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A Bedouin Kindred with Infantile Nephronophthisis Demonstrates Linkage to Chromosome 9 by Homozygosity Mapping

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Summary

A novel type of infantile nephronophthisis was identified in an extended Bedouin family from Israel. This disease has an autosomal recessive mode of inheritance, with the phenotypic presentation ranging from a Potter-like syndrome to hyperechogenic kidneys, renal insufficiency, hypertension, and hyperkalemia. Affected individuals show rapid deterioration of kidney function, leading to end-stage renal failure within 3 years. Histopathologic examination of renal tissue revealed variable findings, ranging from infantile polycystic kidneys to chronic tubulointerstitial nephritis, fibrosis, and cortical microcysts. A known familial juvenile nephronophthisis locus on chromosome 2q13 and autosomal recessive polycystic kidney disease on chromosome 6p21.1-p12 were excluded by genetic linkage analysis. A genomewide screen for linkage was conducted by searching for a locus inherited by descent in all affected individuals. Pooled DNA samples from parents and unaffected siblings and individual DNA samples from four affected individuals were used as PCR templates with trinucleotide- and tetranucleotide-repeat polymorphic markers. Using this approach, we identified linkage to infantile nephronophthisis for markers on chromosome 9q22-31. The disorder maps to a 12.9-cM region flanked by markers D9S280 and GGAT3G09.

Introduction

Several syndromes involving disruption of kidney development and function exist (Lundin and Olow 1961; Isdale et al. 1973; Welling and Grantham 1996). These disorders are heterogeneous (Medhiob et al. 1994) and display both autosomal recessive and autosomal dominant modes of inheritance, with variable age at onset. Nephronophthisis is characterized by the development of cysts at the corticomedullary junction, in association with chronic tubulointerstitial nephritis (Strauss and Sommers 1967), and is distinguished from other medullary cystic disorders—such as Senior-Loken syndrome (Loken et al. 1961; Senior 1973) and autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) (Kaplan et al. 1989; Shaikewitz and Chapman 1993; Zerres et al. 1994)—in that nephronophthisis has a purely renal pathophysiology. Juvenile nephronophthisis (NPH1; MIM 256100) presents late in the first decade of life. This autosomal recessive disorder has been mapped to chromosome 2q13 (Antignac et al. 1993), and recent molecular studies have identified, at this locus, a gene (NPHP1) that is involved in most cases of NPH1 (Hildebrandt et al. 1997). Gagnadoux et al. (1989) described a group of infants who reached end-stage renal disease (ESRD) before 2 years of age, with chronic tubulointerstitial nephritis that had pathological features similar to juvenile nephronophthisis. This disorder has been designated "infantile nephronophthisis" (NPH2).

In the current study, an inbred Bedouin kindred with multiple cases of NPH2 (fig. 1) was used to search for a disease locus by genetic linkage analysis. The pattern of inheritance within the kindred and the presence of consanguinity indicate an autosomal recessive mode of inheritance. Because of the inbred nature of the family, all the affected individuals were assumed to have descended from a common ancestor. A homozygosity mapping strategy (Lander and Botstein 1987) was employed to search for a locus causing infantile nephronophthisis in this kindred.

Material and Methods

Clinical Evaluation

Medical records of all infantile nephronophthisis patients receiving treatment at the Pediatric Nephrology Clinic at the Soroka Medical Center in the past 16 years were reviewed. All examined patients belonged to the same kindred (fig. 1) and were products of consanguineous matings. Subjects VII-3, VII-7, and VII-17 came to

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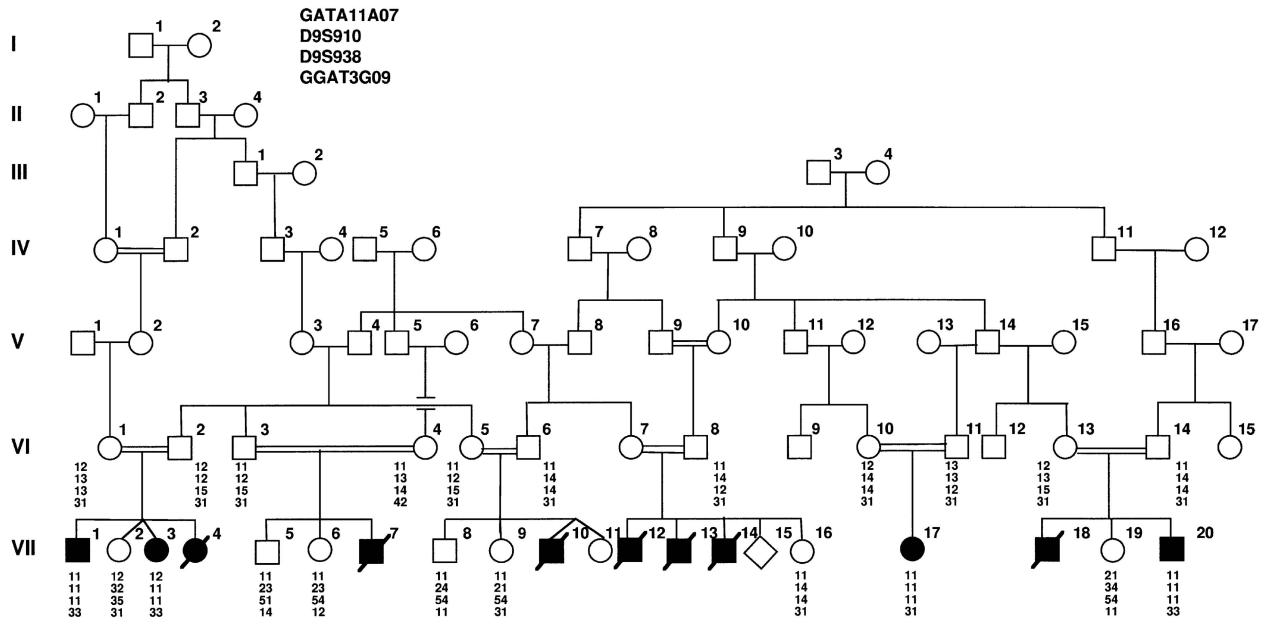

Figure 1 Pedigree of infantile nephronophthisis kindred. Solid symbols denote affected individuals; open symbols denote unaffected individuals. Genotypes of flanking and linked markers are shown below each symbol. Note that all the affected individuals are homozygous for the most tightly linked markers (D9S910 and D9S938).

medical attention at the onset of clinical symptoms, whereas the other affected infants and fetuses were examined because of a previously diagnosed case in the family. Disease onset was determined as the first appearance of symptoms or evidence of renal dysfunction.

Genotyping

DNA was prepared from whole-blood samples by a standard nonorganic protocol (Miller et al. 1988). DNA concentrations were determined by spectrophotometric readings at OD_{260}. Blood samples from unaffected siblings and parents were diluted to 100 ng/μl, and a second reading was taken to confirm the concentrations. DNA samples from 11 parents were pooled together and then diluted to a final concentration of 20 ng/μl. A second pool was created in the same manner with DNA from seven unaffected siblings, yielding a final concentration of 20 ng/μl. DNA samples from affected individuals were diluted separately to a final concentration of 20 ng/μl. All of the DNA samples, both pools and individual samples from the affected individuals, were PCR amplified with several short tandem-repeat polymorphisms (STRPs) to verify the quality of amplification and integrity of allele frequencies found in the pooled samples. STRPs were amplified with 40 ng of DNA in an 8.3-μl PCR reaction containing 1.25 μl of PCR buffer (100 mM Tris-HCl, pH 8.8, 500 mM KCl, 15 mM $MgCl_2$, and .01% w/v gelatin); 200 μmol each of dATP, dCTP, dGTP, and dTTP; 2.5 pmol of each forward and reverse primer; and 0.25 U *Taq* polymerase. When possible, markers were multiplexed. PCR reactions were subject to the following cycling conditions: 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s. PCR products were electrophoresed on denaturing (7.7 molar urea) polyacrylamide (6%) gels. The gels were visualized by silver staining (Bassam et al. 1991). The genetic markers used in this study were developed by the Cooperative Human Linkage Center (CHLC). A modified version of the CHLC STRP screening set, version 6.0, was used in the genome screen. The screening set was modified by replacing dinucleotide repeat markers with trinucleotide and tetranucleotide STRPs.

Statistical Analysis

LOD scores analysis was performed on the Bedouin family by means of the MENDEL program (Lange et al. 1988), which accommodated the inbreeding loops in the family. The disease was assumed to be autosomal recessive with complete penetrance. Allele frequencies were assumed to be equal for each marker.

Results

Clinical Evaluation

Ten affected subjects (seven males and three females) were the offspring of six Bedouin couples (fig. 1). The clinical features are summarized in table 1. The manifestations of NPH2 range from prenatal fetal oliguria and oligohydramnion resulting in postnatal respiratory

Table 1

Clinical Features at Presentation of Infantile Nephronophthisis Patients

Patient	Age at Onset (mo)	Echogenic Kidneys	HTN	Hgb (g/dl)	GFR (ml per min/1.732 m^2)	Serum K^+ (mmol per liter)
VII-1	30	+*	...	9.2	41	5.3
VII-3	30	+*	...	8.7	48	5.3
VII-4	8	+	+	6.4	20	6.8
VII-7	11	+	...	8.2	30	5.8
VII-10	3	NA	+	7.0	22	7.7
VII-12	3	+*	NA	8.9	41	7.0
VII-13	2	NA	...	9.9	36	6.5
VII-17	3	+	+	6.9	22	5.6
VII-18	0	++	NA	NA	NA	NA
VII-20	3	+*	...	9.2	61	6.1
Mean	7.8 ± 10.4	8/8	3/8	8.3 ± 1.2	36 ± 13	6.2 ± .8

NOTE.—Hypertension (HTN), hemoglobin value (Hgb), and glomerular filtration rate (GFR) were calculated by the Schwartz formula. Asterisks (*) indicate that echogenic kidneys preceded clinical renal failure. Moderately enlarged kidneys are indicated by a plus sign (+); massively enlarged kidneys are indicated by two plus signs (++). Prepartum onset is indicated by a zero (0) in the age at onset column; NA indicates that data were not available.

failure and death (patient VII-18) to postnatal onset of disease at ⩽30 mo of age. None of the postnatally diagnosed patients had a history of either oligohydramnios or neonatal respiratory symptoms. Patients VII-1, VII-3, VII-12, and VI-20 were identified early because of family history. Prospective serial renal sonograms performed on these four patients revealed hyperechogenic kidneys prior to the development of symptoms and abnormal laboratory findings. Renal sonography of all patients revealed enlarged and echogenic kidneys that lacked corticomedullary differentiation. All affected individuals developed anemia, hyperkalemic metabolic acidosis, and increased serum creatinine. The patients were not initially hypertensive; however, hypertension developed concomitantly with the deterioration of renal function. All patients reached end-stage renal failure, excluding the youngest patient, who now has chronic renal insufficiency, hypertension, and anemia. Progression from disease onset to end-stage renal failure or death due to renal complications was rapid (mean time, 7.8 mo; range, 3–18 mo). None of the affected subjects had polyuria, polydypsia, or associated ocular or hepatic complications.

The patients in this study showed most of the clinical and histopathologic features reported by Gagnadoux et al. (1989). Histopathologic examination of renal tissue from four patients revealed cysts associated with atrophic or undifferentiated tubules, with hyaline casts in some of the lumens. The interstitium showed chronic inflammation and fibrosis. Glomeruli were sclerotic or had collapsed tufts. In the prenatally diagnosed case, cystic formations of various sizes were evident, mainly in the cortex, but also focally in the medullary areas. Thickening of the tubular basement membrane was rarely seen in the patients examined. Microcystic dilatations of tubules were present in the cortex.

Exclusion of Candidate Loci

Before performing a genomewide search for linkage among the Bedouin family, we evaluated two loci where diseases with overlapping phenotypes to NPH2 have been mapped: the NPH1 locus on chromosome 2 (Medhiob et al. 1994) and the ARPKD locus on chromosome 6 (Guay-Woodford et al. 1995). The family was evaluated with STRPs both flanking and contained within the candidate disease loci. Each locus was excluded at LOD ⩽−2.0, indicating that NPH2 is not allelic with either of these diseases.

Homozygosity Mapping

Once the candidate loci were excluded, a genomewide screen to identify a locus for infantile nephronophthisis was conducted. To efficiently identify the disease locus, we genotyped each of the four affected individuals in search of markers for which the affected individuals were homozygous for the same allele. Two control DNA pools were also genotyped, to distinguish markers that were homozygous by descent in the affected individuals from those that were monomorphic in the kindred. These pooled DNA samples consisted of a parental pool containing DNA from parents of the affected individuals and a sibling pool containing DNA from unaffected siblings of the affected patients. This mapping strategy relies on the assumption of identity by descent (IBD); that is, affected individuals share a chromosomal region with the same disease-causing mutation inherited from a common ancestor. The DNA samples were used as templates for PCR amplification of STRPs developed by CHLC (Sheffield et al. 1995). Three hundred STRPs, distributed across the genome at ~10-cM density, were used for the initial screening. PCR products were electrophoresed on a denaturing polyacrylamide gel and visualized by silver

staining. STRPs for which all four affected individuals were homozygous for the same allele, and for which the parental and sibling pools showed multiple alleles, were selected for further evaluation (fig. 2). Ten candidate STRPs were identified for which at least three of the four affected individuals were homozygous for the same allele, and for which the unaffected pools showed multiple alleles. These loci were further evaluated by genotyping markers flanking each of the candidate STRPs.

Genotyping of the four affected individuals with markers flanking each of the 10 candidate STRPs revealed a single region on chromosome 9 consistent with linkage (table 2). All four affected individuals are homozygous for the same allele with markers D9S938 and D9S910 (which lies 6 cM centromeric to D9S938). Three of the four affected individuals are homozygous for centromeric flanking marker GATA11A07 and telomeric flanking marker GGAT3G09. The other nine candidate regions identified with markers from the genomewide screen showed allele sharing with the primary marker but not with flanking STRPs.

All available family members were individually genotyped with markers from the chromosome 9 candidate region, and linkage of infantile nephronophthisis to markers on chromosome 9q22-31 was revealed (fig. 3). The disease interval is defined by D9S280 as the proximal flanking marker and GGAT3G09 as the distal flanking marker. The distance between these markers is estimated to be ~12.9 cM on the basis of existing genetic maps.

Statistical Analysis

We performed two-point LOD score analysis using data generated by genotyping all 23 members of the family with markers in the region flanked by GATA11A07 and GGAT3G09 (table 3). A maximum LOD score (Z_{max}) of 3.17 was obtained at recombination fraction (θ) of zero for marker D9S938. This marker is informative in all matings, and all affected individuals are homozygous for the disease allele.

Table 2

Genotypes of Affected Individuals from the Infantile Nephronophthisis Pedigree

	Affected Individuals			
Markers	VII-1	VII- 3	VII- 17	VII-20
GATA11A07	1 1	2 1	1 1	1 1
D9S197	3 2	1 2	3 3	1 3
D9S280	2 3	4 3	2 2	3 2
D9S910	1 1	1 1	1 1	1 1
D9S277	1 1	1 1	1 1	1 1
D9S306	2 2	2 2	2 2	2 2
D9S938	1 1	1 1	1 1	1 1
GGAT3G09	3 3	3 3	3 1	3 3
D9S105	1 3	1 3	1 5	2 5

Note.—Recombination events in individuals VII-1, VII-3, and VII-20 define the proximal flanking marker as D9S280. The distal flanking marker is defined by individual VII-17 as GGAT3G09. The region between the flanking markers is 12.9 cM, as defined by the Marshfield chromosome 9 recombination map data (Center for Medical Genetics. Note that all four affected individuals are homozygous for a shared haplotype with markers D9S910, D9S277, D9S306, and D9S938.

Discussion

This study identifies a locus for infantile nephronophthisis that further demonstrates the heterogeneous nature of kidney disorders. The disease entity described here is an uncommon cause of ESRD in infancy and early childhood. The most common etiologies for ESRD in infancy and early childhood are congenital structural nephrourological anomalies, including dysplasia and obstructive uropathy (Qamar and Balfe 1991). The infants

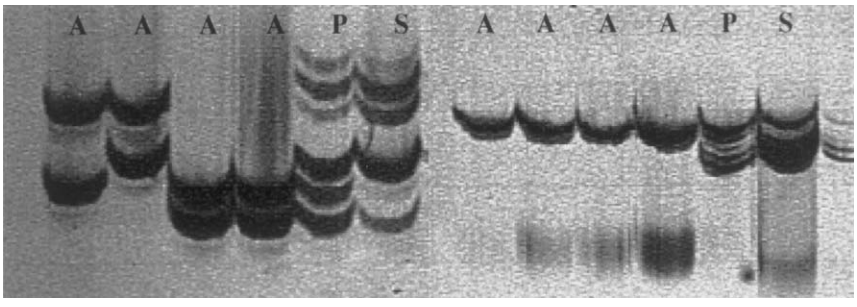

Figure 2 Silver-stained gel of PCR products of DNA samples from the Bedouin kindred shown in figure 1. DNA from the affected individuals (A), pooled DNA of parents (P), and pooled DNA of unaffected siblings (S) were used as a template to amplify STRPs in a genomewide screen. The six lanes on the left depict results from an unlinked marker. All the affected individuals are heterozygous, and the pooled parental and unaffected sibling samples show multiple alleles as well. The six lanes on the right depict results from a linked marker. All four affected individuals are homozygous for the same allele, whereas the parental and unaffected sibling samples show multiple alleles, indicating that the marker is informative in the kindred.

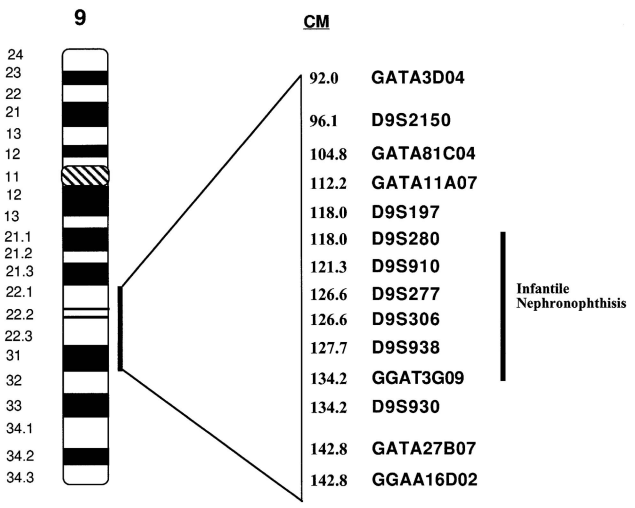

Figure 3 Genetic map of markers on the long arm of chromosome 9. Recombination distances are shown in centimorgans. This map is based on the CHLC chromosome 9 recombination minimization map data. The disease interval is flanked by markers D9S280 and GGAT3G09.

in this study had a clinical picture of early-onset, rapidly deteriorating kidney function, associated with metabolic acidosis, anemia, and hypertension. It is unclear whether the hyperkalemic metabolic acidosis described here is part of the advanced renal insufficiency or is a result of hyporeninemic hypoaldosteronism, as described in chronic tubulointerstitial nephropathies (Schambelan et al. 1980). The pathological picture of chronic tubulointerstitial nephritis with cortical microcysts differs from the one described in NPH1, in which cysts are identified at the corticomedullary junction. In addition, there was no liver involvement, which differentiates this entity from ARPKD. This is the first report of a prenatal clinical onset of nephronophthisis resulting in severe oligohydramnion and postpartum death due to pulmonary hypoplasia. This manifestation may resemble ARPKD; however, the association of severe tubulointerstitial nephritis with nephronophthisis in other cases in this kindred differs from the clinical findings seen in ARPKD. The mapping of NPH2 to chromosome 9 in this study demonstrates that NPH2 is not allelic to other renal disorders such at ARPKD and NPH1.

The consanguineous nature of the Bedouin family used in this study allowed the mapping of this disorder by searching for homozygous regions of the genome shared by the affected patients. An assumption of IBD was made on the basis of pedigree information, the cultural isolation of this population, and the rarity of the disease in the general population. Individual DNA samples from affected individuals were used to identify regions of homozygosity. Pooled DNA samples from the parents and unaffected siblings were used to evaluate the informativity of the markers in the kindred. This study identified a locus for infantile nephronophthisis on 9q22-q31. A significant LOD score of 3.17 with marker D9S938 at $\theta = 0$ supported linkage. Further evidence of linkage was demonstrated by extensive allele sharing among the affected individuals over a 12.9-cM interval. The assumption of IBD at the disease locus was confirmed by the fact that the affected individuals share a common haplotype.

Identifying a disease locus is the first step toward isolating the gene responsible for infantile nephronophthisis. Because of the relatively large genetic interval defined by the flanking markers, the identification of the disease gene for this disorder will require the evaluation of candidate genes. Candidate genes are considered on the basis of their genetic location, expression pattern, known function, and similarity to the NPH1 gene. A database search indicates that there are ~159 putative transcripts in this interval. The Genebridge 4 panel (Walter et al. 1994) was used to generate a radiation hybrid map of the NPH2 interval, with STRPs as a scaffold to map candidate genes relative to the genetic interval. Genes that map to this region include tropomodulin (Sung et al. 1996) and a new member of the forkhead family, FKHL15 (Chadwick et al. 1997). Tropomodulin is involved in regulating tropomyosin and is expressed in the kidney. FKHL15 is part of a family of eukaryotic transcription factors (Grossniklaus et al. 1992). FKHL15 contains the forkhead DNA–binding domain as well as an alanine-rich region that is frequently associated with transcriptional repression. FKHL15 has a wide tissue-expression pattern, including a 4.5-kb message in the kidney.

Current morphological as well as molecular understanding of human polycystic kidney disease (PKD) has been greatly aided by the existence of several animal models (Schieren et al. 1996). Both by genetic manipulation and through spontaneous mutations, several murine models for PKD have been identified. The C57BL/6J–cpk/cpk mouse model is the most extensively studied murine model of inherited infantile PKD (Gattone et al. 1996; Martinez et al. 1997). These mice have a strictly renal pathology. Using an outbred mouse background, Gattone et al. (1996) showed strain-related variability of renal and hepatic pathology and suggested that these changes may reflect the influence of modifier genes expressed in a particular mouse strain. In a recent study, QTL mapping identified two modifier loci of PKD progression (MOP 1 and MOP 2) in mice (Woo et al. 1997). The MOP 1 locus maps to a region on mouse chromosome 4 that is syntenic to human chromosome 9p22–9q32. MOP 1 alleles interact with MOP 2 alleles to modulate the progression of PKD. The identification of a PKD modifier locus in mice that is syntenic to the

Table 3

Pairwise Linkage Data between Infantile Nephronophthisis and Markers on Chromosome 9

	LOD Score at θ_{max} =								
Marker	.0	.025	.05	.10	.20	.30	.40	θ	Z_{max}
GATA11A07	$-\infty$	.634	.795	.829	.651	.451	.192	.75	.835
D9S910	2.72	2.50	2.29	1.86	1.099	.513	.152	.00	2.72
D9S938	3.169	2.94	2.71	2.27	1.43	.742	.260	.00	3.169
GGAT3G09	$-\infty$	1.19	1.28	1.17	.745	.358	.104	.05	1.278

human NPH2 locus is interesting, and it suggests that the NPH2 gene may play a role in modifying PKD in humans.

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Electronic-Database Information

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

Center for Medical Genetics, http://www.marshmed.org/genetics/ (for a comprehensive genetic map of human chromosome 9)

Cooperative Human Linkage Center, http://www.chlc.org (for STRPs)

Gene Map of the Human Genome, http://www.ncbi.nlm.nih.gov/cgi-bin/SCIENCE96/msrch2 (for cDNAs in 9q22-32)

Human/Mouse Homology Maps, http://www.ncbi.nlm.nih.gov/Omim/Homology/human9.html (for a mouse region syntenic to human 9q22-32)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for ARPKD and NPH1)

UniGene, Unique Gene Sequence, http://www.ncbi.nlm.nih.gov/cgi-bin/SCIENCE96/msrch2 (for ESTs located on chromosome 9)

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