The NPHP1 Gene Deletion Associated with Juvenile Nephronophthisis Is Present in a Subset of Individuals with Joubert Syndrome

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Joubert syndrome (JS) is an autosomal recessive multisystem disease characterized by cerebellar vermis hypoplasia with prominent superior cerebellar peduncles (the “molar tooth sign” [MTS] on axial magnetic resonance imaging), mental retardation, hypotonia, irregular breathing pattern, and eye-movement abnormalities. Some individuals with JS have retinal dystrophy and/or progressive renal failure characterized by nephronophthisis (NPHP). Thus far, no mutations in the known NPHP genes, particularly the homozygous deletion of NPHP1 at 2q13, have been identified in subjects with JS. A cohort of 25 subjects with JS and either renal and/or retinal complications and 2 subjects with only juvenile NPHP were screened for mutations in the NPHP1 gene by standard methods. Two siblings affected with a mild form of JS were found to have a homozygous deletion of the NPHP1 gene identical, by mapping, to that in subjects with NPHP alone. A control subject with NPHP and with a homozygous NPHP1 deletion was also identified, retrospectively, as having a mild MTS and borderline intelligence. The NPHP1 deletion represents the first molecular defect associated with JS in a subset of mildly affected subjects. Cerebellar malformations consistent with the MTS may be relatively common in patients with juvenile NPHP without classic symptoms of JS.
Saraiva and Baraitser 1992). A severe form of JS, with congenital cystic dysplastic kidneys in conjunction with retinal blindness, has been termed “Dekaban-Arima syndrome” (Dekaban 1969; Satran et al. 1999; Gleeson et al. 2004). Juvenile-onset nephronophthisis (NPHP [MIM 256100]) has been described in some individuals with JS (Hildebrandt et al. 1998; Apostolou et al. 2001) and is another renal manifestation occurring in this disorder. NPHP, or tubulointerstitial medullary cystic kidney disease, presents with concentration defects and leads to renal failure (i.e., end-stage renal disease [ESRD]) within the first 2 decades of life (Hildebrandt et al. 1997b). Of individuals with NPHP, ~15% also have retinal dystrophy, a combination known as “Senior-Loken syndrome” (SLS [MIM 266900]) (Loken et al. 1961; Senior et al. 1961; Caridi et al. 1998), and a few individuals with SLS also demonstrate the MTS accompanied by mental retardation (Satran et al. 1999; Gleeson et al. 2004). Four genes have been identified as causative in individuals with NPHP or SLS (Hildebrandt et al. 1997a; Otto et al. 2002, 2003; Olbrich et al. 2003), and most have a familial form with autosomal recessive inheritance (Otto et al. 2002), with ~80% of patients demonstrating an ~290-kb homozygous deletion that encompasses the NPHP1 gene at 2q13 (Konrad et al. 1996; Hildebrandt et al. 1997b, 2001; Saunier et al. 2003).

Given the finding of NPHP in a subset of patients with JS, we sought to determine if the NPHP1 gene, implicated as causative in the majority of familial cases of NPHP, may also be involved in JS. Three groups (W.B.D., J.G.G., and M.A.P.) evaluated their total cohort of subjects with JS, as defined by clinical criteria (Saraiva and Baraitser 1992; Maria et al. 1999a; Parisi and Glass 2003), for those with either renal involvement, retinal changes, or both. Fulfilling these criteria were 25 probands, with features summarized in table 2. Informed consent for genetic studies from each patient or legal guardian was obtained under protocols approved by the authors’ respective institutional review boards. Of the 25 JS probands studied, 32% had both retinal and renal involvement, whereas 24% had renal involvement alone, and 44% had only retinal dysplasia. Five probands had documented NPHP. For the three subjects without MRI confirmation of the MTS, cerebellar vermis hypoplasia was reported on computed tomography scans, prior to the description of the MTS (Maria et al. 1997). A presumptive diagnosis of SLS with the MTS was made in three subjects.

Clinical details of the subjects with positive results for NPHP1 analysis are summarized in table 3. Of special interest, subject K76-1, who exhibited mild gross motor delay, hypotonia, and mild cognitive delay, has a history of a congenital head tilt and unusual eye movements. She was diagnosed with NPHP at the age of 10 years and is being treated with chronic peritoneal dialysis at

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**Table 1**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Dekaban-Arima Syndrome</th>
<th>COACH</th>
<th>Juvenile NPHP</th>
<th>SLS</th>
<th>Cogan Syndrome</th>
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<tbody>
<tr>
<td>MTS</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td>0</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>Mental retardation</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>OMA</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Breathing abnormalities</td>
<td>(+)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NPHP</td>
<td>+</td>
<td>0</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Cystic dysplastic kidneys</td>
<td>(+)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal dystrophy</td>
<td>(+)</td>
<td>(+)</td>
<td>?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coloboma</td>
<td>(+)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic fibrosis</td>
<td>0</td>
<td>(+)</td>
<td>(+)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* a = present; 0 = absent; (+) = sometimes present; ? = unknown or not described.
* b JS with retinal dystrophy and renal symptoms is sometimes designated type B.
* c Genetic loci JBTS1, CORS2, NPHP1 (present results), and others.
* d Genetic loci unknown or not described.
* e COACH = cerebellar vermis hypoplasia, oligophrenia, ataxia, colobomas, and hepatic fibrosis.
* f Genetic loci NPHP1, 2, 3, 4, and others.
* g Genetic loci NPHP1, 3, 4, and others.
* h Genetic loci NPHP1 and others unknown or not described.
* i Present results.
* j Episodic tachypnea and/or apnea.
* k May include severe congenital blindness defined as Leber congenital amaurosis.
age 11 years 8 mo. Her MRI scan at the age of 3 years showed cerebellar vermis hypoplasia with long, mildly thickened superior cerebellar peduncles, consistent with a mild MTS (fig. 1A and 1B and table 3). At 10 years of age, she manifested cyclorotatory nystagmus with hypometric saccades, consistent with a mild form of OMA. The retinal examination was unremarkable, with normal visual evoked potential and electroretinogram studies. Her sister, subject K76-2, has a history of a head tilt and did not alter the encoded amino acid (Caridi et al. 2001).

Two subjects with NPHP and known homozygous and heterozygous NPHP1 deletions, respectively, were recruited from the nephrology registry at the University of Washington, to serve as controls for molecular analyses. As summarized in table 3, subject K84-1 was diagnosed with NPHP at age 8 years and progressed to ESRD and transplantation at age 9 years. He was identified elsewhere as having a homozygous deletion of NPHP1 on genetic testing (R.M., unpublished data). He had mild motor and learning delay, with an IQ of 76 at the age of 6.5 years. He lacks OMA, retinal dystrophy, and cerebellar signs, such as ataxia, but has mild incoordination. However, an MRI revealed mild cerebellar vermis hypoplasia with a mild MTS (fig. 1C and 1D).

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Subjects</th>
<th>%</th>
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<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>56</td>
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<tr>
<td>Male</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Consanguinity</td>
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<tr>
<td>MTS</td>
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<td>88</td>
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<tr>
<td>OMA</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Renal involvement:</td>
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<td>56</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
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<td>28</td>
</tr>
<tr>
<td>NPHP</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Other renal pathology</td>
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<td>8</td>
</tr>
<tr>
<td>Retinal dystrophy:</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>LCAa</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Colobomas</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Combined retinal and renal involvement</td>
<td>8</td>
<td>32</td>
</tr>
</tbody>
</table>

* N = 25.

a LCA = Leber congenital amaurosis.

Table 3

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Alteration in NPHP1</th>
<th>Age at ESRD (years)b</th>
<th>Retinal Dystrophya</th>
<th>OMAa</th>
<th>MTSb</th>
<th>Developmental Delaya</th>
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<tbody>
<tr>
<td>K76-1</td>
<td>11</td>
<td>F</td>
<td>Homozygous deletion</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>(Mild)</td>
<td>+</td>
</tr>
<tr>
<td>K76-2</td>
<td>8</td>
<td>F</td>
<td>Homozygous deletion</td>
<td>–</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>NE</td>
</tr>
<tr>
<td>K84-1</td>
<td>17</td>
<td>M</td>
<td>Homozygous deletion</td>
<td>+</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>(Mild)</td>
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<tr>
<td>K89-1</td>
<td>15</td>
<td>M</td>
<td>Deletion/W490fsX507</td>
<td>+</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* + = present; – = absent; NE = not examined.

b NA = not applicable.
Figure 1  Midline sagittal T1 images (A, C, and E) and associated axial T2 images through the level of the superior cerebellar peduncles (SCPs) (B, D, and F) in subjects indicated above each column. Note the superiorly positioned fourth ventricle with moderate inferior vermis hypoplasia (small white arrows) on the sagittal images of subjects K76-1 (A) and K84-1 (C), compared with the normal fourth ventricle with mild inferior vermis deficiency in subject K89-1 (E). Elongated SCPs are demonstrated on axial images (B and D, black arrows), with associated mild MTS, compared with normal SCPs (F).

1, K76-2, and K84-1 (known to have a homozygous deletion of NPHP1) had this marker deleted. The haplotype analysis of family K76 is consistent with inheritance by each affected daughter of the same two alleles from both parents, who each carry an NPHP1 deletion. Several markers within the NPHP1 commonly deleted region and within the 330-kb inverted repeat regions (Saunier et al. 1997a, 2000; Nothwang et al. 1998) were tested to map the extent of the homozygous NPHP1 deletion in subjects K76-1, K76-2, and K84-1 (fig. 4). We generated a junction fragment marker (junction-R), at the boundary of the proximal 330-kb repeat and the 45-kb direct repeat, and new STS markers at the 5' and 3' regions of the genes within the commonly deleted region (LOC205251, NPHP1, and BENE), by inspection of the UCSC human genome browser. Of note, a full copy of the BENE gene was deleted, but the final exon that is known to be duplicated at the distal end of the proximal 330-kb inverted repeat, outside the commonly deleted interval (Saunier et al. 1997a), was present in the deletion control subject K84-1. Characterization of the deletion in these subjects with JS by STS mapping showed concordance with the “classic” NPHP1 deletion, seen in control subject K84-1 (fig. 4). All STS markers located in the 330-kb inverted repeat region (47A, 53A, 57A, N123, R30E, R30A, and C40) were present in subjects K76-1 and K76-2, suggesting that a homozygous deletion encompassing a larger interval than that seen in patients with classic NPHP can be excluded. However, the presence of a larger-than-normal heterozygous deletion in the affected members of family K76 cannot be excluded.

To exclude the presence of a compound heterozygous mutation consisting of one deleted NPHP1 allele and a cryptic point mutation in the other allele, we analyzed a set of 10 polymorphic markers, including 5 microsatellite markers described elsewhere (Heninger et al. 2001) and the 5 intragenic SNPs within the common NPHP1 deletion region, in each of the 25 probands. The presence of at least one heterozygous marker would indicate that the patient does not harbor a full NPHP1 gene deletion. For subjects in which parental and/or sibling DNA samples were available, haplotypes of the region encompassing the common 2q13 deletion were constructed, to determine if the segregation pattern was suggestive of a heterozygous deletion. For 21 of the subjects, excluding
Figure 2

Southern analysis of EcoRI-digested genomic DNA from members of family K76 and from control subjects, confirming the presence of a homozygous deletion of NPHP1 in the two affected daughters (blackened circles). The probe is a 405-bp PCR fragment, including exons 9–10 (forward primer: 5’-TGGAAAGCAAGTTCTTAGTAAGCAGCG-3’, reverse primer: 5’-GGCAGAATTTGGACTTGCTACCTTGA-3’). The number of wild-type alleles in control samples is indicated by the genotype symbols underneath the black line (below “NPHP1”). Dosage is apparent by intensity of the 3.94-kb band that hybridizes to the intragenic NPHP1 probe. A ß-actin control probe detected a band of almost equal intensity for all samples, confirming equal loading of DNA (data not shown).

K89-1, K84-1, and affected members of family K76, at least one polymorphic marker or SNP within the common NPHP1 deletion region could be identified. In several cases, familial haplotype segregation analysis provided further evidence against inheritance of a deleted allele (data not shown). For three subjects, there was insufficient DNA available to complete the analysis. For the three subjects with homozgyous deletions, these markers could not be amplified. As anticipated, analysis of polymorphic markers within the deleted region did not uncover any heterozygous alleles from control subject K89-1. These results provide evidence that none of the subjects with JS is a heterozygous deletion carrier in whom the second mutation was not identified by mutational analysis.

The 18 families with JS that were suitable for haplotype analysis (either multiplex families with at least two affected children or those with consanguinity) were analyzed for evidence of linkage, with the use of six polymorphic microsatellite markers and one sequence-tagged site (D2S2216, D2S293, D2S340, D2S1893, STS 9657T, D2S160, and D2S363) within a 27-Mb region on chromosome 2q13 surrounding the NPHP1 gene. Four of the probands in these families were part of the set of 25 subjects included in the comprehensive NPHP1 sequence analysis. Of the 18 families, all but one (K76) were incompatible with linkage to 2q13 (data not shown).

From these investigations, we have identified the first molecular defect associated with JS—a homozygous deletion of the NPHP1 gene—in two siblings with mild JS and a documented MTS. However, on the basis of these results, we believe that the frequency of this mutation in the renal-retinal subtypes of JS, often termed “type B,” is low, as it was only identified in 1 (4%) of 25 families in our cohort, which was selected for retinal and/or renal involvement. Even in multiplex, unselected families with JS, haplotype segregation analysis excludes this locus in all but one family (K76), providing further evidence that NPHP1 is not likely to be a major locus associated with JS. In addition, other surveys, which included a total of 12 families with 15 affected individuals, have failed to identify the NPHP1 deletion in patients with JS type B (Hildebrandt et al. 1998; Apostolou et al. 2001).

What, then, differentiates our subjects with JS and NPHP1 deletions from other subjects with JS who do not have the NPHP1 deletion? Our subjects with JS and an NPHP1 deletion have a form of JS at the mild end of the clinical spectrum for this disorder, as they are not severely mentally retarded and their presenting symptoms in infancy were head tilt and mild hypotonia with gross motor delay, with a lack of the respiratory disturbance often seen in this disorder. In fact, the younger sibling (K76-2) has not yet demonstrated cognitive delay. Although the MTS was, in retrospect, visible on the MRI of the older child (K76-1), this scan was interpreted initially as normal. Comprehensive ophthalmologic evaluation failed to identify any evidence of retinal dystrophy in the proband, indicating that these subjects are not examples of JS type B, nor do they have SLS. It is also intriguing that our NPHP deletion control subject, K84-1, was identified as having a mild MTS, and we established, retrospectively, the presence of nonspecific delays prior to the onset of NPHP. Although this subject has the MTS, he does not fulfill all clinical criteria for JS (Saraiva and Baraitser 1992; Maria et al. 1999a; Parisi and Glass 2003). Thus, the severity of the pleiotropic features in JS appears to be variable.

Extrarenal findings have been described in some individuals with NPHP (Antignac et al. 1998). There are several reports of families with congenital OMA (Cogan syndrome) accompanied by NPHP who have documented deletions and/or point mutations in the NPHP1
gene (Saunier et al. 1997b; Betz et al. 2000). Some individuals with Cogan syndrome have abnormalities of the cerebellar vermis (Whitsel et al. 1995; Sargent et al. 1997). One recent case report showed hypoplasia of the brainstem and cerebellar vermis in a boy with NPHP and homozygous deletion of NPHP1 (Takano et al. 2003); in fact, this child may have a JS phenotype that was not recognized, but confirmation from the provided MRIs is impossible. We suspect that several of these patients with Cogan syndrome ( ), at least three with NPHP or Cogan syndrome with cerebellar MRIs is impossible. We suspect that several of these patients with Cogan syndrome ( ), at least three with NPHP or Cogan syndrome with cerebellar involvement and NPHP1 mutations may have an MTS not identified explicitly (Saunier et al. 1997b; Betz et al. 2000; Takano et al. 2003); however, since MRI details are not included in these reports, this assertion remains speculative. In two separate series of MRI findings in patients with Cogan syndrome ( \( n = 21 \)), at least three of the images show the MTS, but these cases were published before the MTS was recognized and the association with NPHP1 mutations was established (Whitsel et al. 1995; Sargent et al. 1997). Systematic evaluations by cranial MRI studies of the cerebellum in individuals with NPHP to identify the MTS have not been described. Presumably, other children with NPHP and either SLS or learning delays have been screened for NPHP1 deletions, and some may have had this molecular abnormality without being considered as affected with JS. This lack of diagnostic assignment to JS may be owing to either lack of MRI studies or failure to identify the MTS even if an MRI scan was obtained. In our NPHP heterozygous control subject (K89-1), with a known intragenic frameshift mutation of NPHP1 in association with the classic deletion, an essentially normal cerebellum is present on MRI without the MTS. Thus, there is likely to be a spectrum of cerebellar findings on MRI in subjects with NPHP1-associated NPHP, with the majority not exhibiting a typical MTS. Until comprehensive surveys of brain imaging studies of patients with NPHP are undertaken, the question of what proportion of subjects with only NPHP manifests an MTS will remain unresolved.

One of the questions that arises from these results is whether the NPHP1 deletion in JS patients is different from that described in patients with NPHP alone. On the basis of the available evidence, given the current limitations of mapping breakpoints within a complex repetitive region of the human genome, the deletion appears to be identical to the classic deletion in patients with NPHP. Although three genes reside within the unique deleted NPHP1 locus (LOC205251, NPHP1, and BENE), only NPHP1 has been implicated in the etiology of NPHP, and no differences in the extent of the deletion between subjects were identified by STS mapping. A more subtle or complex rearrangement, such as a second larger heterozygous deletion, cannot be excluded by the current analysis. Such a heterozygous deletion in combination with the common deletion may expand the disease phenotype because of the deletion of one (or more) dosage-sensitive gene(s). However, support for a common shared deletion that results in a broad clinical phenotype is provided by identification of the identical deletion in subjects who have NPHP with and without OMA (in both cases, some subjects are heterozygous for a deletion and a point mutation) (Saunier et al. 1997b; Betz et al. 2000) and by large genomic deletions mediated by duplicated repetitive elements that cause disorders, such as Charcot-Marie-Tooth syndrome and neurofibromatosis type 1, with highly variable phenotypes despite a common mechanism (Stankiewicz and Lupski 2002).

If the NPHP1 deletion is the same in NPHP, JS, and other CORS, what accounts for the widely divergent phenotypes? One possibility is that the other ORFs within the NPHP1 deleted region may contribute to the CORS phenotypes through unknown genetic or epigenetic factors, as their functions have not yet been completely elucidated. One of these genes, BENE, appears to encode a protein involved in membrane trafficking in apical cells of various tissues, including the renal epithelium (de Marco et al. 2001).

Alternatively, other as-yet unknown genes outside of the 2q13 deletion may work in concert with NPHP1 to contribute to OMA or to the MTS brain malformation and other clinical features that typify JS and related disorders. The nephrocystin protein encoded by NPHP1 is hypothesized to be important in mediating cell adhesion and signal transduction in the ciliated kidney epithelium.

Figure 3  Haplotype analysis in family K76, showing markers compatible with linkage to the 2q13 region surrounding NPHP1. The deleted STS marker 9657T is indicated in affected subjects K76-1 and K76-2. The 290-kb deletion is mediated by two inverted duplicated segments (invdup) of ~330 kb each, via a complex mechanism.
Figure 4  Comparison of the NPHP1 deletion in subjects with JS (K76-1 and K76-2) and in a control subject with the classic deletion (K84-1). The results of STS deletion mapping are indicated in C and D as ticks (to indicate the marker was present in these three subjects) and crosses (to indicate the marker was absent in all three subjects). A, Scale bar indicating 850 kb of contiguous DNA sequence at 2q13, isolated from the UCSC genome browser. B, BAC clone contig of the interval. (Note that clone 385J6 flanks both ends, demonstrating the difficulty presented by genomic duplications in generating accurate contigs.) C, Map of STS markers in the region that was used for deletion mapping. The NPHP1 deletion interval is indicated by a gray bar, and arrow diagrams outline the repeat regions: large blue arrows indicate the 330-kb inverted repeat, and short black arrows indicate the three copies of the 45-kb repeat, of which the two direct repeats are known to mediate unequal crossover. D, Gene locations included within the region encompassing the 45-kb repeats, mapped with orientation indicated by arrowheads. The shaded gray box indicates the only unique DNA sequence of the deleted region, which includes LOC205251, NPHP1, and all but the 3’ portion of the BENE gene.

(Konrad et al. 1996; Hildebrandt et al. 1997a; Otto et al. 2003) and interacts with the NPHP2, NPHP3, and NPHP4 proteins in a multimeric complex (Mollet et al. 2002; Olbrich et al. 2003; Otto et al. 2003). These other NPHP genes may contribute to the CORS phenotype via rare polymorphisms, thereby acting as potential genetic modifiers. Alternatively, JS, like Bardet-Biedl syndrome, may be due to a complex genetic segregation pattern, known as triallelic inheritance, in which some affected individuals must inherit three, rather than two, separate disease-associated alleles in order to manifest the complete disorder (Katsanis et al. 2001; Beales et al. 2003). Under this hypothesis, another JS locus, in addition to NPHP1, may harbor a mutation that modulates the phenotype of the NPHP1 deletion, generating the JS phenotype. Indirect evidence for this hypothesis is provided by nonconsanguineous pedigrees linked to the NPHP3 locus, in that only one NPHP3 mutation was identified in six of seven families with NPHP (Olbrich et al. 2003), suggesting that other genes (including other NPHP genes) may be providing a second or third mutation necessary to cause disease. In addition, the development of renal disease in mice deficient for the murine ortholog of NPHP3 (pck) has been shown
to be highly dependent on modifier loci, with 37% of the variance in renal cyst phenotype owing to a single locus in the region of the mouse NPHP2 gene (Woo et al. 1997; Otto et al. 2003). Thus, it is highly likely that modifier loci influence the known phenotypic variability in human renal cystic disorders. Since there is known genetic heterogeneity in JS, complex inheritance remains a formal possibility but is not testable until additional causative genes for JS are identified. An obvious next step is to examine the other recently identified NPHP genes for mutations in patients with JS.

The evidence for a role of NPHP1 in brain development remains unexplored. Although known to be expressed in a wide variety of tissues that includes skeletal muscle, heart, pancreas, and brain in addition to kidney, the temporospatial and developmental expression in the cerebellum has not been documented. It is possible that NPHP1, in addition to its hypothesized roles in cell adhesion and primary cilary function in the epithelia of the kidney and retina (Caridi et al. 1998; Otto et al. 2002, 2003; Olbrich et al. 2003), may also have a similar function in cells important in embryonic brain development. Other examples of proteins with related functions are those whose genes cause conditions, such as Bardet-Biedl syndrome and other hepatorenal fibrocystic syndromes, for which common genetic mechanisms are being clarified (reviewed in Johnson et al. [2003] and in Watnick and Germino [2003]).

Finally, any child with the MTS and either JS, Cogan syndrome, SLS, or NPHP should be considered for deletion analysis of the NPHP1 gene. Subjects with OMA or JS are at risk for the development of NPHP, and routine screening for renal compromise is recommended in this cohort (Parisi and Glass 2003). It is hoped that as additional causative genes for JS and related CORS are identified, the association of specific phenotypes with known genotypes will be elucidated.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/ (for SNP numbers rs2271245, rs2271244, rs3817140, rs1509417, and ss22970415)


