Molecular Genetics of Nephronophthisis and Medullary Cystic Kidney Disease

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Abstract. Nephronophthisis (NPH) and medullary cystic kidney disease (MCKD) constitute a group of renal cystic diseases that share the macroscopic feature of cyst development at the corticomedullary border of the kidneys. The disease variants also have in common a characteristic renal histologic triad of tubular basement membrane disintegration, tubular atrophy with cyst development, and interstitial cell infiltration with fibrosis. NPH and, in most instances, MCKD lead to chronic renal failure with an onset in the first two decades of life for recessive NPH and onset in adult life for autosomal dominant MCKD. There is extensive genetic heterogeneity with at least three different loci for NPH (NPHP1, NPHP2, and NPHP3) and two different loci for MCKD (MCKD1 and MCKD2). Juvenile nephronophthisis, in addition, can be associated with extrarenal organ involvement. As a first step toward understanding the pathogenesis of this disease group, the gene (NPH1) for juvenile nephronophthisis (NPH) has been identified by positional cloning. Its gene product, nephrocystin, is a novel protein of unknown function that contains a src-homology 3 domain. It is hypothesized that the pathogenesis of NPH might be related to signaling processes at focal adhesions (the contact points between cells and extracellular matrix) and/or adherens junctions (the contact points between cells). This hypothesis is based on the fact that most src-homology 3–containing proteins are part of focal adhesion signaling complexes, on animal models that exhibit an NPH-like phenotype, and on the recent finding that nephrocystin binds to the protein p130cas, a major mediator of focal adhesion signaling.

Definition and Clinical Features

Juvenile nephronophthisis (NPH), also termed nephronophthisis type 1 (NPH1), is an autosomal recessive cystic kidney disease that constitutes the most frequent genetic cause of end-stage renal disease (ESRD) in children and young adults (1). NPH1, together with medullary cystic kidney disease (MCKD), belongs to a group of diseases (NPH-MCKD) (2) that share common features regarding the following three criteria: (1) clinical symptoms, (2) macroscopic pathology, and (3) renal histology (3) (Table 1).

Initial symptoms are relatively mild and consist of polyuria and polydipsia; in children, anemia and growth retardation also are seen. In NPH1, children usually start to drink regularly during the night around age 6 yr. In all variants of NPH, ESRD inescapably ensues at characteristic age ranges. In most instances, MCKD also leads to ESRD but at a much later age. As far as macroscopic pathology is concerned, cysts occur primarily at the corticomedullary border of the kidneys. This location of cyst development is distinct from autosomal dominant polycystic kidney disease (ADPKD1 and ADPKD2) and autosomal recessive polycystic kidney disease (ARPKD), in which cysts are distributed uniformly over the entire organ. Another distinction from PKD is that in NPH-MCKD, kidneys as a rule maintain normal size, whereas there is significant renal enlargement in PKD. On renal ultrasonography, kidneys exhibit increased echogenicity and diminished corticomedullary differentiation. Later in the course of the disease, cysts can be detected at the corticomedullary junction (4). The third shared feature of NPH-MCKD concerns renal histology. Alterations are restricted mainly to the tubules and the interstitium and show a characteristic triad of tubular basement membrane disintegration, tubular atrophy with cyst development, and interstitial cell infiltration with fibrosis. The only significant glomerular change in early stages is periglomerular fibrosis.

Among the different variants of NPH-MCKD are also three main distinguishing features: (1) the mode of inheritance, (2) the age of onset for ESRD, and (3) the form of extrarenal organ involvement (Table 1). With regard to the mode of inheritance, transmission can be either autosomal recessive or autosomal dominant. For the recessive forms of the disease group, the term nephronophthisis (NPH) is used. Three different forms have been distinguished: NPH1, NPH2, and NPH3. The respective gene loci are NPHP1, NPHP2, and NPHP3. The designation MCKD denotes the dominant variants of NPH-MCKD (5–7). The related loci are MCKD1 and MCKD2 (7a–7c). The second distinction pertains to the age of onset for ESRD. In NPH, chronic renal failure develops within the first two decades of life. There is a juvenile (1,8,9), an infantile (10,11), and an adolescent (12) form of NPH, which are
Table 1. Shared and distinguishing features among diseases of the NPH-MCKD group of diseases

<table>
<thead>
<tr>
<th>Feature</th>
<th>NPH</th>
<th>MCKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shared Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• symptoms: polyuria, polydipsia, anemia, growth retardation, ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• macroscopic pathology: corticomedullary cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• histology: tubuli—basement membrane disruption (thickening and attenuation), distal tubular atrophy and cysts; interstitium—round cell infiltration, fibrosis; glomeruli—periglomerular fibrosis only</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distinguishing Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>• median onset of ESRD</td>
<td>Juvenile NPH1: 13 (7–25) yr</td>
<td>MCKD1: 62 (50–70) yr</td>
</tr>
<tr>
<td></td>
<td>Infantile NPH2: 1–3 yr</td>
<td>MCKD2: 32 (20–60) yr</td>
</tr>
<tr>
<td></td>
<td>Adolescent NPH3: 19 (11–28) yr</td>
<td></td>
</tr>
<tr>
<td>• extrarenal associations</td>
<td>Only in juvenile NPH1 (involving cerebellum, liver, bones)</td>
<td>Hyperuricemia, gout</td>
</tr>
</tbody>
</table>

* NPH, nephronophthisis; MCKD, medullary cystic kidney disease; ESRD, end-stage renal disease.

Molecular Genetics of Juvenile Nephronophthisis

All variants of the NPH-MCKD group of diseases are caused by defects in different genes at distinct chromosomal loci. Aspects of disease nomenclature, gene loci, and extrarenal involvement are summarized in Table 2. Since the first descriptions of NPH1 in 1945 (8) and 1951 (9), no specific protein defect has been recognized as being responsible for the characteristic histologic changes of NPH-MCKD. We and others have therefore tried to identify the gene that is responsible for the most well known variant of the NPH-MCKD group of diseases, NPH1. Through linkage analysis by total genome search, Antignac et al. (24) and Hildebrandt et al. (25) identified a gene locus for NPH1 to human chromosome 2q12-q13. We have subsequently cloned the critical genetic region in YAC and PAC contigs (26–29). Within this region, the presence of large (250 kb) homozygous deletions was demonstrated in approximately 80% of children with NPH1 (30).

Recently, we identified the gene (NPH1) responsible for NPH1 through the detection of putative loss-of-function point mutations in affected children (31). The NPH1 gene spans 83 kb, consists of 20 exons, and encodes a mRNA of 4.5 kb. The identity of this gene as mutated in NPH1 has since been confirmed (32). More than 80% of children with NPH1 harbor homozygous deletions of the gene, whereas some carry point mutations in combination with heterozygous deletions. As a consequence of the identification of NPH1 as the gene responsible for NPH1, molecular genetic diagnosis in NPH1 has become possible. Confirmation of the presence of a homozygous deletion of NPH1 (13) can be taken as proof of the diagnosis of NPH1 and renal biopsy can be avoided. If a homozygous deletion is not found, then a heterozygous deletion can be detected by fluorescence in situ hybridization (14) and a corresponding heterozygous point mutation can be sought by direct sequencing of all 20 NPH1 exons (31). If all of these studies are negative but history and renal ultrasound strongly suggest NPH, then renal biopsy is warranted. If histology is consistent with NPH in the absence of molecular defects in NPH1, then adolescent nephronophthisis (NPH3) should be considered (12), for which there is no molecular genetic diagnostic test available.

The NPH1 gene is flanked by two large (330 kb) inverted duplications. In addition, a second sequence of 45 kb, which is located between the centromeric inverted duplication and the NPH1 gene, is repeated directly within the telomeric inverted duplication. In several NPH1 families, the deletion breakpoints have been localized to the 45 kb direct repeats using pulsed field gel electrophoresis (21). Chromosomal misalignment followed by unequal cross-over or the formation of a loop structure on a single chromosome has been suggested as a potential cause for these deletions. In addition, a high degree of further rearrangements are known to occur in this region of chromosome 2 (21). We have recently molecularly characterized an unusual maternal deletion in a child with NPH1. By direct sequencing, we showed that the centromeric breakpoint was localized within a long interspersed nuclear element-1,
Table 2. Disease variants, gene loci, and extrarenal involvement in the NPH-MCKD group of diseases

<table>
<thead>
<tr>
<th>Disease (OMIM#)</th>
<th>Inheritance</th>
<th>Chromosome (Locus)</th>
<th>Gene (Product)</th>
<th>Genetic Defect</th>
<th>Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH1 (256100)</td>
<td>AR</td>
<td>2q12-q13 (NPHP1)</td>
<td>NPHP1</td>
<td>Homozygous deletion or heterozygous deletion with point mutation</td>
<td>Kidney (+), Eye (−), Cerebellum (−)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nephrocystin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH2 (602088)</td>
<td>AR</td>
<td>9q22-q31 (NPHP2)</td>
<td>?</td>
<td></td>
<td>Kidney (+), Eye (−), Cerebellum (−)</td>
</tr>
<tr>
<td>NPH3 (604387)</td>
<td>AR</td>
<td>3q21-q22 (NPHP3)</td>
<td>?</td>
<td></td>
<td>Kidney (+), Eye (−), Cerebellum (−)</td>
</tr>
<tr>
<td>Cogan syndrome</td>
<td>AR</td>
<td>2q12-q13 (NPHP1)</td>
<td>NPHP1 (with additional defect?)</td>
<td>Homozygous deletion or heterozygous deletion with point mutation</td>
<td>Kidney (+), Eye (OMA) (−), Cerebellum (−)</td>
</tr>
<tr>
<td>with ocular motor apraxia (257550)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior-Løken syndrome early onset (266900)</td>
<td>AR</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Kidney (+), Eye (RP) (−), Cerebellum (−)</td>
</tr>
<tr>
<td>late onset</td>
<td>AR</td>
<td>2q12-q13?</td>
<td>?</td>
<td>Homozygous deletion? (67)</td>
<td>Kidney (+), Eye (RP) (−), Cerebellum (−)</td>
</tr>
<tr>
<td>Joubert syndrome type B (243910)</td>
<td>AR</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Kidney (+), Eye (Coloboma), Cerebellum (CVA)</td>
</tr>
<tr>
<td>MCKD1 (174000)</td>
<td>AD</td>
<td>1q21 (MCKD1)</td>
<td>?</td>
<td></td>
<td>Kidney (+), Eye (gout, hyperuricemia) (−), Cerebellum (−)</td>
</tr>
<tr>
<td>MCKD2 (603860)</td>
<td>AD</td>
<td>16p13 (MCKD1)</td>
<td>?</td>
<td></td>
<td>Kidney (+), Eye (gout, hyperuricemia) (−), Cerebellum (−)</td>
</tr>
</tbody>
</table>

a NPH, nephronophthisis; MCKD, medullary cystic kidney disease; AR, autosomal recessive; AD, autosomal dominant; OMA, ocular motor apraxia; RP, retinitis pigmentosa; CVA, cerebellar vermis aplasia.

which belongs to an abundant group of transposable elements within the human genome (33). Whether the long interspersed nuclear element-1 sequence is causally related to the deletion event in this case cannot be answered.

**NPHP1 Expression Studies**

To gain some insight into NPHP1 gene function, expression studies were performed in human and mouse, after cloning of the full-length murine Nphp1 cDNA. Northern dot blot analysis revealed a broad tissue expression pattern primarily in pituitary gland, spinal cord, thyroid, testis, skeletal muscle, trachea, and kidney (in decreasing order of strength). In addition, in situ hybridization studies of whole mount mouse embryos showed ubiquitous but weak Nphp1 expression at all embryonic stages between days 7.5 and 11.5 p.c. (34). In the adult mouse, there was also strong expression in testis. This expression occurred specifically in cell stages of the first meiotic division and thereafter. The broad tissue expression pattern is hard to reconcile with the fact that in NPHP1, symptoms are known to occur only in the kidney. However, several examples for a lack of correlation between the tissue expression pattern of a disease gene and the target organs involved are known (35–37). To resolve this issue, a mouse model of targeted gene disruption of the Nphp1 gene will have to be generated. This would permit extensive studies into differential tissue expression of NPHP1 and nephrocystin.

**Nephrocystin Contains Multiple Domains of Protein–Protein Interaction**

The product of the NPHP1 gene is nephrocystin. We performed sequence comparisons using the program BLAST (http://www.ncbi.nlm.nih.gov/BLAST/) with electronic databases that contain all known nucleotide sequences studied from many organisms (“nr,” “dbest,” “HTGS”) and searching the protein database “swissprot.” This analysis revealed that in NPHP1, we had identified a novel gene that was not related to any of the known gene families. To generate a hypothesis on putative nephrocystin function, we used the deduced amino acid sequence of nephrocystin to perform computer-aided theoretical modeling of nephrocystin secondary structure. Although the sequence of nephrocystin was found to be novel, it contained a hitherto unknown association of domains of protein–protein interaction, which was conserved in evolution (Figure 1). Specifically, there were three putative coiled-coil domains, an Src-homology 3 (SH3) domain, which was highly similar in sequence to the human proto-oncogene product Crk. The SH3 domain is flanked by two glutamic acid-rich domains (Figure 1) (34). The model of nephrocystin secondary structure was well conserved in mouse and even in a homologous sequence of Caenorhabditis elegans, which was identified from the sequencing project of the nematode. Amino acid sequence similarity was 42% (23% identity), indicating high sequence conservation of this domain structure throughout evolution.

Figure 1 shows a model of deduced nephrocystin secondary structure. At the N-terminus, the program COILS modeled three putative amphipathic helices, which are known to engage in protein–protein interaction by formation of a “coiled-coil” structure. This structure resembles a cylinder, which exposes on one side hydrophobic amino acid residues in a row slightly oblique to its longitudinal axis. Two such coiled-coil cylinders may bind to each other through the summation of hydrophobic interaction between these residues. The structure resembles two aligned rods that are slightly intertwined (38). It is interesting that the gene products polycystin 1 and 2 of the genes for ADPKD1 and ADPKD2 interact through a coiled-coil domain on polycystin 2 (39,40).

In addition, there were two highly negatively charged domains that contained two thirds glutamic acid residues (E-rich domains) (Figure 1). Similar domains are found in proteins such as the Ran GTPase activating protein. The E-rich domains flank an SH3 domain. SH3 domains are modular protein-binding domains that are known to bind specifically to proline-rich consensus sequences on other proteins (41). The minimal SH3 recognition consensus is PxxP (where P is proline and x any amino acid). More than 300 SH3 domains are expected to be encoded by genes in the human genome (42).

**A Functional Hypothesis for the NPHP1 Gene Product Nephrocystin**

On the basis that nephrocystin contained an SH3 domain, we formulated a testable hypothesis on putative nephrocystin function (43). Because most SH3 domains are found in adapter proteins such as Crk, which have a function in focal adhesion signaling complexes of cell-matrix contacts (38,44), the hypothesis assumed that nephrocystin, by virtue of its SH3 domain, might be part of focal adhesion signaling complexes (44–47). To test this hypothesis, we sought to identify protein-binding partners of the nephrocystin SH3 domain. We also reasoned that such proteins, through their interaction with nephrocystin, might represent candidate gene products for any of the other disease genes of the NPH-MCKD group of dis-
The nephrocystin SH3 domain sequence was subcloned into pGPT9 (Clontech, La Jolla, CA) to be used as a bait in a yeast-2-hybrid screen for protein–protein interaction of a human fetal kidney cDNA library (48). From this yeast-2-hybrid screen, the protein p130^cas (“crk-associated substrate”) was identified as a binding partner for the nephrocystin SH3 domain (GenBank accession no. AF218451; E. Otto et al., unpublished observations).

As an alternative technique, the nephrocystin SH3 domain was used to isolate proline-rich binding peptides using a phage display procedure (49); N. Horn et al., unpublished observations). The resulting peptide consensus sequence RPLPPxP contained the bona fide SH3 binding consensus PxxP and was highly similar in sequence to the known SH3 binding consensus on the protein p130^cas RPLPSPP, to which the proto-oncogene products SRC and FYN are known to bind (45). p130^cas, which is a major mediator of focal adhesion assembly, binds to focal adhesion kinase (FAK), thereby connecting integrin-mediated signaling from the extracellular matrix to the Rho and Rac MAP kinase signaling pathways (45). It also mediates stress fiber formation.

It has recently been shown by yeast-2-hybrid screening using the C-terminal half of murine p130^cas that p130^cas binds to nephrocystin, which competes at the recognition sequence RPLPSP for binding to the SH3 domains of Src and Fyn (50). Those authors were also able to show that nephrocystin co-localizes with p130^cas and E-cadherin at adherens junctions of cell-cell contacts in MDCK cells. Figure 2 summarizes a revised hypothesis stating that nephrocystin might be involved in focal adhesion and/or adherens junction signaling. Recently, a pathogenetic hypothesis related to focal adhesion and/or adherens junction signaling has also been proposed for ADPKD (51,52).

The finding that several domains of protein–protein interac-

Figure 2. Hypothesis of putative nephrocystin function, stating that nephrocystin might be involved in focal adhesion and/or adherens junction signaling. An illustration of a renal epithelial cell is shown on the left (modified from reference (38); components of adherens junctions and focal adhesions are shown on the right. Adherens junctions of epithelial cells represent E-cadherin-containing cell-cell contacts; focal adhesions represent integrin-containing cell-matrix contacts. Focal adhesions mediate signal transduction from the extracellular matrix to the nucleus. One of the routes is relayed over integrin molecules, focal adhesion kinase (FAK), proteins such as p130^cas (cas), adapter proteins such as Crk (containing SH2 and SH3 domains), guanine nucleotide exchange factors (GEF), and small GTPases such as Rho, Rac, or Ras to the nucleus (arrow). Major molecular components of focal adhesion complexes are shaded gray (44); components with proposed involvement in NPH are shown in color. Nephrocystin might be a component of focal adhesion signaling complexes, because it is a binding partner to and co-localizes with p130^cas. It might also be an adherens junction component, because it co-localizes with E-cadherin. The hypothesis, that nephrocystin might play a role in focal adhesions, is emphasized by the fact that the tensin knockout mouse (symbolized by red cross bars over “tensin”) exhibits a phenotype very similar to human nephronphthisis, where tensin is an important constituent of focal adhesion signaling complexes (36). The Rho GDIα-deficient mouse exhibits an NPH-like phenotype. In children with NPH, strong α5β1 integrin expression in proximal tubules, from which α5 integrin is normally absent, was described, which is most likely a result from defective α6 integrin expression (66). Together, these findings may point to a pathogenesis of NPH, which involves focal adhesion or adherens junction signaling processes. Additional binding partners of nephrocystin (? bp) might represent candidate gene products for any of the other disease genes of the NPH-MCKD group of diseases.
tion (SH3 and coiled-coil) are encoded by NPHP1 suggests that there might be additional binding partners of nephrocystin. Defects in such proteins may cause a phenotype similar to NPH1. Therefore, isolation of such binding partners might lead to the identification of proteins that represent gene products of other disease genes from the NPH-MCKD group of diseases. This approach as well as identification of further disease genes by positional cloning might help to shed some light on the pathogenesis of NPH-MCKD. It might also elucidate some general mechanisms of renal fibrosis and cyst development.

**Animal Models of NPH-MCKD**

Several animal models that have been shown to share characteristic clinical and histologic features with human nephronophthisis are summarized in Table 3. They can be distinguished from animal models for PKD on the basis of the presence of the histologic triad typical for NPH-MCKD, namely tubular basement membrane disruption, tubular atrophy, and cyst development and tubulointerstitial infiltration with fibrosis. None of the respective gene loci, however, are syntenic with any form of human NPH-MCKD, with the exception of the pcy mouse, which shows synteny with the NPHP3 locus, as has been noted by H. Omran et al. (unpublished observations).

There are three mouse models of targeted gene disruption (“knockout mouse”) that concern genes involved in focal adhesion signaling:

1. In the tensin knockout mouse model, the only organ that shows alterations is the kidney with a histologic picture highly reminiscent of human NPH (36). There is marked tubular basement membrane disruption, ectasia and cyst development, and interstitial inflammatory infiltration. Electron microscopy demonstrated lack of focal adhesions in cystic tubules. Tensin is an F-actin-binding component of focal adhesions, contains a src-homology-(SH2) domain, associates with p130Cas, and plays a central role in focal adhesion signaling. In distinction to human NPH, cysts of tensin-deficient mice were primarily localized in proximal rather than distal tubular segments. There was also the finding of an empty renal pelvis. Because there was no evidence of urinary outflow obstruction, we interpret these findings as most likely not representing true “hydronephrosis” (i.e. pressure-dependent distension of the renal pelvis) but rather may be the result of tissue destruction on the basis of large intrapyramidal cysts, as are seen in the pcy mouse model (53). Because of the overall striking similarity to human NPH, the tensin knockout mouse model supports the focal adhesion hypothesis for nephrocystin function.

2. In the human kidney, tubular epithelial cells express mostly α2β1 integrins, α6β1 integrins, and in the distal tubule α6β4 integrins, whereas α3β1 integrins are expressed in podocytes of the glomerulus. α3β1-deficient mice died in the neonatal period with severe glomerular defects based on disorganized podocyte to basement membrane contacts. However, there were also cystic alterations of proximal tubules (54).

3. The small GTPase Rho (an equivalent to Ras) is known to regulate various actin cytoskeleton-dependent cell functions. To assess the function of its GDP dissociation inhibitor Rho GDIα, a knockout mouse model had been generated (55). These mice postnatally developed massive proteinuria mimicking nephrotic syndrome. However, there was also marked degeneration of tubular epithelial cells, dilation of distal and collecting tubular cells, and interstitial cell infiltration, as is seen in NPH-MCKD. These changes underwent age-dependent progression. In addition, mice were infertile with impaired spermatogenesis. On the basis of the focal adhesion hypothesis, one would expect p130Cas-deficient mice to show an NPH-MCKD–like phenotype. However, p130Cas knockout mice died

<table>
<thead>
<tr>
<th>Mouse Modela</th>
<th>Similarities to Human NPH</th>
<th>Dissimilarities to Human NPH</th>
<th>Chromosomal Localization</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knockout model (focal adhesion related)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tensin</td>
<td>Triadb</td>
<td>Proximal tubular cysts</td>
<td>1</td>
<td>2q35-q36</td>
</tr>
<tr>
<td>α3β1 integrin</td>
<td>Microcysts, triadb</td>
<td>Mostly glomerular changes, proximal tubular cysts</td>
<td>α3: 11</td>
<td>α3: 17</td>
</tr>
<tr>
<td>Rho GDIα</td>
<td>Triadb</td>
<td>Nephrotic syndrome also</td>
<td>?</td>
<td>17q25.3</td>
</tr>
<tr>
<td>Knockout model (apoptosis related)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Triadb</td>
<td>Marked apoptosis</td>
<td>2</td>
<td>18q21.3</td>
</tr>
<tr>
<td>Ace</td>
<td>Triadb</td>
<td>Marked apoptosis</td>
<td>11</td>
<td>17q23</td>
</tr>
<tr>
<td>AP2β</td>
<td>Triadb</td>
<td>Nephrotic syndrome also</td>
<td>3</td>
<td>6p12</td>
</tr>
<tr>
<td>Spontaneous genetic defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kdkd</td>
<td>Triadb</td>
<td>–</td>
<td>10</td>
<td>6q21</td>
</tr>
<tr>
<td>pcy</td>
<td>Triadb, age of onset similar to NPH3</td>
<td>–</td>
<td>9</td>
<td>?</td>
</tr>
</tbody>
</table>

a Autosomal recessive.
b Classic histologic triad of NPH: tubular basement membrane disruption, tubular atrophy, and cyst development and tubulointerstitial infiltration with fibrosis.
atrophy, interstitial inflammation, water wasting, and uremia in the male and are phenotypically affected by a nephronoph-
enzyme (Ace)

NPH is the knockout mouse for the
formation, as has also been shown by Woo (60).

Bcl-2 epithelial cell cysts when cultured in type I collagen gel, that
kidney (MDCK) cells, which regularly develop into simple
chronic renal interstitial inflammatory infiltrates in all affected
age (53). Like in NPH, individual cysts were found to be lined
nephron and collecting duct and progressively enlarged with
components of focal adhesion signaling was altered. Thus, tubular expression of integrins as major
those proximal tubular cells, which were affected by typical
lesions, showed no expression of fibronectin receptors α4β1 integrin and α5β1 integrin, whereas α6β1 integrin expression
was increased. Thus, tubular expression of integrins as major
components of focal adhesion signaling was altered.

In pcy mice, renal cysts were identified in all segments of the
nephron and collecting duct and progressively enlarged with
age (53). Like in NPH, individual cysts were found to be lined by a single layer of epithelial cells in most areas, with focal
polyps and mounds of cells principally in collecting duct cysts. Late stages of the disease were characterized by azotemia and
chronic renal interstitial inflammatory infiltrates in all affected
animals and cerebral vascular aneurysms in a few. Therefore, the pcy mouse may represent another model of NPH-MCKD.
Finally, a phenotype highly reminiscent of NPH-MCKD has been described in the Norwegian elkhound dog (65).

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