

# A Locus for Adolescent and Adult Onset Familial Focal Segmental Glomerulosclerosis on Chromosome 1q25–31

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**Abstract.** Focal segmental glomerulosclerosis is a nonspecific renal lesion observed both as a primary (idiopathic) entity and in a secondary form, typically in association with reduced functional renal mass. Familial forms have been observed and two loci for autosomal dominant FSGS have been mapped. This study shows that an adolescent/adult form of recessive FSGS maps to a locus on chromosome 1q25–31, which overlaps with a region previously identified as harboring a locus for an early childhood onset recessive form of nephrotic syndrome (*SRNI*). Evaluation of a large family demonstrated linkage with a maximum two-point lod score of 3.98 at *DIS254* and *DIS222*. Lod score calculations support the conclusion of

linkage in four of five additional families. Haplotype analysis suggests that this FSGS gene is located in a 19-cM region flanked by *DIS416* and *DIS413*, of which 6 cM overlaps with *SRNI*, suggesting that these distinct clinical subsets of kidney disease may be allelic. These regions may also overlap with the syntenic region of the glomerulosclerosis susceptibility locus in the *BUF/Mna* rat. Because the presentation of FSGS may be subtle, inherited FSGS may be much more common than generally realized and grossly underestimated because of the absence of clear familial patterns. This result increases the suspicion that polymorphisms at this locus may contribute to sporadic FSGS.

Focal segmental glomerulosclerosis (FSGS) is a common glomerular histopathologic finding defined by the presence of segmental glomerular sclerosis involving some, but not all, glomeruli. FSGS occurs not only as an isolated idiopathic disease, but also in association with (and presumably secondary to) a large number of conditions associated with reduced functional renal mass, including vesicoureteral reflux, hypertension, diabetes, sickle cell disease, and HIV infection. Clinically, FSGS is characterized by proteinuria, progressive renal insufficiency, and the nephrotic syndrome, and is the underlying lesion in 7 to 15% of cases of nephrotic syndrome in children and 15 to 20% in adults who undergo renal biopsy (1–3). It is a particularly common form of renal histopathology in individuals of African descent. FSGS often progresses to end-stage renal disease (ESRD) and accounts for 20% of children and 5% of adults with this condition. Although FSGS

generally occurs as a sporadic disease, familial occurrence of FSGS is being increasingly recognized. Autosomal dominant and recessive modes of inheritance have been described (4–6). Because FSGS is seen not only in individuals with isolated glomerular disease but also in association with multiple disease entities predisposing to chronic renal injury, identification of genes involved in the development of FSGS could have importance beyond understanding the rare familial forms.

About 80% of children with nephrotic syndrome respond to steroid therapy and usually display a histologic picture known as “minimal change,” referring to the absence of light microscopic findings and typically fusion of epithelial cell foot processes. The other 20% of the patients frequently show histologic features of FSGS and/or diffuse mesangial proliferation and are generally resistant to steroid treatment. Fuchshuber *et al.* (7) investigated a subgroup of childhood nephrotic syndrome characterized by early onset (age less than 6 yr), autosomal recessive inheritance, and steroid resistance, and mapped the disease gene to a locus on chromosome 1q25–31, named *SRNI*. In contrast to congenital or early onset steroid resistant forms of nephrotic syndrome, the disease in patients with autosomal dominant FSGS (OMIM 603278) is usually less severe and progresses to end-stage renal disease later in life (8,9). We recently performed linkage analysis in a large FSGS family with autosomal dominant inheritance and mapped the locus to chromosome 19q13 (8), a 7-cM region

Received September 30, 1999. Accepted February 16, 2000.

Dr. Clifford Kashtan served as Guest Editor and supervised the review and final disposition of this manuscript.

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1046-6673/1109-1674

Journal of the American Society of Nephrology

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flanked by markers *D19S223* and *D19S213*. Interestingly, this FSGS region includes *NPHS1*, which is mutated in patients with congenital nephrotic syndrome of the Finnish type (10). A second dominant locus has been identified recently on chromosome 11q (6).

To further investigate the genetic basis of adolescent and adult onset FSGS, we performed linkage analysis in six FSGS families with inheritance consistent with an autosomal recessive pattern. Here we show evidence of linkage to chromosome 1q25–31 in five of six such families. The locus identified overlaps with *SRNI*, indicating that a gene (or genes) on chromosome 1q plays an important role in development of glomerulosclerosis of variable severity and age of onset. The fact that this locus causes distinct glomerulopathies and likely underlies a considerable fraction of recessive FSGS cases suggests that this locus may be of general importance in the pathobiology of glomerular disease.

## Materials and Methods

### Patients

Of multiple families under study, six families with FSGS were included in this analysis on the basis of an inheritance pattern consistent with adolescent or adult-onset recessive transmission. Evaluations of family members included, whenever possible, medical and family history, and urine protein quantification. The diagnosis of FSGS in at least one member of each family was demonstrated histologically by renal biopsy. Pedigrees are shown in Figure 1. There was no evidence of other disease associated with secondary FSGS in affected family members. Blood samples for DNA extraction were collected from a total of 67 individuals. Studies were performed after obtaining informed consent in accordance with a protocol approved by the Human Research Committee of the Brigham and Women's Hospital.

### Genotype Analysis

Genomic DNA was extracted from peripheral blood cells or transformed lymphocytes by use of the QIAamp DNA blood kit (Qiagen, Valencia, CA). Individuals were genotyped using microsatellite markers spanning a 22-cM interval on chromosome 1q regions (*DIS452*, *DIS242*, *DIS416*, *DIS466*, *DIS240*, *DIS254*, *DIS202*, *DIS222*, *DIS238*, and *DIS413*). Briefly, genotypes were determined by PCR amplification using one [<sup>32</sup>P]- $\gamma$ -ATP end-labeled primer. PCR products were separated by electrophoresis on a 6% polyacrylamide gel and visualized by autoradiography. The marker order and the approximate distances follow the maps from the public databases of the Whitehead Institutes for Biomedical Research, the Cooperative Human Linkage Center, and the Genome Database.

### Linkage Analysis

For the purposes of this analysis, an individual was considered "affected" if he/she had: (1) renal biopsy evidence of FSGS; (2) end-stage renal disease without another cause; or (3) clinical albuminuria (microalbumin >300 mg/g creatinine). An individual was considered "unaffected" if he/she had no microalbuminuria (<30 mg/g creatinine). An individual was categorized as "unknown" if he/she had microalbuminuria between 30 and 300 mg/g creatinine or if he/she had more severe proteinuria but another reason for proteinuria. Two-point linkage analysis was performed using the MLINK program version 5.1; multipoint analysis was performed using LINK-

MAP (11). Lod scores were calculated assuming a disease penetrance of 1.0 under a recessive model of inheritance. Disease gene frequency was set at 0.0001, and two-point lod score calculations were performed. Allele frequencies were set at 1/N, but for the fully informative markers indicated in bold type (*i.e.*, both parents heterozygous), lod score calculations were independent of allele frequency assumptions. Haplotype analysis was performed to identify critical recombination events. When ambiguous, phase was assigned by minimizing recombination events within a given pedigree. Genetic heterogeneity was assessed using the HOMOG program (11).

## Results

### Family FS-W

We investigated a three-generation Brazilian family (FS-W) with familial FSGS with phenotypic similarity to a previously described family with dominant inheritance and linkage to chromosome 19q (8). Seven of 10 members of the second generation, all offspring of the same parents, had FSGS, end-stage renal failure, or marked proteinuria. The average age of presentation of disease among these individuals was 26 yr. Light microscopy of renal biopsy obtained from affected individual 3 showed typical pathologic features of FSGS. Two of the seven affected family members have progressed to ESRD.

To define the mode of disease transmission, we evaluated the clinical history and phenotypes of the members in this pedigree. The father of the seven affected sibs (FS-W, individual 1, in Figure 1) had moderate proteinuria (microalbumin 670 mg/g creatinine) but also longstanding untreated hypertension, a cause of secondary glomerular disease. Given the milder phenotype in the father despite significantly more advanced age than his children (70 yr), the presence of long-standing untreated hypertension (BP 180/120 at time of ascertainment), and absence of renal insufficiency, we felt that hypertension was the most likely cause of his proteinuria (although for the purposes of linkage analysis, he was classified as phenotype "unknown"). Despite the presence of diabetes in the first-generation mother (FS-W, individual 2), a condition predisposing to the development of nephropathy, she has only minimal evidence of kidney disease (microalbumin 54 mg/g creatinine) and no renal insufficiency. Like individual 1, she was classified as phenotype "unknown" for the purpose of linkage analysis. No members of the father or mother's extended families (FS-W, individuals 1 and 2), with the exception of their offspring, have any history of kidney disease. Based on the presence of definite disease in a single generation of this large family, we concluded that inheritance of FSGS was following a recessive pattern. Furthermore, none of the 12 offspring of the seven affected individuals has shown overt proteinuria, although the young ages of these children (average age 11.6 yr), well below the average age at which disease was diagnosed in affected members, makes any conclusions based on this fact unreliable.

Because loci for recessive nephrotic syndromes had been reported on chromosome 19q13 (which also harbors a locus for dominant disease) and chromosome 1q25–31 (7), we evaluated linkage at these chromosomal regions. After first excluding the chromosome 19 locus as harboring the disease gene, we geno-

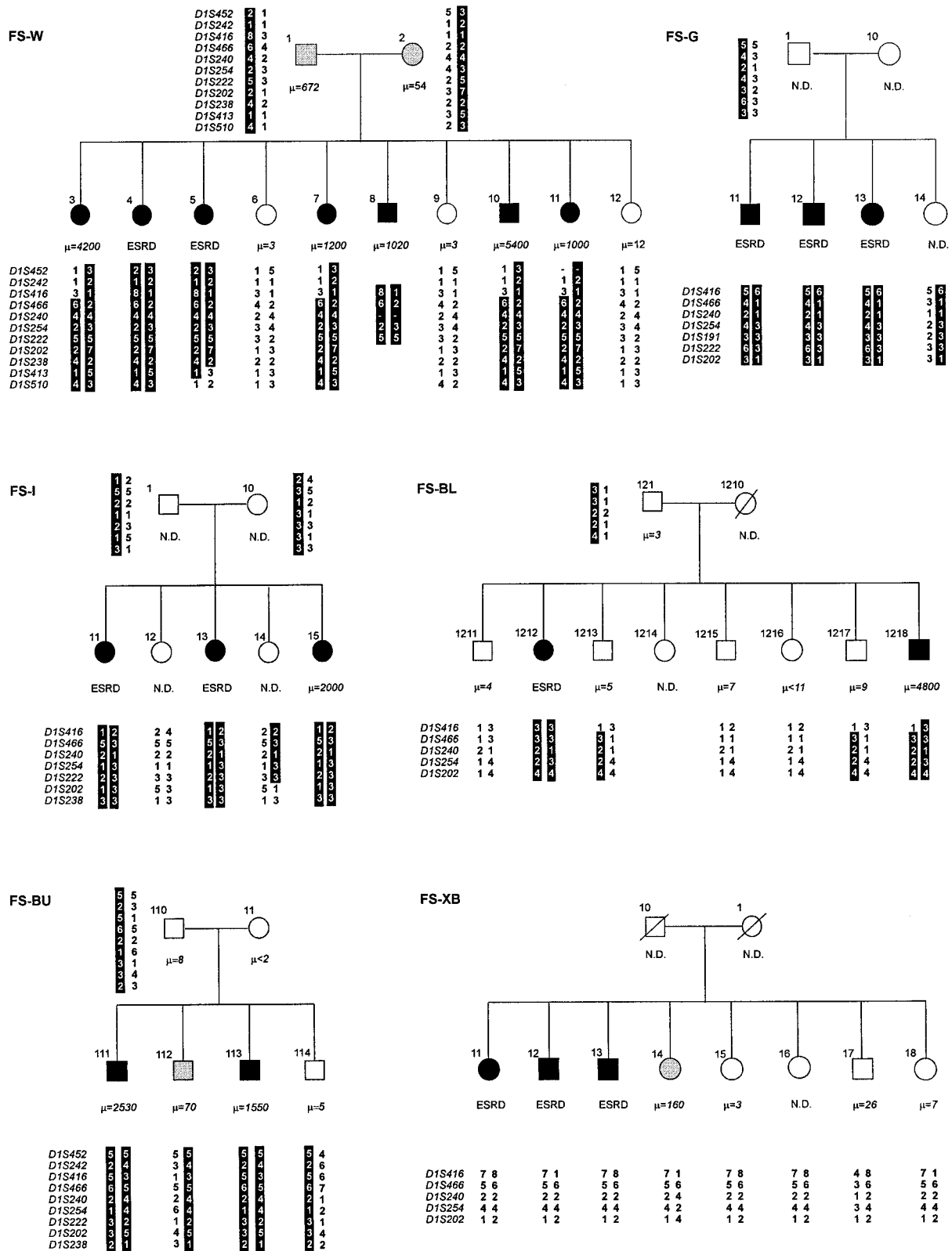


Figure 1. Pedigrees and haplotype analysis. Pedigrees of families with focal segmental glomerulosclerosis (FSGS). Filled symbols, affected individuals; open symbols, unaffected individuals; gray symbols, individuals of unknown status. Allele numbers are indicated below pedigree symbols. The darkened haplotype represents the disease-associated allele in each family (under the assumption of linkage to the 1q region). Urine protein excretion is indicated below the pedigree symbol, given either as urine microalbumin ( $\mu$ , mg per gram creatinine). ESRD, end-stage renal disease.

typed individuals at markers from the chromosome 1q25–31 region harboring the *SRNI* locus. Fully informative markers *DIS254* and *DIS222* yielded a maximum two-point lod score of 3.98 at a recombination distance of 0.0 cM. Haplotype analysis with these and other markers in this region is shown in Figure 1. To define the minimal interval containing the FSGS gene, we constructed haplotypes for marker alleles in this region. The observed recombination events suggest that this FSGS gene is located telomeric to *DIS416* and centromeric of *DIS413*. Assuming that the *SRNI* and *FSGS* genes are the same, the responsible gene is located in a 6-cM region flanked by *DIS416* and *DIS466* (Figure 2).

**Additional Families**

To further investigate the contribution of this locus to familial FSGS, we subsequently studied 39 subjects (14 affected, 23 unaffected, 2 unknown) from an additional five small families (Table 1). Autosomal recessive transmission was supported by: (1) absence of proteinuria in the parents of affected subjects; (2) no disease transmission through multiple generations; and (3) the occurrence of disease in more than two siblings in each family (Figure 1). Five families (FS-BL, FS-XB, FS-G, FS-BU) are of North American and one (FS-I) is of Australian origin. When all six families are considered, the mean age of clinical presentation was 21 (range, 9 to 31), and 70% of affected subjects progressed to ESRD. The mean age at which ESRD developed was 26 (range, 14 to 36). No recurrence of FSGS was reported in patients undergoing renal

transplantation. Two individuals were considered “unknown status” because of the presence of mild proteinuria.

We performed linkage analysis of the 1q25–31 locus in these five additional families. The results of lod score calculations are shown in Table 2. In four families, lod score calculations at informative markers supported linkage of the disease phenotype to this chromosome 1q region. Two-point lod scores were 1.45 (family FS-I), 1.32 (family FS-G), 1.22 (family FS-BL), and 0.73 (family FS-BU), which are the maximum attainable for these families under the model used. In family XB, two-point lod score calculations using the same parameters did not provide any evidence of linkage. Multipoint analysis yielded lod scores of less than -1.84 throughout the FSGS critical region. Further analysis of genetic homogeneity *versus* heterogeneity using the HOMOG program gave evidence of heterogeneity for family FS-XB ( $\chi^2 = 3.33, P = 0.034$ ) and supported the conclusion of linkage to the 1q25–31 locus in each of families FS-W, FS-BU, FS-I, FS-G, and FS-BL.

**Discussion**

In this study, we present strong evidence that a locus for an adult-onset form of recessive familial FSGS maps to chromosome 1q25–31. The data convincingly demonstrate linkage in one large family, and suggest linkage in several smaller families. Because of the small size of four of these families, high lod scores are not attainable. However, because we tested linkage only to one locus, lod scores 1.45 and 1.32 (families FS-I and FS-G) can be considered demonstrative of linkage, while a lod score of 1.22 is highly suggestive (family FS-BL). In one family, lod score calculations using the same parameters were not suggestive of linkage, and values obtained by multipoint analysis approach the generally accepted criteria of lod score less than -2.0 throughout the region under consideration. As noted, application of the HOMOG program supported the hypothesis of linkage to a single locus on chromosome 1q25–31 in all families except FS-XB. In the FS-XB family, however, we found no recombinations between markers from *DIS466* to *DIS202* and disease status in affected individuals, raising the possibility that the same locus is involved, but the disease is not fully penetrant. Alternatively, under the assumption of full penetrance, our data suggest that there may be another FSGS recessive gene on an as yet unidentified chromosome locus, similar to the observation that linkage to 1q25–31 was excluded in one of eight recessive *SRN* families (7).

The phenotype described here has several important differences from the *SRN* phenotype described by Fuchshuber *et al.* They describe a phenotype characterized by nephrotic syndrome with onset at age less than 6 yr and rapidly progressive renal insufficiency (by age 10). In all of the families described in the present report, disease presentation occurs at a significantly later age (mean 21), and frank nephrotic syndrome is not always present. While some degree of proteinuria may have been detected in these individuals at an earlier age had it been measured, the earlier absence of clinically obvious disease is nevertheless a striking difference. Despite the variable rate of progression, most affected FSGS individuals developed ESRD

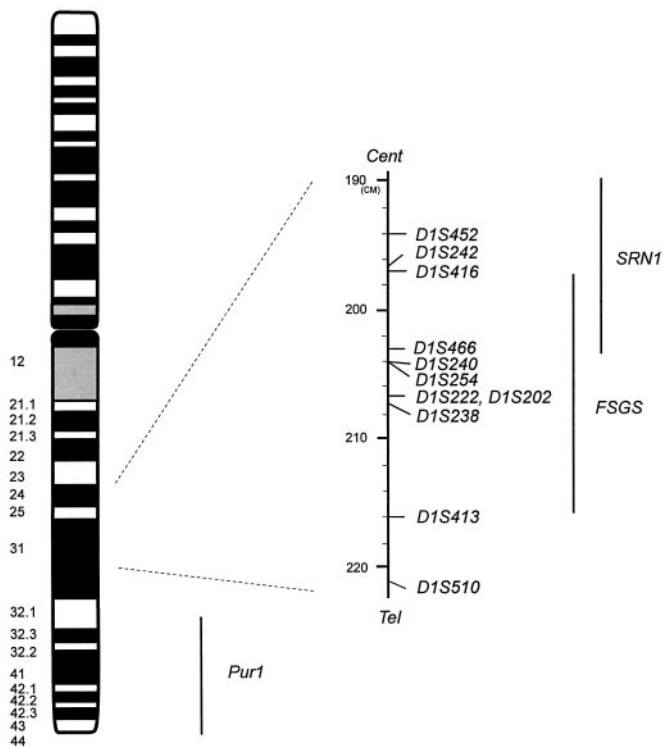


Figure 2. Pictogram of chromosome 1, showing the *SRN* region, the FSGS region defined in this study, and the region of chromosome 1 syntentic to the major glomerulopathy locus in the *BUF* rat.

Table 1. Characteristics of affected family members<sup>a</sup>

Family/Patient	Age of Presentation (yr)	ESRD (Age, yr)	Proteinuria (mg albumin/g creatinine)	Histology (if biopsied)
FS-W				
3	36	No	4200	FSGS
4	33	Yes, (33), Txp (34)	NA	
5	22	Yes, (31), Txp (33)	NA	
7	28	No	1200	
8	25	No	1020	
10	20	No	5400	FSGS
11	18	No	1000	
FS-BU				
111	23	No	2530	FSGS
113	9	No	1550	
FS-I				
11	15	Yes (29); Txp (31)	NA	FSGS
13	19	Yes (32); Txp (35)	NA	FSGS
15	28	No	2000	FGGS
FS-BL				
1212	21	Yes (29); Txp (31)	NA	FSGS
1218	25	No	4800	FSGS
FS-G				
11	19	Yes (19)	NA	FSGS
12	14	Yes (14)	NA	FSGS
13	14	Yes (15)	NA	FSGS
FS-XB				
11	20	Yes (25); Txp (32)	NA	FSGS
12	20	Yes (21); Txp (29)	NA	FSGS
13	31	Yes (36); Txp (38)	NA	

<sup>a</sup> Age of presentation, presence of ESRD (and age at which ESRD developed), proteinuria, and renal histology are indicated. Txp indicates that individual has undergone kidney transplantation. ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; NA, not available; FGGS, focal global glomerulosclerosis.

in the second or third decade of life (mean age 26). Colocalization of this FSGS locus and *SRNI* raises the possibility that these clinically distinct proteinuric disorders are allelic. For example, the severe recessive form may result from total loss of function mutations at both alleles, whereas the milder disease may result from partial loss of function of the same gene at one or both alleles. An alternative possibility is that distinct but physically close genes underlie these related phenotypes. Whether the families described here are fundamentally different from those in the original *SRNI* report (7) is not clear.

For the following reasons, we suspect that inherited renal disease due to defects in this chromosome 1 gene may be a much more common contributor to renal dysfunction than generally realized. Proteinuria, unless massive, will likely not cause symptoms, and it is not routine to test the urine of family members of individuals with kidney disease for elevated protein. Unless an affected individual is a member of a large sibship, the genetic nature of this disorder will not be apparent. Furthermore, selection of families with Mendelian forms of disease represents a form of selection bias for particularly severe mutations, as these are the mutations in which pen-

etrance is likely to be highest and the familial nature of disease most easily recognized. While the mutations causing the highly penetrant forms of recessive disease described here may be rare, polymorphisms causing more subtle disease may be more common, and lead to increased susceptibility to renal dysfunction from such diverse conditions as high BP, diabetes, HIV infection, obesity, and surgical reduction in renal mass. The variability in age of onset now demonstrated suggests that great variability may exist in disease caused by a gene or genes at this locus.

Given that FSGS is a common pathologic finding resulting from a heterogeneous group of underlying conditions, it is not surprising that FSGS is genetically heterogeneous. Because the pathologic phenotype appears to be restricted to the renal glomeruli, autosomal recessive FSGS is likely caused by the loss of a gene product normally expressed in kidney. The disease gene may encode a structurally essential component of the glomerulus and/or a regulatory protein necessary for kidney development. Defects in the gene encoding a novel glomerular protein, Nephtrin, were recently identified as the cause of congenital nephrotic syndrome of the Finnish type (CNF)

Table 2. Two-point linkage between disease and chromosome 1q markers<sup>a</sup>

	Recombination Fraction ( $\theta$ )			
	0.00	0.05	0.10	0.30
FS-W				
<i>DIS416</i>	-3.72	-2.49	-1.58	-0.27
<i>DIS466</i>	2.15	1.97	1.77	0.88
<i>DIS240</i> <sup>b</sup>	1.87	1.73	1.53	0.73
<b><i>DIS254</i></b>	<b>3.98</b>	<b>3.67</b>	<b>3.33</b>	<b>1.69</b>
<b><i>DIS202</i></b> <sup>b</sup>	<b>3.38</b>	<b>3.11</b>	<b>2.82</b>	<b>1.40</b>
<b><i>DIS222</i></b>	<b>3.98</b>	<b>3.67</b>	<b>3.33</b>	<b>1.69</b>
<i>DIS413</i> <sup>b</sup>	$-\infty$	0.43	0.58	0.37
FS-BU				
<b><i>DIS416</i></b>	<b>0.73</b>	<b>0.62</b>	<b>0.51</b>	<b>0.14</b>
<b><i>DIS466</i></b>	<b>0.73</b>	<b>0.62</b>	<b>0.53</b>	<b>0.16</b>
<i>DIS240</i>	0.07	0.06	0.05	0.01
<b><i>DIS254</i></b>	<b>0.73</b>	<b>0.62</b>	<b>0.51</b>	<b>0.14</b>
<b><i>DIS202</i></b>	<b>0.73</b>	<b>0.62</b>	<b>0.53</b>	<b>0.16</b>
<b><i>DIS222</i></b>	<b>0.73</b>	<b>0.62</b>	<b>0.53</b>	<b>0.16</b>
FS-I				
<b><i>DIS416</i></b>	<b>1.45</b>	<b>1.29</b>	<b>1.13</b>	<b>0.43</b>
<i>DIS466</i>	0.55	0.49	0.43	0.16
<i>DIS240</i>	0.56	0.50	0.44	0.16
<i>DIS254</i>	0.56	0.50	0.44	0.16
<b><i>DIS202</i></b>	<b>1.45</b>	<b>1.29</b>	<b>1.13</b>	<b>0.43</b>
<i>DIS222</i>	0.85	0.76	0.67	0.26
FS-G				
<i>DIS416</i>	0.27	0.24	0.20	0.06
<i>DIS466</i>	1.14	1.00	0.85	0.29
<i>DIS240</i>	1.02	0.88	0.75	0.22
<b><i>DIS254</i></b>	<b>1.32</b>	<b>1.18</b>	<b>1.03</b>	<b>0.38</b>
<i>DIS202</i>	1.02	0.88	0.75	0.22
<i>DIS222</i>	0.27	0.24	0.20	0.06
FS-BL				
<i>DIS416</i>	$-\infty$	<b>-0.2</b>	<b>-0.03</b>	<b>0.01</b>
<b><i>DIS466</i></b>	<b>1.22</b>	<b>1.07</b>	<b>0.91</b>	<b>0.30</b>
<i>DIS240</i>	-0.04	-0.03	-0.03	-0.01
<b><i>DIS254</i></b>	<b>1.22</b>	<b>1.09</b>	<b>0.95</b>	<b>0.36</b>
<i>DIS202</i>	0.22	0.19	0.17	0.07
FS-XB				
<i>DIS416</i>	$-\infty$	<b>-0.82</b>	<b>-0.40</b>	<b>0.00</b>
<i>DIS466</i>	0.34	0.31	0.27	0.10
<b><i>DIS240</i></b>	$-\infty$	<b>-0.59</b>	<b>-0.16</b>	<b>0.09</b>
<b><i>DIS254</i></b>	$-\infty$	<b>-0.59</b>	<b>-0.16</b>	<b>0.09</b>
<i>DIS202</i>	0.04	0.03	0.03	0.01

<sup>a</sup> Lod scores of fully informative markers are shown in bold.

<sup>b</sup> Lod scores were calculated from 11 FS-W family members with the exception of affected individual 8.

(10,12), a recessive disorder with a more severe phenotype and earlier onset than SRN. Nephritin, a putative transmembrane protein, shares weak structural homology with cell adhesion molecules belonging to the Ig superfamily. This discovery raises the possibility that the autosomal recessive FSGS gene

may encode a protein essential to maintain structural glomerular integrity, similar to nephrin, or a gene whose product interacts with or lies in the same biologic pathway as nephrin.

Several animal models of FSGS have been described. Of particular interest, the *BUF/Mna* strain develops FSGS in addition to thymoma and myopathy, which segregate independently of the FSGS. Genetic studies of the *BUF/Mna* rat have suggested the existence of two recessive loci involved in the pathogenesis of this nephropathy (13). Recently, the major proteinuria susceptibility gene *Pur 1* has been localized to rat chromosome 13, flanked by the *D13Mgh3* and *D13Mgh4* (14). Rat-human comparative maps (15) indicate that the human chromosomal region syntenic to the *Pur1* locus is located on the long arm of human chromosome 1 and may overlap with the *SRNI*/FSGS region. It is thus plausible that *Pur1*, *SRNI*, and this FSGS gene are allelic. If this proves to be true, it gives additional weight to the notion that identification of this and other glomerulosclerosis-causing rat genes, such as those in the fawn-hooded hypertensive rat (16), may also be important in the pathogenesis of human kidney disease.

Potential candidate genes lie within this FSGS region. Several laminin genes, which encode heterotrimeric basement membrane glycoproteins, are clustered at 1q25–31. Although human laminin beta-2 does not lie within this region, the fact that mice with targeted disruption of mouse *lamb 2* develop nephrotic syndrome increases the suspicion that laminin gene defects could cause human FSGS (17). Mice lacking cyclooxygenase 2 (COX2, gene symbol *PTGS2*), the rate-limiting enzyme in prostaglandin production, develop severe nephropathy (18). COX2 is induced at high levels in migratory and other responding cells by proinflammatory stimuli and generally is considered to be a mediator of inflammation. COX2 is located between *DIS240* and *DIS202* and therefore lies within the candidate FSGS region (between *DIS416* and *DIS413*), but outside the *SRNI* region (between *DIS452* and *DIS466*), excluding the possibility of involvement of this gene in SRN. Our analysis has not revealed any likely disease-causing gene defects in the coding sequence of COX2.

Treatment of nephrotic syndrome and FSGS is unsatisfactory at present. Clarification of genes underlying these conditions may allow early identification of those individuals unlikely to respond to treatment with corticosteroids. Elucidation of the mechanism of the development and progression of glomerulosclerosis is an essential step toward the prevention of ESRD. Although familial FSGS appears to be much less common than sporadic and secondary forms, genetic analysis may provide insight into common biologic pathways underlying glomerular injury. The cloning of relevant genes may help clarify the causes of the more common sporadic form of FSGS, as well as secondary forms of glomerulosclerosis. While this article was in press, Boute *et al.* (19) identified the *SRNI* gene (renamed *NPHS2*), encoding Podocin.

## Acknowledgments

This work was supported by grants from the National Kidney Foundation, the Burroughs-Wellcome Fund, and the National Institutes of Health (DK54931) to Dr. Pollak and a fellowship from Uehara

Memorial Foundation to Dr. Tsukaguchi. We are indebted to the family members for their assistance and cooperation in these studies, Lori Ann Correia for help with clinical ascertainment, and Jon Seidman, Calum MacRae, and Yoav Segal for helpful comments.

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