

## Clinical and genetic heterogeneity in familial focal segmental glomerulosclerosis

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### Clinical and genetic heterogeneity in familial focal segmental glomerulosclerosis.

**Background.** Familial forms of focal segmental glomerulosclerosis (FSGS) that exhibit autosomal dominant or recessive patterns of inheritance have been described. The genetic basis of these hereditary forms of FSGS is unknown. One recent study of a kindred from Oklahoma with an autosomal dominant form of FSGS linked this disease to a region of chromosome 19q. In addition, polymorphisms in a gene in this region on chromosome 19q13 have been linked to congenital nephrotic syndrome of the Finnish type. We have ascertained and characterized a large family with autosomal dominant FSGS (Duke 6530).

**Methods.** Families were compared for clinical and genetic heterogeneity. To test for linkage of our family to this portion of chromosome 19, genomic DNA was isolated from 102 family members, and polymerase chain reaction was performed using eight microsatellite markers that spanned the area of interest on chromosome 19. Data were evaluated using two-point linkage analysis, multipoint analysis, and an admixture test.

**Results.** Linkage was excluded at a distance of  $\pm 5$  to 10 cM for all markers tested with two-point  $\log_{10}$  of the odds of linkage (LOD) scores and from an approximate 60 cM interval in this area of chromosome 19q via multipoint analysis.

**Conclusions.** FSGS has been called the “final common pathway” of glomerular injury, as it is a frequent pathological manifestation with diverse etiologies. This diversity likely correlates with the genetic heterogeneity that we have established. Thus, our data demonstrate that there are at least two genes responsible for this disease, and there is genetic as well as clinical heterogeneity in autosomal dominant FSGS.

Focal segmental glomerulosclerosis (FSGS) is a pathological entity of unknown etiology. It has been reported

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in patients of diverse ethnic background, including individuals who are of Northern European, African, North American, and Spanish descent. FSGS is a significant cause of end-stage renal disease (ESRD), comprising up to 5% of adults and 20% of children with ESRD. Although the idiopathic form of FSGS is the most common, FSGS can also occur in association with reflux nephropathy, human immunodeficiency virus (HIV) infection, and sickle cell disorder. Recently, autosomal dominant and recessive forms of familial FSGS have been described [1–8]. The autosomal dominant form of FSGS is generally less severe, and patients present at a later age than with the autosomal recessive form. FSGS has also been associated with other congenital syndromes, including Laurence-Moon-Biedl syndrome [9], craniomandibular dermatodysostosis [10], and Charcot-Marie-Tooth disease [11].

The clinical hallmarks include proteinuria, nephrotic syndrome, and frequently the progressive loss of renal function. Hypertension is also a common finding. The diagnosis of FSGS is based on renal biopsy and requires the presence of areas of glomerular sclerosis and tuft collapse that are both focal and segmental. Segmental hyalinosis, glomerular deposits that are positive for immunoglobulin m and/or C3 by immunofluorescence microscopy, and epithelial cell foot process effacement by electron microscopy are often seen but are not required to make the diagnosis.

The molecular basis of FSGS is not known. Previous studies suggest that macrophages [12] or a circulating factor in the plasma [13] may be involved in the development of the glomerular injury seen in FSGS. Other studies propose that FSGS is a disorder of mesangial extracellular matrix metabolism [14]. Because FSGS occurs as the end result of a number of diverse medical conditions, defining its pathogenesis has been difficult. Although the

familial forms of FSGS are relatively rare, identifying their genetic causes should contribute to understanding the pathogenesis of the more common, sporadic forms of FSGS.

A dominant form of familial renal disease characterized by proteinuria, progressive renal failure, and FSGS on renal biopsy was described by Mathis et al and was linked to a 7 Mb region of chromosome 19q spanned by the microsatellite markers D19S223 and D19S213 [15]. Congenital nephrotic syndrome of the Finnish type has also been mapped to chromosome 19 [16]. Recently, variants in a gene identified and named *nephrin*, which encodes a glomerular protein, have been shown to be the defect in Finnish nephropathy, and this gene is located within the region on chromosome 19 that is spanned by D19S223 and D19S213 [17]. In this study, we have investigated a large kindred with familial FSGS and tested for linkage of their renal disease to this area of chromosome 19.

## METHODS

### Ascertainment and evaluation

Clinical material on Duke family 6530 was initially identified by the Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand (Fig. 1). Evaluation of this family included a complete family history and an assay of serum creatinine and urinalysis where appropriate. Asymptomatic individuals were examined for proteinuria with qualitative urinalysis. Of the individuals who had undergone renal biopsy, renal pathology slides were available for review in six cases, and the pathology reports were reviewed on the remainder.

### DNA isolation and genotyping

Genomic DNA was isolated from peripheral blood through the Center for Human Genetics, Duke University Medical Center, using PureGene™. Genotyping was carried out as described by Pericak-Vance et al, with the microsatellite markers D19S714, D19S213, D19S425, D19S208, D19S191, D19S220, D19S223, and D19S589 [18]. Touchdown polymerase chain reaction was performed using a protocol as previously described in Hecker et al [19], and markers were optimized with differing concentrations of dimethyl sulfoxide as needed [20].

### Diagnostic criteria

For linkage analysis, individuals were considered to be “*affected*” if they had a renal biopsy demonstrating FSGS without evidence of other systemic diseases that have been known to cause FSGS, if they were on dialysis, or if they had undergone renal transplantation. Family members with 3+ to 4+ proteinuria by qualitative urinalysis, in the absence of other systemic diseases likely to lead to proteinuria, were classified as “*probably affected*.”

Individuals were categorized as “*unknown*” if they had 1 or 2+ proteinuria or with 500 mg or less of proteinuria on 24-hour collection and “*unaffected*” if they had no detectable proteinuria on qualitative urinalysis or were unrelated married-in spouses.

### Linkage analysis

Duke family 6530 was analyzed as an autosomal dominant trait with variable penetrance. A frequency of 0.0001 was assumed for the FSGS disease allele. For those family members who were diagnosed as “*affected*,” a misclassification parameter of 0.005 was used. Those diagnosed as “*probably affected*” were assigned genotype penetrance values of 0.80 for the *AA/Aa* genotypes and 0.20 for the *aa* genotype, where *A* represents the FSGS allele. Individuals with the diagnosis of “*unknown*” were given a risk of 0.05 of carrying the FSGS allele. These frequencies were assigned based on our previous observations in this cohort (abstract; *Am J Hum Genet* 61:A116, 1997).

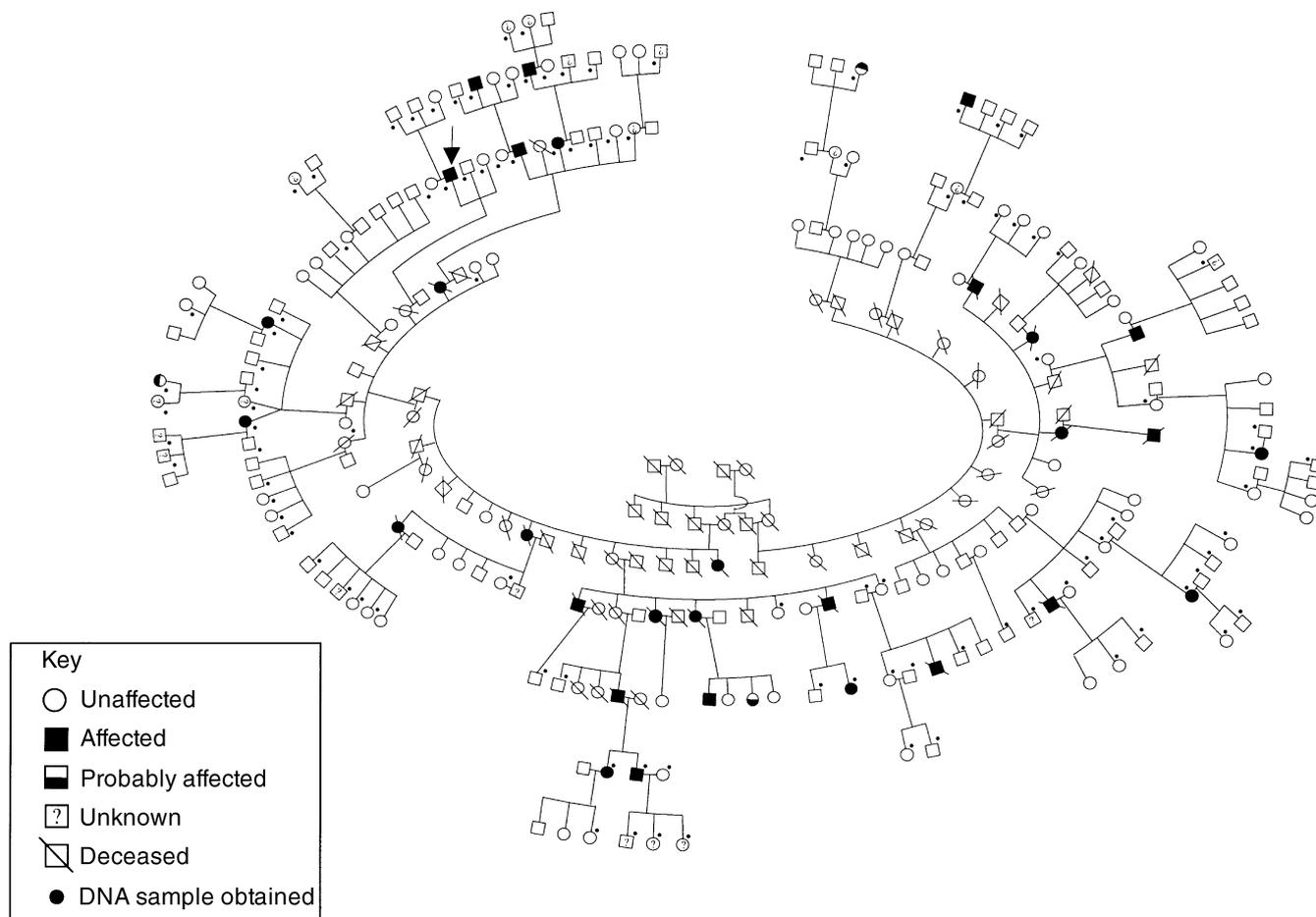
Log<sub>10</sub> of the odds of linkage (LOD) scores were calculated using the Vitesse Program Package [21]. Marker allele frequencies were calculated using 100 unrelated white controls (<http://www2.mc.duke.edu/depts/medicine/medgen/>). The marker allele/control frequencies did not differ substantially from those calculated from the unrelated spouses in the family (*N* = 17). Additionally, a low-penetrance “*affecteds-only*” analysis was performed to assure that results obtained were not due to asymptomatic individuals who were nonpenetrant carriers of the FSGS gene. Map distances for the marker loci were obtained from published data (<http://www.gdb.org/>) [15].

Finally, to exclude the possibility that differences in diagnostic criteria between our study and that reported by Mathis et al could account for differences in the outcome of the linkage analysis, we analyzed the data separately using the classification system as Mathis et al described [15]. Heterogeneity was evaluated using the admixture test as implemented in the HOMOG computer program [22].

## RESULTS

### Family data

Family 6530 (Fig. 1) is a 399 member kindred of British heritage dating back seven generations from the south of New Zealand. Segregation of the disease in the family followed an autosomal dominant pattern of inheritance. Of the 14 renal biopsies that were available, 13 were classified as FSGS, and one was classified as nonspecific glomerular changes without evidence of other types of kidney disease. Fourteen deceased individuals had ESRD. Fourteen living family members were on dialysis or had undergone renal transplantation, and three individuals were found to have proteinuria greater than 3+ by qualitative urinalysis. Blood samples for DNA were



**Fig. 1. Family 6530 pedigree (simplified for clarity).**

obtained from a total of 102 individuals, including 13 *affected*, 2 *probably affected*, 17 *unknown* individuals (14 of which were below the mean age of presentation for FSGS) and 17 *unaffected* married-in spouses. Of the individuals evaluated with renal disease, the mean age at presentation to a physician was 33 (range 16 to 61 years), with the majority being in their third and fourth decade. The mean amount of proteinuria on presentation to a physician was 3.3 g per 24 hours (range 0.3 to 6.5), and the mean serum creatinine was 1.6 mg/dl (range 0.6 to 4.1). In the patients with ESRD, the average time between initial presentation and the development of ESRD was 10 years (range 4 to 20 years). Medical problems such as diabetes that might be an alternative cause of proteinuria were not present among the individuals classified as affected. Also, none of these individuals displayed any evidence of other congenital abnormalities.

#### Linkage analysis

The results of the two-point LOD scores for full pedigree and affecteds-only models is as shown in Table 1. This analysis does not support linkage to chromosome

19q13 in this family. Linkage was excluded ( $\text{LOD} < -2.00$ ) at a distance of  $\pm 5$  to 10 cM for all markers tested. As depicted in Figure 2, multipoint linkage analysis of the markers D19S213, D19S191, and D19S223 conclusively excludes a span of approximately 60 cM in this region for both penetrance models.

When individuals were reclassified based on the diagnostic criteria of Mathis et al, nine individuals moved from the “*probably affected*” and “*unknown*” categories to the “*affected*” category [15]. Re-analysis of the data using this classification scheme extended the region of exclusion and thus did not change the outcome of the analysis (data not shown). Furthermore, analysis of homogeneity using the full pedigree model combining the two-point results from our study and the study of Mathis et al confirmed evidence of locus heterogeneity [15]. All markers trended in support of heterogeneity. Marker D19S191 showed significant evidence of heterogeneity under both the Duke and Mathis et al models with LOD scores of 4.12 (Duke criteria) and 4.38 (Mathis et al criteria), respectively, which is equivalent to odds of more than 10,000:1 in favor of heterogeneity.

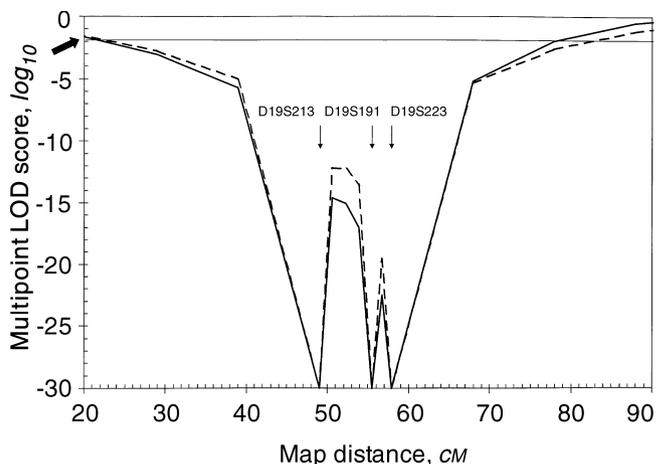
**Table 1.** Full pedigree and affecteds only LOD scores for all markers tested

Theta	0.00	0.05	0.10	0.15	0.20	0.30	0.40
<b>Full Pedigree</b>							
D19S714	-5.52	-2.45	-1.72	-1.38	-1.22	-0.94	-0.38
D19S213	-∞	-2.94	-1.74	-1.10	-0.70	-0.27	-0.07
D19S425	-∞	-5.30	-3.21	-2.09	-1.39	-0.27	-0.19
D19S208	-9.87	-3.01	-1.83	-1.18	-0.76	-0.60	-0.07
D19S191	-∞	-4.79	-3.17	-2.24	-1.59	-0.29	-0.18
D19S220	-∞	-5.08	-2.72	-1.47	-0.72	-0.03	0.08
D19S223	-∞	-6.26	-3.44	-1.95	-1.05	-0.16	0.09
D19S589	-∞	-4.85	-2.99	-1.94	-1.26	-0.49	-0.14
<b>Affecteds only</b>							
D19S714	-1.50	-0.16	-0.09	-0.11	-0.36	-0.64	-0.34
D19S213	-∞	-2.20	-1.22	-0.74	-0.47	-0.19	-0.08
D19S425	-∞	-5.15	-3.26	-2.21	-1.53	-0.71	-0.26
D19S208	-5.29	-1.94	-1.13	-0.73	-0.49	-0.24	-0.11
D19S191	-∞	-4.77	-3.24	-2.28	-1.59	-0.68	-0.20
D19S220	-∞	-3.34	-1.63	-0.79	-0.32	0.07	0.12
D19S223	-∞	-6.14	-3.80	-2.55	-1.75	-0.80	-0.29
D19S589	-∞	-3.45	-2.06	-1.30	-0.83	-0.30	-0.08

## DISCUSSION

We have reported a large kindred with familial FSGS. The pedigree analysis of kidney disease in this family is most consistent with an autosomal dominant inheritance pattern. The patients with kidney disease typically presented initially to a physician in their third decade and had high-grade proteinuria with a progressive course leading to ESRD in a relatively large percentage of affected individuals. In this study, we have demonstrated genetic heterogeneity within familial FSGS. Unlike the analyses of another family with FSGS and patients with Finnish nephropathy, our studies conclusively exclude linkage of renal disease in our family to chromosome 19q. Indeed, inspection of the diagnostic data on our family suggests that the genetic heterogeneity observed may represent an underlying clinical heterogeneity between the two data sets as well (Table 2). Duke 6530 has a larger proportion of individuals with high-grade proteinuria on presentation, a more progressive course, and more individuals who develop ESRD. The age of presentation to a physician was also generally earlier in our family. Interestingly, the main similarity between the two data sets was the pathology results. This divergence of clinical presentation supports the genetic linkage evidence presented here for the heterogeneity in FSGS.

Finnish nephropathy is linked to chromosome 19 as well, and a gene, which is mutated in this disorder (an autosomal recessive congenital nephrotic syndrome), has recently been cloned on 19q13.1 [16, 17, 23]. This is of interest because congenital nephrotic syndrome of the Finnish type has some similarities in pathology, as well as clinical manifestations to FSGS. In both Finnish nephropathy and FSGS, there is evidence of tubular atrophy, foot process effacement of glomerular epithelial



**Fig. 2.** Multipoint analysis of family 6530 using flanking markers (D19S213 and D19S223) and D19S191. The solid line signifies the “affecteds only” analysis for Duke 6530 families. The dashed line is the full pedigree analysis for the Duke 6530 families. The arrow on the vertical axis denotes a LOD score of  $-2.00$ .

cells, and sclerosis of glomeruli, and both disorders typically present with nephrotic syndrome. Finnish nephropathy is different from familial FSGS in that it manifests at or shortly after birth, is most common in Finland, and progresses to death in the first two years of life unless kidney transplantation is performed. Our data indicate that the familial FSGS in Duke family 6530 and Finnish nephropathy involve lesions at distinct genetic loci.

We have excluded linkage of Duke 6530 to the 19q13 region. Our criteria for assigning the diagnosis of FSGS were very stringent, resulting in a conservative data set. Despite this, we were able to exclude an approximately 60 cM region with a full pedigree and affecteds-only model. Family members were not included in the analysis if they had another possible etiology for their renal disease. Additionally, analysis of homogeneity revealed statistically significant heterogeneity for multiple markers.

There are many familial renal disorders that lead to ESRD besides FSGS, including adult polycystic kidney disease, Alport’s nephropathy, and juvenile familial nephronophthisis [24–28]. Genes have been identified in each of these disorders. Because ESRD is a major public health problem, affecting greater than 200,000 patients in the United States [29, 30], and idiopathic FSGS comprises a significant proportion of these patients, it is essential to understand the molecular basis in hopes of developing rational treatments and preventions.

There is much speculation as to the underlying basis of FSGS. It is unclear if FSGS is the result of a primary glomerular defect or a circulating factor [14]. The early recurrence of idiopathic FSGS after renal transplantation makes the latter explanation appealing as a possibility. Others have queried environmental causes [31]. FSGS has been called the “final common pathway” of

**Table 2.** Clinical comparison of Duke and Mathis et al FSGS families

	Duke	Mathis et al [17]
No. of individuals with proteinuria > 1 g/24 hr	10 <sup>a</sup>	10 <sup>b</sup>
No. of Individuals with proteinuria < 1 g/24 hr	2	18
Male:Female	1:1	1:1
Average age of presentation	3rd Decade	5th Decade
No. individuals with ESRD	28/46	12/47

<sup>a</sup> Four individuals with qualitative urinalysis only are not included

<sup>b</sup> Two individuals with diabetes are included

glomerular injury, as it is a common pathological manifestation of diverse forms of renal injury (for example, intravenous drug use, reflux nephropathy, medications, and cancer) [32–38]. We speculate that this genetic heterogeneity reflects the complex pathogenesis of FSGS. With further research, novel genes may soon be identified that are involved in the etiology of ESRD. With the exclusion of the 19q region in Duke 6530, we are conducting a genome-wide screen to identify additional regions and eventually, genes that will provide insight into the factors involved in the pathophysiology of FSGS.

### Postscript

We are continuing to recruit families with FFSGS and are eager to hear from any physicians caring for patients with this disorder and invite them to the International Collaborative Group on Familial FSGS (<http://www2.mc.duke.edu/depts/medicine/medgen/index.html>). Please contact Michelle P. Winn, M.D., Duke University Medical Center, Box 3014, Durham, North Carolina, USA (Tel: 919-681-5546, Fax 919-681-7894, E-mail: [mwinn@chg.mc.duke.edu](mailto:mwinn@chg.mc.duke.edu)).

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