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Report

Familial Juvenile Hyperuricemic Nephropathy: Localization of the Gene on Chromosome 16p11.2—and Evidence for Genetic Heterogeneity

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Familial juvenile hyperuricemic nephropathy (FJHN), is an autosomal dominant renal disease characterized by juvenile onset of hyperuricemia, gouty arthritis, and progressive renal failure at an early age. Using a genomewide linkage analysis in three Czech affected families, we have identified, on chromosome 16p11.2, a locus for FJHN and have found evidence for genetic heterogeneity and reduced penetrance of the disease. The maximum two-point LOD score calculated with allowance for heterogeneity (HLOD) was 4.70, obtained at recombination fraction 0, with marker D16S3036; multipoint linkage analysis yielded a maximum HLOD score of 4.76 at the same location. Haplotype analysis defined a 10-cM candidate region between flanking markers D16S501 and D16S3113, exhibiting crossover events with the disease locus. The candidate interval contains several genes expressed in the kidney, two of which—uromodulin and NADP-regulated thyroid-hormone–binding protein—represent promising candidates for further analysis.

Familial juvenile hyperuricemic nephropathy (FJHN), or familial juvenile gouty nephropathy (FJGN [MIM 162000]), is an autosomal dominant renal disease characterized by juvenile onset of hyperuricemia, gouty arthritis, and progressive renal failure at an early age. This condition was first noted by Duncan and Dixon (1960). More than 50 kindred originating from various ethnic groups—Whites (for review, see Cameron et al. 1993), Hungarians (Korom et al. 1979), Chinese (Lam and Peh 1995), Japanese (Saeki et al. 1995), and Polynesians (Reiter et al. 1995)—have been described so far. The biochemical hallmarks of the disease are hyperuricemia and reduced fractional excretion of uric acid. Ultrasound imaging studies show decreased kidney size, parenchymal atrophy and abnormal echogenicity in a majority of the patients, and infrequent occurrence of renal cysts (Prieto and Berrocal 1994; Sebesta et al. 1994; Saeki et al. 1995; Pavelka et al. 1996). Histological findings show unspecific tubulointerstitial nephropathy with a rare incidence of urate deposits (Cameron et al. 1993; Puig et al. 1993; Sebesta et al. 1994; Saeki et al. 1995; Pavelka et al. 1996; Lhotta et al. 1998). The pathogenesis of the renal disease is unknown. McBride et al. (1997, 1998) have provided evidence implicating the hyperuricemia associated with urate hypoexcretion as being a primary cause of nephropathy. In contrast, Puig et al. (1993) have presented data suggesting the opposite mechanism, with hyperuricemia as a consequence of primary renal hemodynamics disruption. Other hypotheses have suggested that urate hypoexcretion may be caused either by a gain-of-function mutation of a luminal anion exchanger, leading to intracellular proximal tubular epithelial acidosis and subsequent apoptosis (Lhotta et al. 1998), or by abnormal endogenous production of a hypothetical protein or metabolite affecting renal urate handling (Cameron et al. 1993). Therapy with allopurinol, although disputed (Miranda 1994), does seem to ameliorate the progression of renal damage in a majority of the patients (Moro et al. 1991; McBride et al. 1998). This finding underscores the importance of presymptomatic diagnosis, especially in children. Mapping the gene and identifying its defects should facilitate such a diagnosis and are thus of great importance.

Three families with FJHN were included in the present study. The pedigrees are shown in figure 1. All of the

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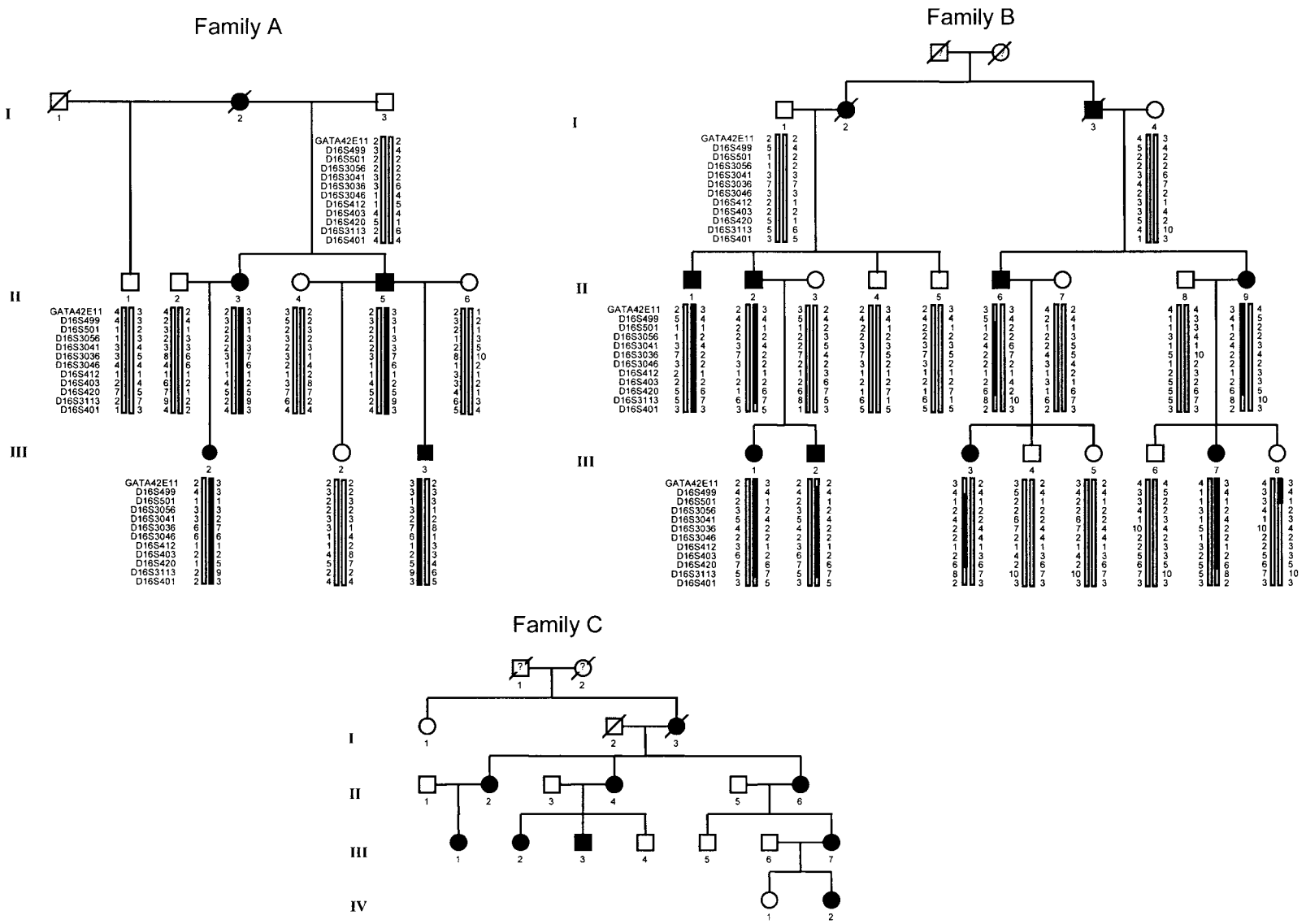

Figure 1 Pedigrees of families with FJHN phenotypes used in this study. Haplotypes for markers on chromosome 16 are shown. The haplotype segregating with the disease locus in families A and B is indicated by a black bar. No haplotype consistent with linkage was found in family C.

Table 1

Two-Point LOD Scores for All Families

Family and Marker	LOD Score at θ =						
	0	.01	.05	.1	.2	.3	.4
GATA42E11:							
A	.96	.95	.88	.80	.63	.44	.23
B	−2.62	−2.05	−1.17	−.73	−.31	−.13	−.04
C	−3.69	−2.51	−1.41	−.91	−.44	−.22	−.10
D16S499:							
A	−.02	−.02	−.02	−.01	−.01	0	0
B	−4.15	−3.39	−2.05	−1.34	−.66	−.31	−.11
C	.02	.01	−.03	−.08	−.12	−.10	−.05
D16S501:							
A	.72	.71	.65	.59	.45	.31	.16
B	.06	.32	.67	.77	.72	.54	.30
C	−5.56	−4.93	−3.16	−2.12	−1.07	−.52	−.19
D16S3056:							
A	.92	.91	.85	.78	.61	.43	.23
B	.13	.13	.10	.08	.04	.01	0
C	−3.64	−3.30	−2.03	−1.28	−.58	−.27	−.11
D16S3041:							
A	.72	.70	.59	.46	.19	−.02	−.08
B	4.05	3.98	3.70	3.34	2.57	1.72	.81
C	−4.45	−3.76	−2.42	−1.65	−.87	−.46	−.19
D16S3036:							
A	1.49	1.46	1.35	1.21	.92	.60	.28
B	4.04	3.97	3.69	3.33	2.56	1.72	.81
C	−4.97	−4.24	−2.46	−1.55	−.76	−.39	−.17
D16S3046:							
A	1.49	1.46	1.35	1.21	.92	.60	.28
B	.75	.73	.67	.60	.45	.31	.16
C	−2.82	−2.43	−1.60	−1.22	−.64	−.37	−.17
D16S412:							
A	−.08	−.08	−.07	−.05	−.03	−.01	0
B	.99	.97	.89	.80	.61	.41	.21
C	−4.15	−3.79	−2.47	−1.66	−.85	−.42	−.16
D16S403:							
A	.96	.95	.88	.80	.63	.44	.24
B	1.68	1.65	1.53	1.38	1.07	.75	.39
C	−7.01	−5.10	−2.91	−1.8	−.79	−.3	−.07
D16S420:							
A	−.04	−.03	−.03	−.02	−.01	0	0
B	2.98	2.93	2.72	2.44	1.85	1.21	.55
C	−7.03	−5.89	−3.69	−2.45	−1.23	−.59	−.22
D16S3113:							
A	1.19	1.17	1.08	.96	.72	.46	.20
B	1.13	2.11	2.52	2.48	2.05	1.43	.71
C	−2.58	−1.10	−.48	−.25	−.09	−.03	−.01
D16S401:							
A	.96	.95	.88	.80	.63	.44	.23
B	−3.13	−.19	.95	1.26	1.26	.96	.51
C	−6.71	−5.51	−3.35	−2.20	−1.09	−.54	−.21

families are of Czech origin. The diagnosis of FJHN was based on characteristic features of the disease, which include clinical evidence of gouty arthritis or renal failure, biochemical evidence of hyperuricemia, reduced fractional excretion of uric acid, and elevated creatinine serum levels. On the basis of these criteria, 19 affected individuals (age 7–53 years) were found among 57 individuals investigated. Urinary purine metabolites were quantified, and erythrocyte hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and phosphoribosylpyrophosphate synthetase (PRPP) enzyme activities were measured, to exclude HGPRT deficiency and PRPP superactivity in affected individuals. Normal karyotypes of selected probands from each family were obtained from phytohemagglutinin-stimulated lymphocytes. After informed consent was obtained, EDTA blood samples were collected from individuals informative for linkage analysis, and DNA was prepared by the DNA Isolation Kit for Mammalian Blood (Boehringer Mannheim). In 45 individuals, a genomewide scan of 348 microsatellite markers was commercially genotyped by GeneSeek, representing an average spacing of ~13 cM. The markers were all part of the version 9 screening set (Center for Medical Genetics, Marshfield Medical Research Foundation). Reference individuals "1331-01" and "1331-02" (National Institute of General Medical Sciences' Human Genetic Mutant Cell Repository) were genotyped for all markers, as positive controls. For fine mapping in selected chromosomal regions, the individual markers were PCR-amplified by Cy5-labeled upper primers (Generi Biotech) and were analyzed on an ALFExpress sequencer (Pharmacia Upjohn). Genotypes were scored by DNA Fragment Analyzer software (Pharmacia Upjohn).

The PEDCHECK program (O'Connell and Weeks 1998) was used to screen for errors in genotype data. Mendelian inconsistencies either were corrected by use of the original gels or, in cases in which bands could not be unambiguously resolved, were assigned the genotype status "unknown." Two-point and multipoint linkage analyses were performed by the MLINK and LINKMAP programs of the FASTLINK software package (Cottingham et al. 1993). The most likely haplotypes for the markers segregating with the disease were determined by SIMWALK2 (Sobel and Lange 1996). Tests for genetic heterogeneity, as well as the calculation of LOD scores in the presence of heterogeneity, were performed by the HOMOG program (Terwilliger and Ott 1994). The analysis was performed under the assumption of a dominant mode of inheritance with 95% penetrance and .001 frequency of the disease allele. Marker-allele frequencies were estimated on the basis of data on the three extended families used in this study.

Preliminary results from a two-point genomewide linkage analysis of 348 microsatellite markers produced no conclusive proof of linkage; however, two candidate regions were identified for further analysis. The first region, on chromosome 4, included markers D4S2394 (maximum two-point LOD score 2.90) and D4S1647 (maximum two-point LOD score 2.01). The second candidate region, on chromosome 16, included markers D16S753 (maximum two-point LOD score 2.25) and GATA81D12 (maximum two-point LOD score 1.05).

Table 2

Maximum Values for Two-Point HLOD Scores, θ, and α

Marker	Maximum HLOD Score	Maximum θ	Maximum α[a]
GATA42E11	.24	0	.25
D16S499	0	0	0
D16S501	.64	.1	.58
D16S3056	.44	0	.48
D16S3041	3.98	0	.63
D16S3036	4.70	0	.66
D16S3046	1.45	0	.63
D16S412	.37	.02	.41
D16S403	1.85	0	.64
D16S420	2.36	0	.49
D16S3113	3.20	.08	1
D16S401	1.30	.1	.63

[a] Proportion of families in which marker is linked to the disease locus.

For both of these regions, fine mapping was performed. Genotyping of additional markers on chromosome 4 did not provide statistically significant LOD scores, whereas the most likely haplotypes were not consistent with this region being linked to the disease locus; however, the additional markers on chromosome 16 indicated linkage with this region, particularly under the assumption of genetic heterogeneity among the families.

Two-point LOD scores for the closely spaced markers on chromosome 16p11.2 are shown in table 1. Visual inspection of the table suggests that only families A and B have linkage to the disease locus in this chromosomal region. A test for genetic heterogeneity at the most informative marker, D16S3036, shows significant evidence of heterogeneity ($\chi^2 = 7.77$; $P = .007$). Table 2 shows maximum LOD scores calculated with allowance for heterogeneity (HLOD), when only a fraction (α) of families in the sample is assumed to have linkage to the disease at a given locus (Terwilliger and Ott 1994). For D16S3036, a maximum two-point HLOD score of 4.70 was obtained at recombination fraction (θ) 0 and α = .66. The probability that family C has linkage to the disease at this locus, conditional on the estimated values of α and θ, is <.0001. A maximum two-point LOD score of 5.53 is obtained for D16S3036 ($\theta = 0$) when only families A and B are considered (i.e., when family C is excluded from the analysis).

Figure 2 shows overlapping four-point HLOD scores obtained by use of a subset of the four most informative markers—D16S499, D16S3041, D16S3036, and D16S3113. A maximum multipoint HLOD score of 4.76 is obtained at marker D16S3041 ($\theta = 0$). The 1-LOD-unit confidence interval spans a region of ~10 cM, centered around D16S3036. The most likely haplotypes are displayed in figure 1, along with family pedigrees. Haplotype analysis shows that the entire region delimited by markers D16S3056 and D16S420 is consistent with linkage to the disease. Flanking markers D16S501 and D16S3113 exhibit crossover events with the disease locus and represent outer boundaries of the linked region of interest.

The linkage analysis provides several important results. It localizes the gene involved in FJHN to an ~10-cM interval on chromosome 16p11.2. It provides evidence for reduced penetrance of the disease, since that person III-7 in family B, now age 24 years, who shares the disease haplotype, initially showed normal clinical and biochemical results but, during the course of the investigation, developed repeatedly elevated serum creatinine concentrations. Furthermore, for family C, no common haplotype was found in the indicated region, while linkage analysis gave substantial evidence for the existence of genetic heterogeneity in FJHN. Unfortunately, when we applied linkage analysis exclusively to family C, we were not able to obtain any significant or even suggestive results from use of the genomewide scan. Hence, we are able to provide evidence only for the existence of a second FJHN locus—but no indication as to its location.

Since familial juvenile gouty nephropathy is associated with an early onset of hyperuricemia, extremely reduced fractional uric acid clearance, gouty arthritis, and progression to renal failure during middle age, its phenotype can be considered as an extreme form of classical gout or can be confused with other renal diseases, such as familial juvenile nephronophthisis type 1 (NPHP1; 2q13), medullary cystic kidney disease type 1 (MCDK1; 1q21), and polycystic kidney disease types 1 (PDK1; 16p13.3) and 2 (PKD2; 4q21-23). On the basis of the data on family C, we were able to exclude linkage with the PKD1, PKD2, MCDK1, and NPHP1 regions (when LOD score <-2 was used as the criterion). We also noted that the inheritance pattern observed in pedigree C is also consistent with an X-linked dominant and/or re-

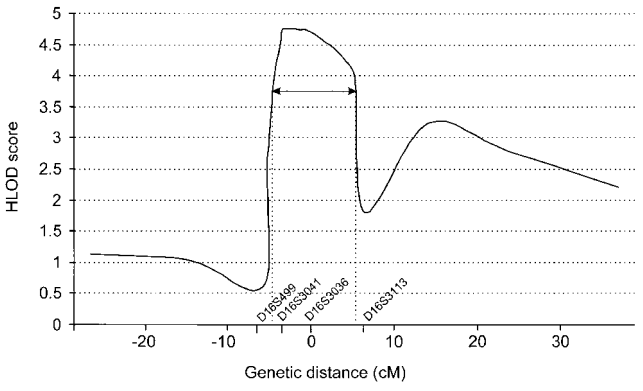

Figure 2 Four-point overlapping HLOD-score analysis of the four most informative markers in the linked region on chromosome 16. The arrow indicates the 1-LOD-unit confidence interval.

cessive segregation. Since such a condition also had been observed by Westberg et al. (1979), we analyzed the X-linked markers in family C under both the dominant and the recessive mode of inheritance; however, no evidence for linkage to the X chromosome was detected.

Interestingly, by using families A and B, we can localize the FJHN gene to the same linkage interval where previous studies (Scolari et al. 1999) have localized the gene for autosomal dominant medullary cystic disease type 2 (MCKD2 [MIM 603860]). This finding raises the question of whether distinct MCDK2 and FJHN genes are both localized within this region or whether these two disorders represent two phenotypic forms of a defect in the same gene. The main clinical features of MCDK2 are small kidneys and numerous corticomedullary and intramedullary cysts lined by low cuboidal epithelium. The patients in the family studied by Scolari et al. (1999) showed features typically diagnostic of MCKD2—but complicated by hyperuricemia and gouty arthritis. A similar phenotype was reported also in other families (Thompson et al. 1978; Fuchshuber et al. 1998; Stavrou et al. 1998). Contrary to the situation with MCKD, the presence of renal cysts among the patients with FJHN is quite rare. We find this clinical difference as being suggestive that FJHN and MCKD may be caused by defects in two distinct genes. Hence, phenotypic distinctions must be considered in the evaluation of families that must be analyzed in order to narrow the critical genomic interval for FJHN. Our data provide a foundation for further analysis, and progress should be relatively straightforward, since more pedigrees with FJHN are known and some of them are currently under study (Greener et al. 1999). The ultimate goal—the identification of the FJHN gene—should be greatly facilitated, since the critical genomic region has been almost completely sequenced and transcriptionally characterized (Loftus et al. 1999).

However, since several theories as to the causes of FJHN have been proposed, and since the pathogenesis of the disease is not clear at present, identification of the candidate gene(s) is difficult. A search through databases has identified several kidney-expressed genes, two of which seem to be the strongest potential candidates. The first of these is uromodulin (Pook et al. 1993), which is the most abundant protein in normal human urine and plays an important role in both ion transport and the maintenance of water impermeability (Hoyer and Seiler 1979). Furthermore, it has been reported as influencing many pathological conditions, such as formation of kidney stones (Gokhale et al. 1996) and development of interstitial nephritis and tubular blockade (Resnick et al. 1978). The other interesting candidate is the mucrystallin homologue—NADP-regulated thyroid-hormone–binding protein (THBP) (Vie et al. 1996, 1997). Thyroid-hormone homeostasis plays an important role in kidney growth, renal hemodynamics, tubular function, and electrolyte excretion (Katz and Lindheimer 1977), and association of hyperuricemia with both hypothyroidism (Klein and Levey 1984; Mooraki and Bastani 1998) and hyperthyroidism (Sato et al. 1995) has been reported. Of the other genes located within the defined critical region and expressed in the kidney, the rat hypertension-associated homologue *SAH* (Iwai et al. 1994) and those for the sodium-permeable non–voltage-sensitive ion channels, *SCNN1B* and *SCNN1G,* also can be considered but do not represent an immediate, obvious candidate for mutation analysis. We are hoping that linkage analyses of the additional available families with FJHN will sufficiently narrow the candidate region to permit sequencing of one or more of the putative genes and, possibly, help to resolve the issue of the distinctness of the FJHN and MCKD2 loci.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for FJGN [MIM 162000] and (MCKD2 [MIM 603860])

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