. Renal survival was significantly worse in subjects who presented with greater than 3 g of protein excretion per 24 hours ($N = 120$) when compared with those with lesser levels of protein excretion ($N = 70$).

independently associated with worse renal survival: younger age at presentation, increased serum creatinine, and increased urinary protein excretion.

Outcome of renal transplantation

A total of 41 patients underwent 48 renal transplant procedures. The 10-year survival of these grafts is outlined in Figure 6. At 10 years, 62% of grafts continued to function. Only one patient demonstrated a recurrence of FSGS in the allograft. Two subjects, who initially appeared unaffected, donated a kidney to an affected sibling and subsequently developed proteinuria and on renal biopsy were demonstrated to have FSGS [29]. Both of these individuals subsequently developed ESRD. The recipient of one of these kidneys developed chronic allograft rejection secondary to noncompliance with medications, and the other kidney functioned for greater than 10 years.

DISCUSSION

In this report, we present a large series of patients with multiple family members affected with FFSGS. The vertical mode of transmission in many of the families and the development of FSGS in both sets of twins establish this as a clearly genetic disorder, rather than the result of some environmental exposure. We have observed the frequent development of ESRD in affected individuals.

In this review, we used the terms SG involvement and MG involvement, as they make no assumptions about pattern of inheritance. It is likely that MG families are families with autosomal dominant inheritance and that SG families have autosomal recessive inheritance, although there are also other possibilities, including autosomal dominant with incomplete penetrance. We have adopted a very conservative technique of labeling families SG in that only families in which both parents were examined and found to be free of renal disease were labeled SG. Families with SG involvement appear to have a more aggressive form of disease, as they presented at a younger age and with heavier proteinuria than MG families. It is possible that this apparently more aggressive deterioration in renal function represents ascertainment bias, in that individuals within families already

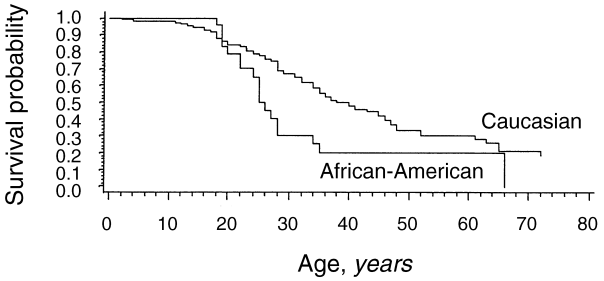

Fig. 5. Renal survival was significantly worse in African American subjects when compared with Caucasians.

Table 5. Variables independently associated with progression to ESRD

	Risk ratio (95% CI)	*P*
Age[a]	0.46 (0.37–0.58)	0.007
Creatinine	1.2 (1.1–1.7)	0.01
Proteinuria	1.13 (1.1–1.5)	0.0002

[a]Expressed for 10 unit change.

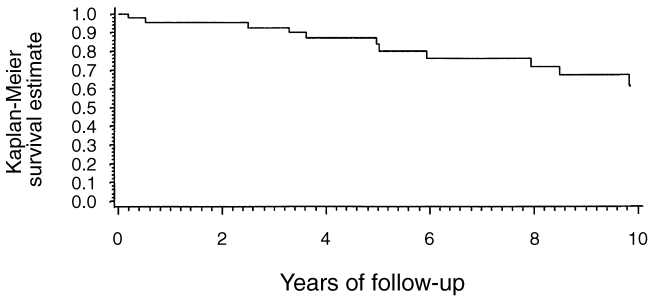

Fig. 6. Survival of renal allograft in patients with FFSGS.

known to be affected by renal disease are more likely to be detected early. However, when the survival analysis was confined to the probands in each family, thus eliminating the effect of ascertainment bias, the same trends in terms of worse serum creatinine, higher proteinuria, and earlier age of ESRD were apparent in the SG families when compared with MG families.

The first reports of the occurrence of an autosomal dominant FSGS came from Walker, Lynn, and Ross in New Zealand in 1982 [24]. Walker et al reported seven patients in three families with familial FSGS that was inherited as an autosomal dominant trait. Prior to this report, there were a number of reports of non-Alport hereditary nephropathy in which the renal pathology was incompletely described because of the absence of electron microscopic and immunofluorescence examinations [30, 31]. There are now many reports of FFSGS in diverse parts of the globe [15–26]. Also, there are a number of reports of multiple members within the same family being affected by FSGS in the kidney in association with other hereditary defects [15, 32–36]. Because the disease is uncommon, the aggregation in a family of more than one affected member is compelling evidence for a major gene.

The weight of existing evidence in experimental models of FSGS and human sporadic FSGS supports a role for a circulating factor that results in increased glomerular permeability [8, 9, 37, 38]. The early recurrence of FSGS after renal transplantation has been observed for more than 20 years and provides a tantalizing clue that a circulating substance may be responsible for glomerular injury in some patients with this entity. Further evidence for the presence of a circulating factor associated with FSGS is supported by the effectiveness of plasmapheresis to treat recurrence of FSGS following renal transplantation [9, 38]. However, unlike sporadic forms of FSGS, we have observed the recurrence of FSGS in only one of 41 renal transplant recipients with FFSGS, suggesting that intrinsic abnormalities of the kidney are responsible for FFSGS, rather than a circulating factor.

Not every subject in this study underwent a renal biopsy to confirm the histological pattern of their glomerular injury; however, most families did have at least two individuals with a renal biopsy. In addition, not every biopsy was subjected to electron microscopic and immunofluorescence examination; however, at least one biopsy from each family did undergo electron microscopy, excluding any changes of basement membrane lamellation or splitting that would be compatible with Alport's-type nephropathy. A potential criticism of these studies is the lack of histological confirmation in every single affected individual, as many of the cases were classified as affected on the basis of the presence of ESRD or proteinuria. However, in an analysis of our largest pedigree, in which we have determined linkage to chromosome 11, each affected individual carried the disease allele, and no unaffected individuals carried it [39].

Developments in molecular biology have enabled investigators to study genetic disorders by a "reverse genetics approach" or "positional cloning" in which the genetic disorder is initially linked to a chromosome marker. Subsequently, mapping of the gene may be followed by identification of the gene itself, the mutations responsible for the disorder, and finally, the gene product. This approach is particularly suitable for a disorder such as this in which there is very little understanding of the underlying pathophysiologic mechanisms responsible for the disorder. Recently, Mathis et al employed this approach in studying a large kindred from Oklahoma (USA) [40]. These investigators found strong evidence for linkage to chromosome 19q. The clinical features of these patients, however, were very different than the patients in our series, in that only a small minority of the patients in

Mathis et al's study progressed to ESRD. The patients in the Mathis study were also poorly characterized in terms of renal pathology. We have also recently demonstrated linkage to chromosome 11q for our large New Zealand family [39], confirming considerable genetic heterogeneity in the molecular pathogenesis of FFSGS.

The cases of FFSGS that we have described here appear clinically and pathologically similar to the much more common disorder of sporadic FSGS. The only characteristic that appeared to be different from the sporadic disorder was the absence of recurrence of FSGS after renal transplantation, which normally occurs in 35% of patients with sporadic FSGS. It is possible that that both sporadic and familial FSGS have the same underlying molecular pathogenesis.

In summary, we have observed a large series of patients with FFSGS. Further study of these families may contribute to our understanding of the molecular pathogenesis of sporadic FSGS.

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POSTSCRIPT

We are continuing to recruit families with FFSGS, and we are anxious to hear from any physicians caring for patients with this disorder. Please contact Dr. Peter J. Conlon, M.D., Beaumont Hospital, Dublin 9, Ireland. Telephone, 353-1-8377755, and Fax, 353-1-8092899. E-mail: PJCONLON@IOL.IE

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