CHAPTER

15 Nephronophthisis—Medullary Cystic Kidney Disease

Friedhelm Hildebrandt • Rannar Airik • John A. Sayer

A group of hereditary renal diseases is summarized under the term NPHP-MCKD complex,[1,2] because the different disease entities share several features regarding (1) macroscopic pathology, (2) microscopic pathology, and (3) clinical symptoms (Table 15.1A). In this way the complex describes a distinct clinicopathologic entity.[3] The term nephronophthisis (NPHP) is used for the autosomal recessive variants, which lead to end-stage renal disease (ESRD) in the first 3 decades of life, whereas the term medullary cystic kidney disease (MCKD) refers to the autosomal dominant forms, in which ESRD develops in the third to seventh decade of life. Extrarenal manifestations such as ocular motor apraxia, retinitis pigmentosa, hepatic fibrosis, skeletal defects, and cerebellar vermis aplasia have exclusively been described in association with juvenile nephronophthisis. The only extrarenal associations in MCKD are hyperuricemia and gout. The identification of causative recessive genes in nephronophthisis has implicated the function of primary cilia and centrosomes in its pathogenesis.

FEATURES SHARED AMONG DISEASES OF THE NEPHRONOPHTHISIS-MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX

Macroscopic Pathology

A major feature shared among the disease entities of the NPHP-MCKD complex (Table 15.1A[i]) is the appearance on macroscopic pathology as described in 27 patients with juvenile NPHP by Waldherr et al.[1] Kidney size is normal or moderately reduced. Cysts primarily appear at the corticomedullary border of the kidneys (Fig. 15.1). This is quite distinct from autosomal dominant and recessive polycystic kidney disease, where kidneys become grossly enlarged as a result of cystic dilatation throughout the organ. From the external surface, the kidney is indistinguishable from the kidney affected by glomerulonephritis or pyelonephritis. The surface usually has a finely granular appearance, most likely due to the protrusion of dilated cortical collecting ducts. Calices and pelvis appear completely normal. There are from 5 to over 50 cysts of 1 to 15 mm in diameter located preferentially at the corticomedullary border (Fig. 15.1). The cysts primarily arise from the distal convoluted and medullary collecting tubules as shown by microdissection,[4] but may also appear in the papilla. Cysts are not always present, but do occur in about 70% of autopsy cases. They apparently arise late in the course of the disease[5] and do not seem to be important for disease progression to renal failure.[6] Therefore, the presence of cysts is not a prerequisite for diagnosis.

Microscopic Pathology

The second shared feature among diseases of the NPHP-MCKD complex pertains to renal histology (Table 15.1A[ii]). The histologic changes are characteristic, but not pathognomonic, for the disease group. The characteristic histologic triad of NPHP-MCKD consists of (1) tubular basement membrane disintegration with irregular thickening as well as attenuation of the tubular basement membrane, (2) interstitial round cell infiltration with marked fibrosis and, (3) later in disease development, tubular atrophy with cyst development, which occurs predominantly at the corticomedullary junction (Fig. 15.2). Cysts seem to be the result rather than the cause of the atrophic process, although this time course could not be corroborated by statistical analysis.[1,7] Sometimes, a communication between a cyst and a tubule can be seen. The tubular basement membrane (TBM) is extremely thickened and multilayered. Fibroblasts are noted between the membrane layers. TBM changes and diverticulum formation are most prominent in the distal tubules, where cysts are lined with a single layer of cuboidal or flattened epithelium. In the advanced stage, the picture merges into a diffuse sclerosing tubulointerstitial nephropathy, the characteristic picture of end-stage NPHP-MCKD. The only significant glomerular change in early stages involves periglomerular fibrosis with a splitting and thickening of the Bowman capsule and glomerular obsolescence only in nephrons that

15.1 Shared and Distinguishing Features Among Diseases of the NPHP-MCKD Complex

A. Shared Features		
(i) Macroscopic pathology:	Corticomedullary cysts	
(ii) Microscopic pathology:	Tubuli: basement membrane disruption (thickening and attenuation), distal tubular atrophy and cysts Interstitium: round cell infiltration, fibrosis Glomeruli: periglomerular fibrosis only	
(iii) Symptoms:	Polyuria, polydipsia, anemia, growth retardation, ESRD	
B. Distinguishing Features		
	NPHP	**MCKD**
(i) Inheritance:	Autosomal recessive	Autosomal dominant
(ii) Median onset of ESRD:	Juvenile NPHP1: 13 yrs Infantile NPHP2: 1–3 yrs Adolescent NPHP3: 19 yrs NPHP4: 20 yrs NPHP5: 13 yrs	MCKD 1: 62 yrs MCKD 2: 32 yrs
(iii) Extrarenal associations:	Retinal degeneration, cerebellar vermis hypoplasia, hepatic fibrosis, cone-shaped epiphyses	Hyperuricemia, gout

ESRD, end stage renal disease; NPHP, nephronophthisis; MCKD, autosomal dominant medullary cystic kidney disease.

have been destroyed by the tubular alterations. An escape of Tamm-Horsfall (uromodulin) protein from damaged collecting tubules into the interstitium has been demonstrated in about 50% of patients with NPHP-MCKD as a periodic acid-Schiff (PAS)-positive material and by specific immunofluorescence staining with an anti-THP antibody.[8] Immunofluorescence does not otherwise contribute to the diagnosis of NPHP-MCKD.

Characteristic changes demonstrated by transmission electron microscopy include thickening, splitting, attenuation, and granular disintegration of the TBM (Fig. 15.3). The transition between these alterations is abrupt.[7] Fibroblasts are seen in direct contact with the TBM. At the base of the tubular epithelial cells, a marked increase of microfilaments is seen. The thickening is either homogeneous or has a lamellated, annular, and ringlike appearance. The glomerular basement membrane is normal. Multiple tubular diverticula are seen but the connections between cysts and distal tubular segments are patent.

Clinical Presentation

The third group of features shared among different diseases of the NPHP-MCKD complex involves clinical symptoms (Table 15.1A[iii]). Classical symptoms are polyuria, polydipsia, decreased urinary concentrating ability and, in children, anemia and growth retardation. The insignificance of the symptoms together with the lack of edema, hypertension, and urinary tract infections characteristically leads to a delayed diagnosis and therapy in NPHP-MCKD. In all variants of NPHP-MCKD, terminal renal failure insidiously ensues at characteristic age ranges, necessitating renal replacement therapy (Fig. 15.4). Disease recurrence has never been reported in kidneys transplanted to NPHP patients.[9]

FEATURES DISTINGUISHING DISEASE ENTITIES OF THE NPHP-MCKD COMPLEX

There are three features that clearly distinguish different disease entities of the NPHP-MCKD complex: (1) the mode of inheritance, (2) the age of onset for ESRD, and (3) the type of extrarenal organ involvement (Table 15.1B).

The Mode of Inheritance

In the NPHP-MCKD complex, the mode of inheritance can be either autosomal recessive or autosomal dominant.

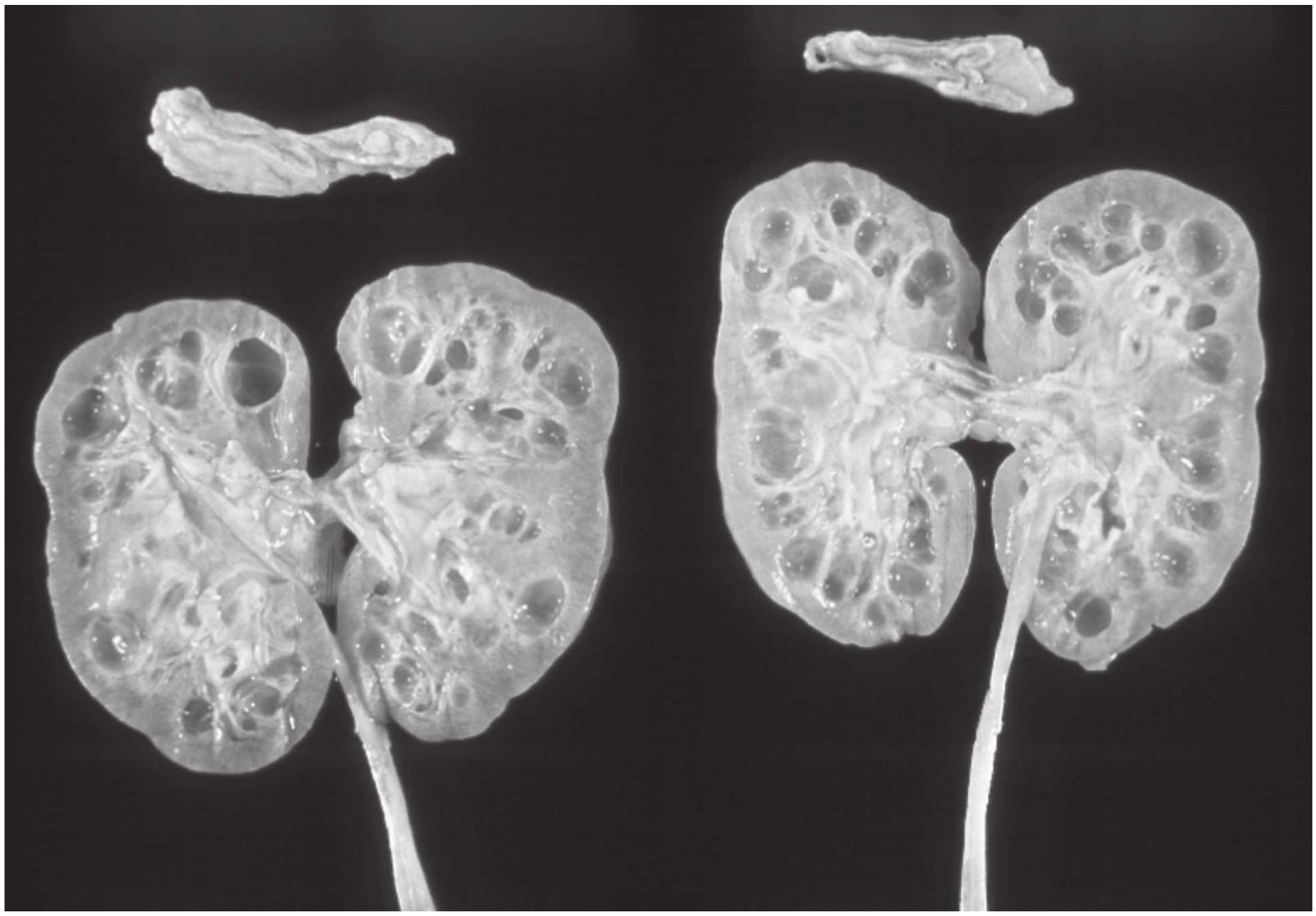


FIGURE 15.1 Juvenile nephronophthisis (autopsy case, 13-year-old girl). Note the numerous cysts of varying size in the medulla and at the corticomedullary junction. (Reproduced with permission from Hildebrandt F, Waldherr R, Kutt R, et al. The nephronophthisis complex: clinical and genetic aspects. *Clin Invest* 1992;70:802.)

For the recessive forms the term nephronophthisis (NPHP) is used, whereas the designation medullary cystic kidney disease (MCKD) denotes the dominant variants of the complex (Table 15.1B[i]).[10,11]

The Onset of End-Stage Renal Disease

The second distinction pertains to the age of onset of ESRD (Table 15.1B[ii]). In all variants of NPHP-MCKD, ESRD ensues at characteristic age ranges, necessitating renal replacement therapy (Fig. 15.4). In NPHP, chronic renal failure develops within the first 3 decades of life.[12–14] In a study conducted in 46 children with juvenile nephronophthisis (NPHP1), a serum creatinine value of 6 mg per deciliter was reached at a median age of 13 years (range: 4 to 20 years).[12,15] In a study by Waldherr et al.[1] ESRD was reached at a median age of 11.5 years. Gretz et al.[16] showed that the rate of deterioration of renal function was homogeneous in a study of 29 patients with NPHP1. The median time elapsing between a serum creatinine of 2 and 4 mg per deciliter was 32 months, between 4 and 6 mg per deciliter was 10 months, and between 6 and 8 mg per deciliter was 5 months.[16] A high concordance of the development of renal failure was noted in monozygotic twins.[17,18] Infantile nephronophthisis (NPHP2) is characterized by an early onset of ESRD between the neonatal period and 3 years of age.[14] In adolescent nephronophthisis (NPHP3), terminal renal failure develops at a median age of 19 years, which is 6 years later than in NPHP1.[13] The median age of ESRD in patients with NPHP4 and NPHP5 mutations is 20 years[19] and 13 years,[20] respectively. If renal failure has not developed by the age of 25 years, the diagnosis of recessive NPHP should be questioned and a pedigree analysis should be intensified to exclude dominant MCKD.

In MCKD, terminal renal failure occurs only in adult life. Two different variants are known, MCKD1 and MCKD2, with a median onset of ESRD of 62 years[21] and 32 years[22] respectively (Fig. 15.4).

Extrarenal Associations

The third distinguishing feature among variants of NPHP-MCKD is represented by the degree to which extrarenal associations occur (Table 15.1B[iii]). Extrarenal disease manifestations have only been described in recessive forms. One exception to this rule is the occurrence

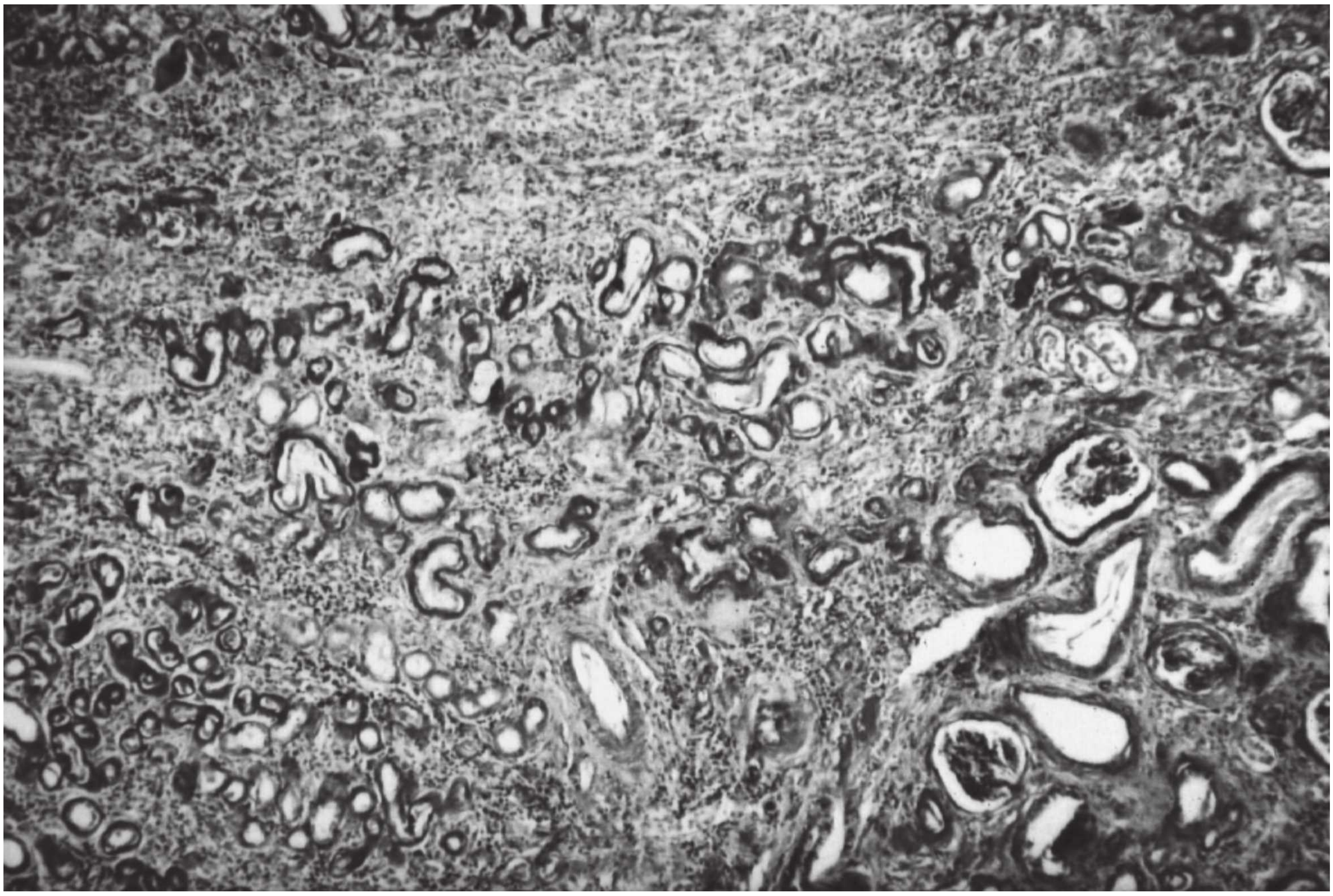


FIGURE 15.2 Renal histology in juvenile nephronophthisis (NPHP1). Note the characteristic triad, which consists of (1) tubular basement membrane disintegration with thickening as well as attenuation of the tubular basement membrane, (2) interstitial round cell infiltration with marked fibrosis, and later on (3) tubular atrophy and cyst development. (Courtesy of Prof. R. Waldherr, Heidelberg, Germany.)

of hyperuricemia and gout in MCKD1[23] and MCKD2.[22] MCKD2 patients with UMOD mutations also may exhibit defects in urine concentrating ability.[24] Recently, an extensive study on genotype–phenotype correlations in mutation of NPHP genes has been published.[25] NPHP1 can occur in combination with ocular motor apraxia Cogan type,[26,27] with retinitis pigmentosa in Senior-Løken syndrome (SLSN),[20] with liver fibrosis[28] with cone-shaped epiphyses in Mainzer-Saldino syndrome,[29] and with coloboma of the optic nerve and cerebellar vermis aplasia in Joubert syndrome type B (JBTSB) (Tables 15.1B[iii] and 15.2).[30] Infantile NPHP (type 2) can be associated with situs inversus[31] and one case report describes a patient with a nonsense inversin mutation with retinitis pigmentosa.[32] NPHP4 patients may have retinitis pigmentosa (SLSN) and Cogan syndrome.[33] NPHP5 patients display early onset retinitis pigmentosa (SLSN) in all known cases.[20] NPHP6 and NPHP8 patients have SLSN, Joubert syndrome, or Meckel-Gruber syndrome (MKS).[25,34,35] NPHP9 is associated with SLSN.[36] NPHP10 patients display SLSN and Bardet-Biedl syndrome (BBS)-like phenotypes,[37] whereas patients with NPHP11 show JBTS, MKS, and liver fibrosis.[38,39] NPHP12 patients exhibit Jeune asphyxiating thoracic dystrophy.[40]

Epidemiology

NPHP and dominant MCKD seem to be distributed evenly among males and females. NPHP has been reported from virtually all regions of the world.[41] Information on the incidence of the disease has been estimated at 9 patients per 8.3 million[42] in the United States or 1 in 50,000 live births in Canada.[1,43] The condition constitutes the most frequent genetic cause for ESRD in the first 3 decades of life and is a major cause of ESRD in children, accounting for 10% to 25% of these patients.[41,44,45] In contrast, in the North American pediatric ESRD population, pooled data indicate a prevalence of less than 5%.[46,47]

MCKD has initially been reported in the United States.[10] Its prevalence in Europe might have been underestimated because recently, kindred have been reported from Cyprus,[23] Italy,[22,48] France,[49] England, Finland,[50,51] Belgium, Czech Republic,[52] and Germany.[53,54] The diagnosis of MCKD may be frequently missed because clinical symptoms and signs are subtle.[55]

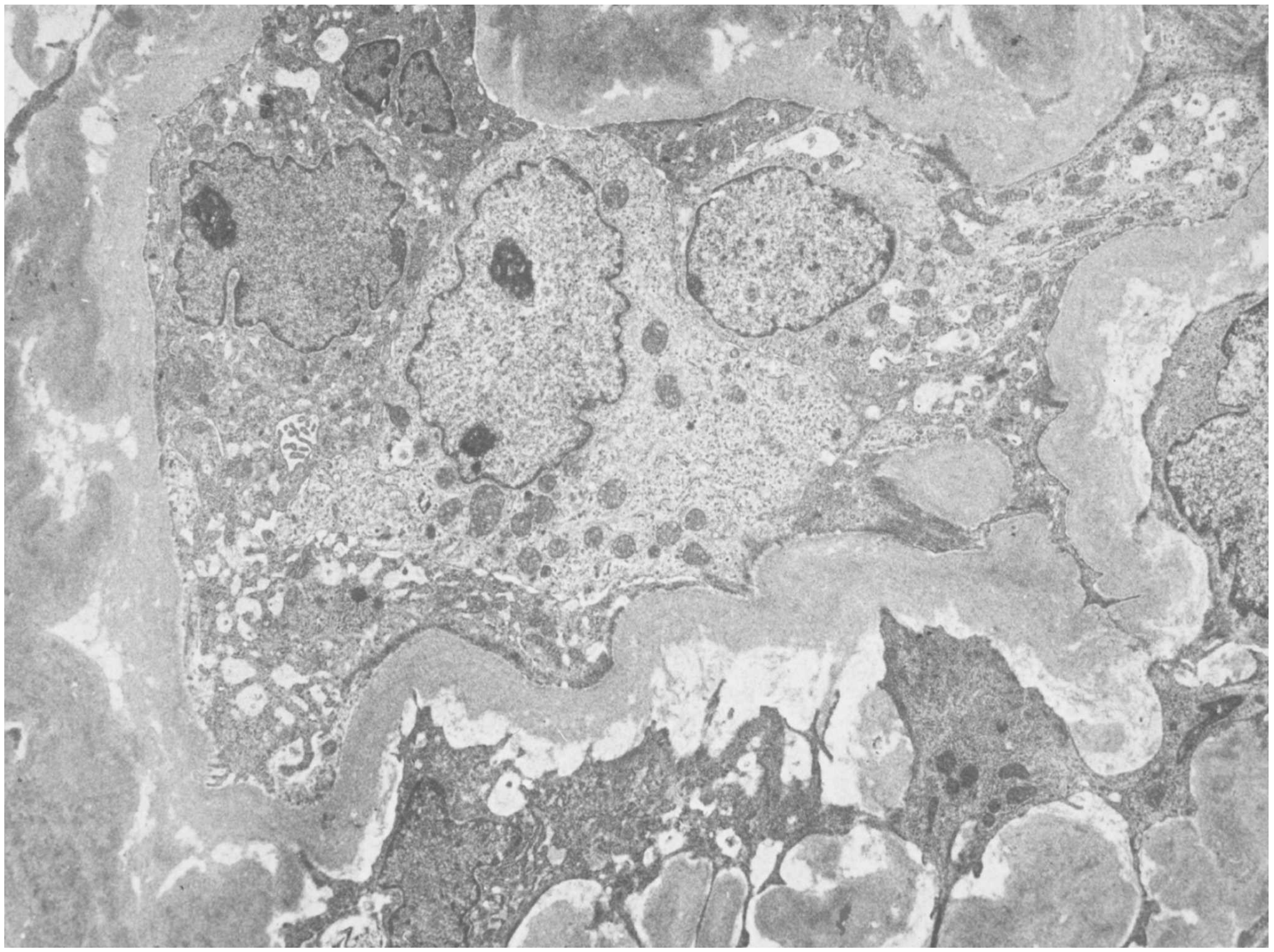


FIGURE 15.3 Thickening, wrinkling, and double layering of tubular basement membranes with intermembranous fibroblasts and dedifferentiation of tubular epithelial cells. An electron micrograph. (Reproduced with permission from Hildebrandt F, Waldherr R, Kutt R, et al. The nephronophthisis complex: clinical and genetic aspects. *Clin Invest* 1992;70:802.)

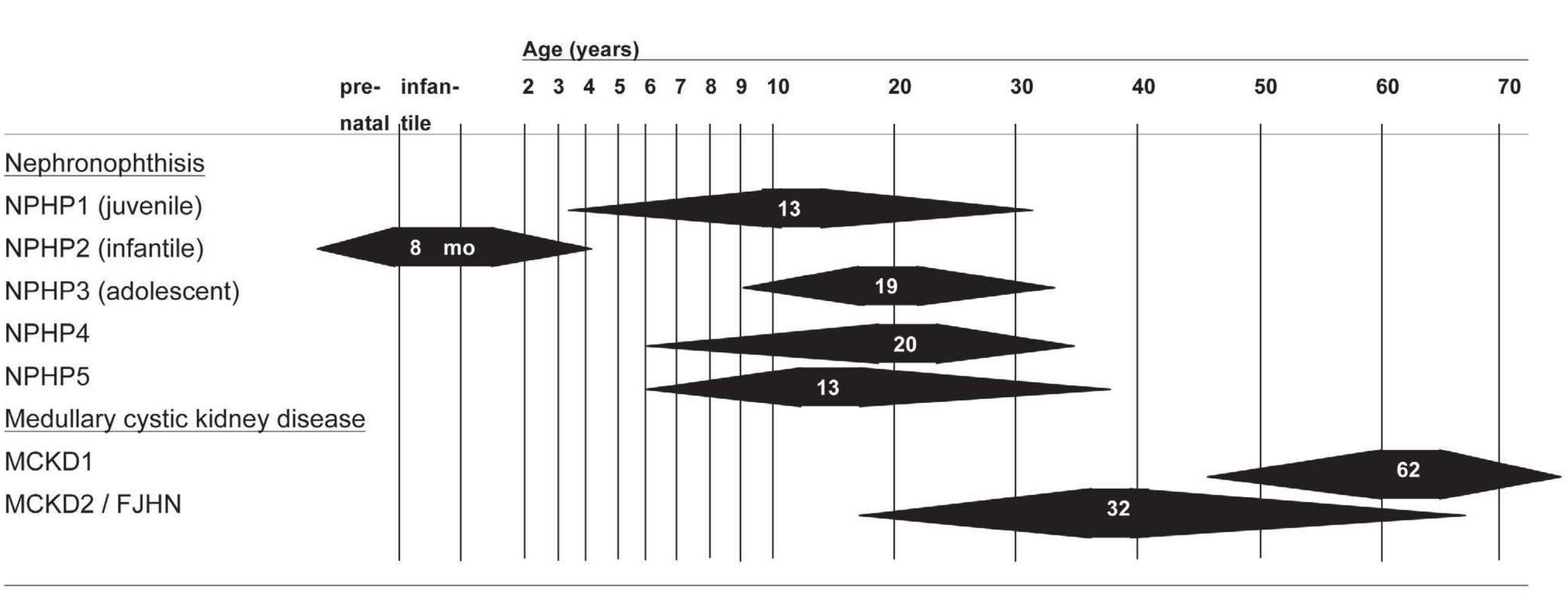


FIGURE 15.4 The time course of renal failure in NPHP-MCKD. Range for age of onset of end-stage renal disease is shown as solid triangles. Numbers indicates median age in years. *NPHP*, nephronophthisis; *MCKD*, medullary cystic kidney disease; *FJHN*, familial juvenile hyperuricemic nephropathy.

MOLECULAR GENETICS OF THE NEPHRONOPHTHISIS-MEDULLARY CYSTIC KIDNEY DISEASE COMPLEX

Classification of disease variants of the NPHP-MCKD complex has recently become more definite through the identification of distinct genes for the different variants. The disease complex is genetically very heterogeneous. Aspects of disease nomenclature, known genes, and extrarenal involvement within the NPHP-MCKD complex are summarized in Table 15.2.

Recessive Disease Variants: Nephronophthisis

Within recessive variants of the NPHP-MCKD complex, the different forms are distinguished on the basis of the mutated gene. To date, thirteen distinct genes (NPHP1–12, NPHPL1) have been identified by positional cloning and massively parallel sequencing.

Nephronophthisis Type 1 (Juvenile Nephronophthisis): Clinical Features

The first case of juvenile nephronophthisis was described by Smith and Graham[56] in 1945. This report of a sporadic case was followed by the publication of two large kindred with familial disease by Fanconi et al.,[57] who introduced the term familial juvenile nephronophthisis. This disease variant is now classified as nephronophthisis type 1 (NPHP1). Since the first description, over 300 cases of NPHP have been published in the literature.[2] NPHP1 is the most common variant within the NPHP-MCKD complex. Penetrance of recessive mutations is 100% by adolescence.

In juvenile NPHP, the symptoms of polyuria, polydipsia, decreased urinary concentrating ability, and secondary enuresis are the earliest presenting symptoms in over 80% of cases[41] and occur at around 4 to 6 years of age. Pallor, weakness, and generalized pruritus are also common. Anemia[51] and, in children, growth retardation occur later and are pronounced. In juvenile NPHP, children usually start to drink regularly at nighttime around age 6 years. This characteristic symptom should actively be sought when taking the patient's history. The mild nature of symptoms, together with a frequent lack of edema, hypertension, and urinary tract infections, characteristically leads to delayed diagnosis and therapy in NPHP-MCKD. Due to the late detection of symptoms, there is a small but definite risk of sudden death from fluid and electrolyte imbalance. For NPHP1, definite molecular genetic diagnosis is possible (see the text that follows). Disease recurrence has never been reported in kidneys transplanted to NPHP patients.[9]

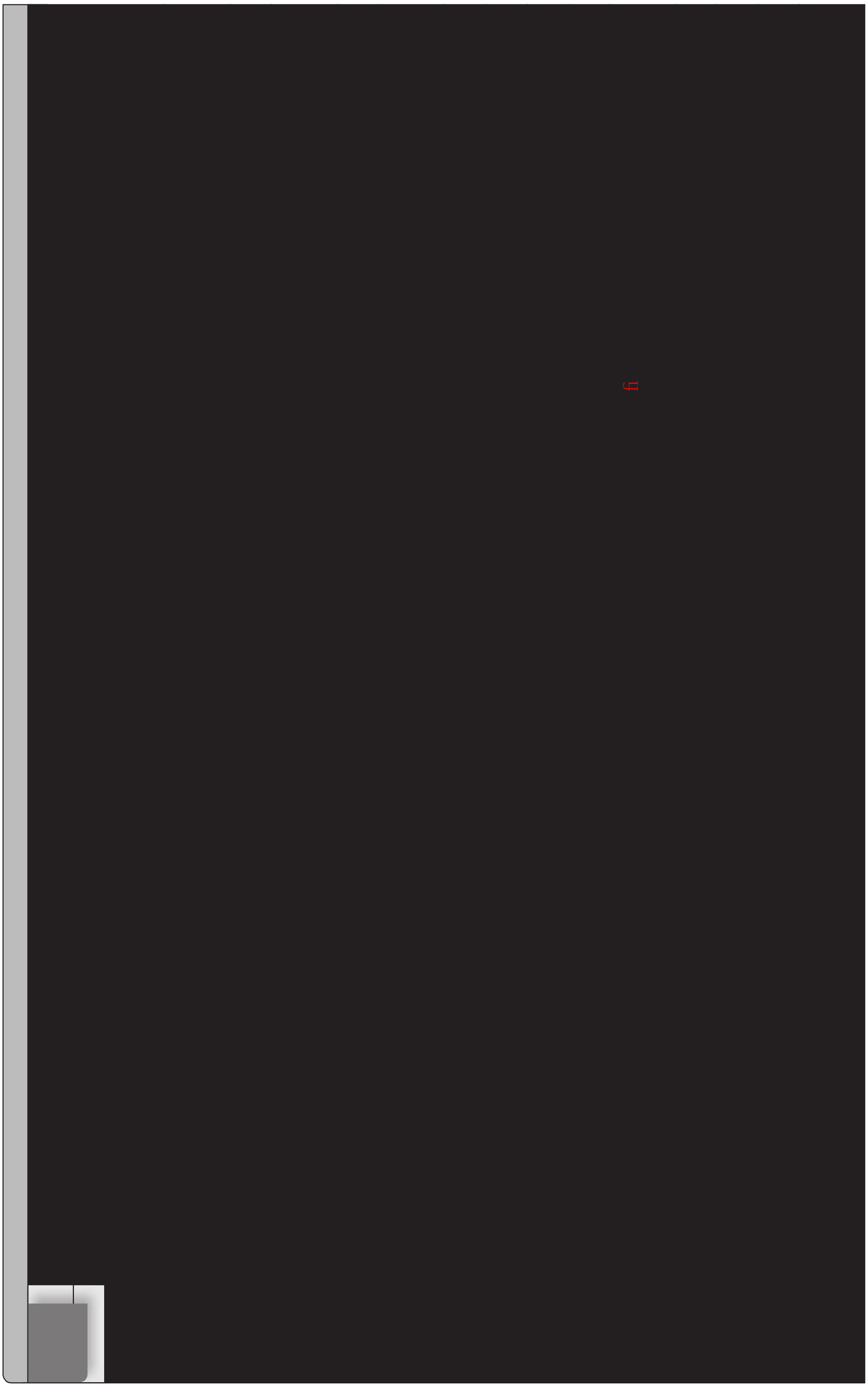
Nephronophthisis Type 1: Molecular Genetics

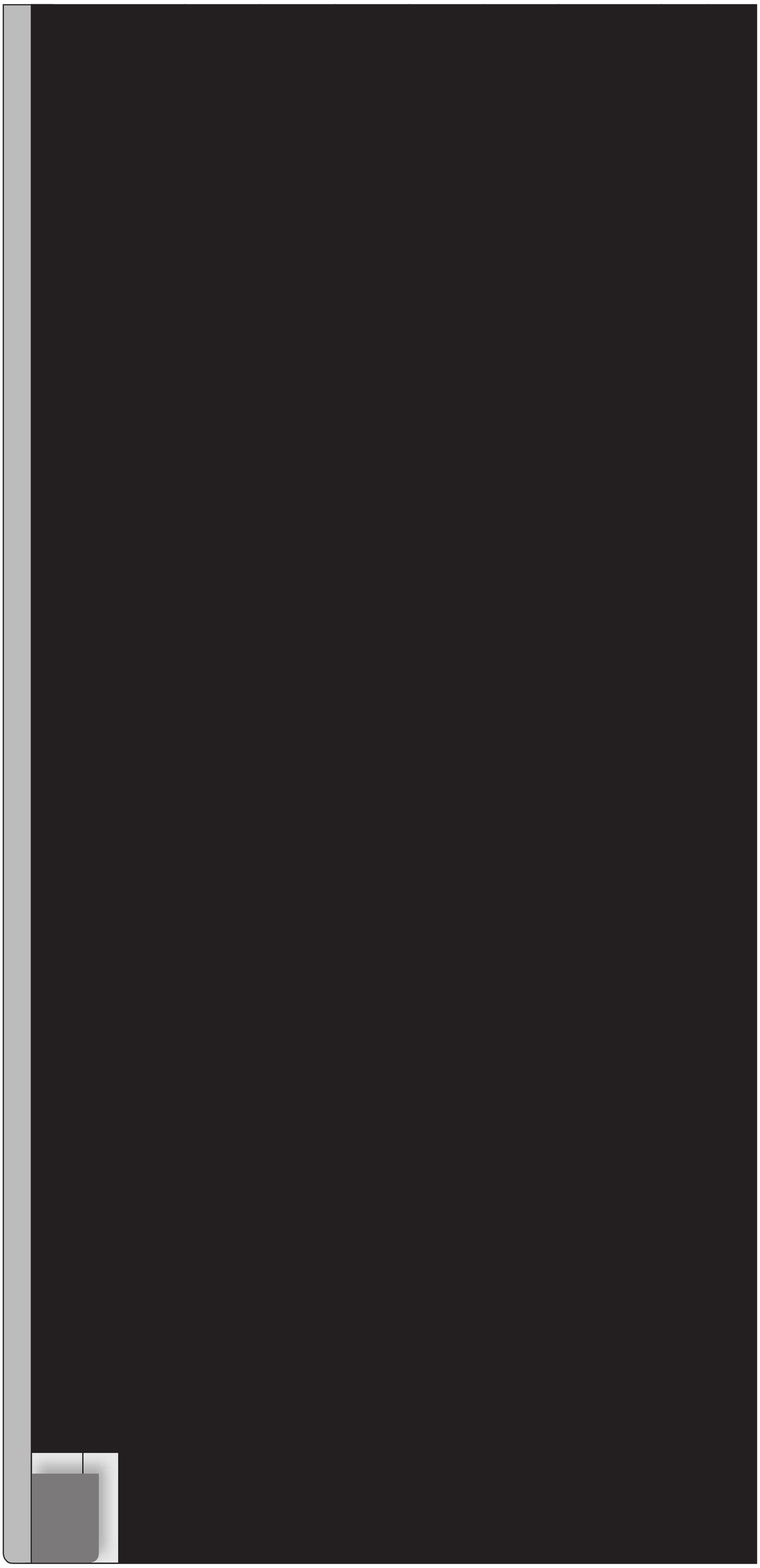
Because little was known about the pathogenesis of NPHP, a positional cloning approach was used for gene identification. By total genome search for linkage, a gene locus for juvenile NPHP1 was mapped to human chromosome 2q12-q13.[58,59] The critical genetic region was subsequently cloned in yeast artificial chromosome (YAC) and P1-derived artificial chromosome (PAC) contigs, which led to the identification of the NPHP1 gene, defects in which are responsible for NPHP1.[60,61] About 66% of children with juvenile NPHP harbor large (250 kb) homozygous deletions of the NPHP1 gene, whereas some carry point mutations in combination with heterozygous deletions.[62–64] Through gene identification, a molecular genetic diagnosis in NPHP1 has become possible (see the text that follows).[64–67]

The NPHP1 gene spans 83 kb, consists of 20 exons, and encodes an mRNA of 4.5 kb. It 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 NPHP1 gene, is repeated directly within the telomeric inverted duplication. In several NPHP1 families, the deletion break points have been localized to the 45 kb direct repeats using pulsed field gel electrophoresis.[63] Chromosomal misalignment followed by unequal crossing over or the formation of a loop structure on a single chromosome has been suggested as a potential cause for these deletions. In addition, there is a high degree of further rearrangements known to occur in this region of chromosome 2.[63] Furthermore, an unusual maternal deletion in a child with NPHP1 molecularly characterized, showing that the centromeric break point occurred within a long interspersed nuclear element-1 (LINE1).[68] The NPHP1 gene is a novel gene, which is not related to any known gene families. Expression studies in humans and mice revealed a broad tissue expression pattern. 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 postconception.[69] In the adult mice, there was also a strong expression in testes.

Nephronophthisis Type 2

A second gene locus (NPHP2) for recessive NPHP has been localized to chromosome 9q31.1 in a large Bedouin pedigree by homozygosity mapping (Table 15.2).[14] This disease variant is termed infantile nephronophthisis (NPHP2) due to its prenatal, perinatal, or infantile onset. The clinical course and histology in this disease are quite different from other forms of NPHP.[70] The inv mouse model, in which a disruption of the protein inversin led to a consistent reversal of the left–right body axis,[71] was noted to have cystic kidney disease.[72,73] These observations led to the identification of inversin (INVS) as the gene mutated in NPHP2 with and without situs inversus.[31] INVS encodes a 1,062 amino acid protein containing 16 ankyrin repeats, a nuclear localization signal, and an IQ calmodulin domain.[74] Yeast two-hybrid and coimmunoprecipitation experiments have confirmed the interaction between inversin and calmodulin. By a knockdown of inversin expression in zebra fish, a polycystic kidney disease (PKD)-like phenotype in addition to a randomization of heart looping was observed.[31]





Inversin localizes to primary cilia, mitotic spindles, and centrosomes[74] and is intimately associated with the microtubule cytoskeleton.[75] INVS/NPHP2 mutations remain a rare cause of NPHP, accounting for <1% of cases.

Nephronophthisis Type 3

A third locus (NPHP3) for NPHP was mapped to chromosome 3q22.1 in a large Venezuelan kindred by a total genome search for linkage by applying the strategy of homozygosity mapping (Table 15.2).[13,76,77] This disease variant was termed adolescent nephronophthisis (NPHP3) because the onset of ESRD occurs 6 years later than in juvenile NPHP1, with a median onset of terminal renal failure occurring at age 19 years (Fig. 15.4).

Identification of the gene NPHP3, which causes adolescent NPHP, was carried out in the same Venezuelan kindred.[78] The novel NPHP3 protein interacts with nephrocystin-1. NPHP3 mutations were found in patients with isolated MPHP and in families with NPHP and hepatic fibrosis or tapetoretinal degeneration. Murine Nphp3 was shown to be expressed in the embryonic node, kidney tubules, retina, respiratory epithelium, liver, biliary tract, and neural tissues. A homozygous missense mutation in Nphp3 was identified as the underlying defect in the polycystic kidney disease (pcy) mouse phenotype.[78]

Nephronophthisis Type 4

By a total genome search for linkage, a fourth gene locus (NPHP4) was localized to chromosome 1p36,[79] including a family with SLSN. The respective gene (NPHP4) was subsequently identified as causing NPHP type 4 and SLSN type 4.[19,33] The gene and its gene product, nephroretinin/nephrocystin-4, are highly conserved in evolution. Nephrocystin-4 protein expression has been demonstrated in primary cilia, centrosomes, and near the cortical actin cytoskeleton, showing partial colocalization with β-catenin in polarized MDCK cells.[33] Co-immunoprecipitation experiments showed that nephrocystin, p130Cas, and Pyk2 are in a complex with nephrocystin-4.[33] More recently, it was demonstrated that NPHP4, in conjunction with NPHP1, interacts with the conserved polarity complex PALS1/PATJ/Crb3.[80] This data may reconcile the involvement of the nephrocystin complex of proteins in both, at the adherens junction and at the cilia/centrosomes (Fig. 15.5).

Nephronophthisis Type 5

NPHP5 (ICQB1) is a novel gene, which was identified by positional cloning as a cause of NPHP type 5.[20] All of the mutations found in NPHP5 and its protein product, nephrocystin-5, are the result of truncating mutations. Interestingly, all mutations were associated with the presence of early onset SLSN/retinitis pigmentosa where blindness occurred before the third year of life.[20] The nephrocystin-5 protein directly interacts with calmodulin and is in a protein complex with the retinitis pigmentosa GTPase regulator (RPGR), thus explaining the renal–retinal phenotype of the disease.

Nephronophthisis Type 6

By positional cloning, mutations in NPHP6 (CEP290) were identified as causing NPHP type 6.[81,82] Patients with truncating NPHP6 mutations displayed JBTS phenotype (JBTS6), whereas missense mutations caused SLSN. NPHP6 was shown to regulate the activity of the cAMP-regulated transcription factor CREB2/ATF4, suggesting that the loss of NPHP6 function leads to aberrant gene expression that may contribute to disease progression in NPHP6.[81] A direct interaction between NPHP5 and NPHP6 was demonstrated in zebra fish, where the depletion of either gene led to almost identical phenotypes.[83]

Nephronophthisis Type 7

Mutations in NPHP7 (GLIS2) have been identified in a single family as causing NPHP type 7.[84] GLIS2 is a transcription factor that negatively regulates the Sonic hedgehog pathway mediator GLI1 transcriptional activity by binding to GLI-binding sites.[85] NPHP7 activity is required in the adult kidney to suppress the Shh pathway activation. Loss of Nphp7 leads to the inactivation of the Snail and Wnt4 genes, which in turn initiates tubular dedifferentiation and epithelial-to-mesenchymal transition in the kidney, resulting in intestinal fibrosis.[86] NPHP7, together with NPHP6, is the second NPHP gene that is implicated in gene expression and regulation.

Nephronophthisis Type 8

Mutations in NPHP8 (RPGRIP-like 1, [RPGRIPL1]) were shown to cause NPHP type 8 in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel-Gruber syndrome.[35,87,88] Mutations in NPHP8 cause a wide range of phenotypes.[25]

Nephronophthisis Type 9

Homozygous mutations in NPHP9 (never in mitosis A-related kinase 8 [NEK8]) were shown to cause NPHP type 9.[36] NEK8 interacts and colocalizes with NPHP2/INV and NPHP3 to the proximal segment of the primary cilia.[89] The interaction of NEK8 with the autosomal dominant polycystic kidney disease (ADPKD) protein PKD2 suggests that NEK8 may regulate both the expression and posttranslational modification (phosphorylation) of both PKD1 and PKD2.[90]

Nephronophthisis Type 10

Mutations in the NPHP10 (SDCCAG8) gene were recently identified by candidate exome capture and massively parallel sequencing as causing NPHP type 10.[37] All patients carried two truncating mutations and developed juvenile NPHP with associated retinitis pigmentosa (SLSN). Interestingly, some patients presented Bardet-Biedl syndrome-like features, including obesity and hypogonadism.[37]

Nephronophthisis Type 11

Homozygous and compound heterozygous missense mutations in the NPHP11 (transmembrane protein 67 [TMEM67/MKS3]) gene were shown to cause NPHP type 11.[39] Similar

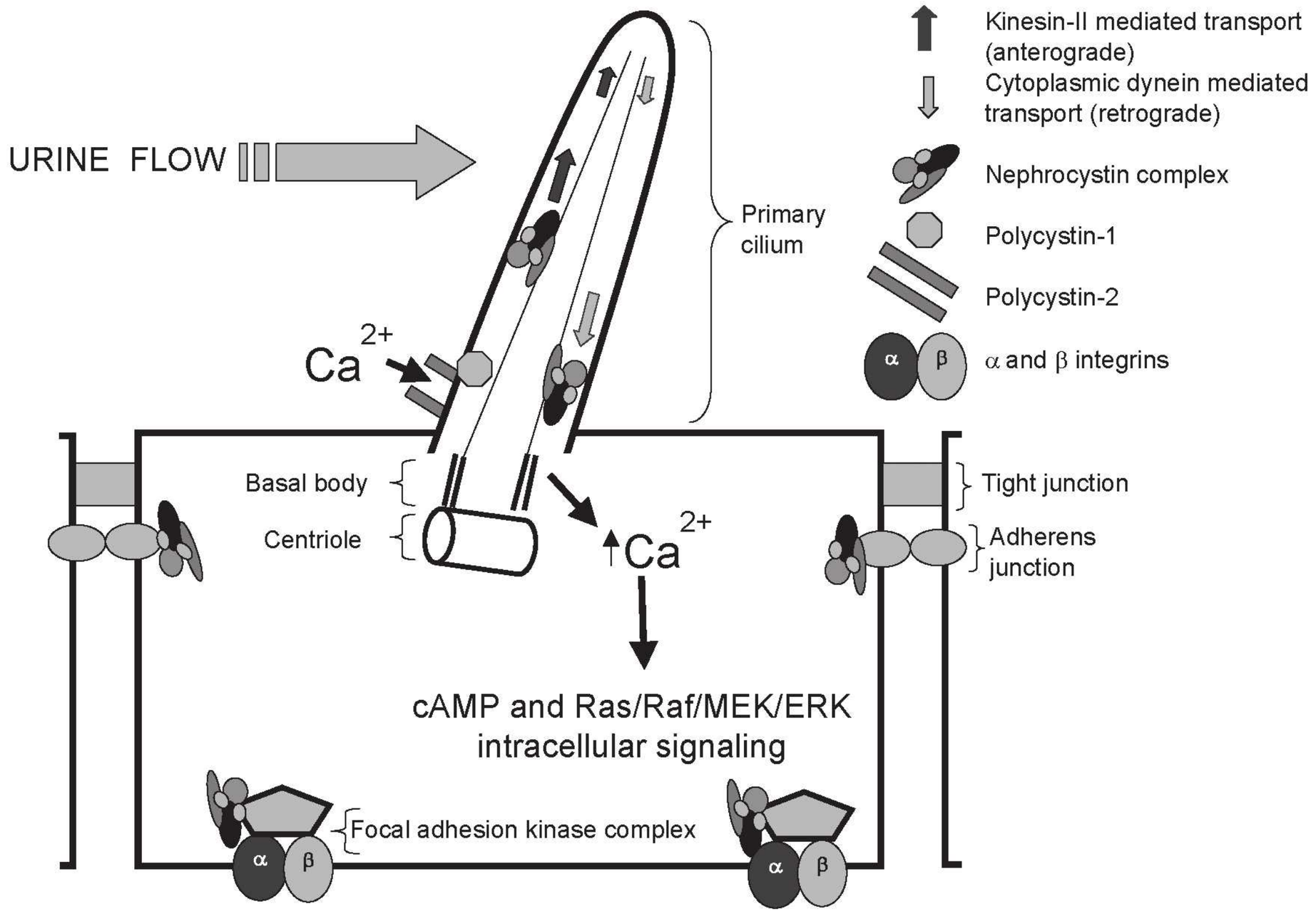


FIGURE 15.5 Localization of the nephrocystin complex to the renal epithelial cell primary cilium, the adherens junction, the focal adhesions, and the microtubule organizing centers (centrosomes). A primary renal cilium is shown bending as a result of urinary flow. Fluid shear forces lead to an increase in intracellular calcium, mediated by calcium permanent channels, such as polycystin-2, localized to the surface of the cilia. This initial calcium influx may lead to multiple downstream effects including calcium-induced calcium release, targeted fusion of cytoplasmic vesicles with the plasma membrane, protein kinase signaling cascades, and gene expression, which may modulate cellular proliferation, differentiation, and apoptosis. (Modified from Nauli SM, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003;33:129; and Praetorius HA, Spring KR. Bending the MDCK cell primary cilium increases intracellular calcium. *J Membr Biol* 2001;184:71.) Nephrocystin complexes are shown within the cilium, where they are moved up the cilium by intraflagellar transport protein complexes (kinesin-II) and down via the cytoplasmic dynein. The precise function of the nephrocystin complex within the cilium remains to be established. In addition to the cilium, inversin and nephrocystins have been localized to the adherens junctions, the centrosomes, and the nucleus (not shown). Nephrocystin complexes are also shown localized to the focal adhesion kinase complex, which includes proteins, such as pyk2 and p130Cas, and binding partners of nephrocystin-1 and nephrocystin-4. (Modified from Mollet G, et al. Characterization of the nephrocystin/nephrocystin-4 complex and subcellular localization of nephrocystin-4 to primary cilia and centrosomes. *Hum Mol Genet* 2005;14:645; and Benzing T, et al. Nephrocystin interacts with Pyk2, p130 (Cas), and tensin and triggers phosphorylation of Pyk2. *Proc Natl Acad Sci USA* 2001;98:9784.) Cell adhesion signaling events and polarity may be regulated by the nephrocystin complex at this location.

to NPHP3, NPHP6, and NPHP8, mutations in NPHP11 can cause a syndromic ciliopathy, with phenotypes ranging from SLSN and JBTS to MKS.[91]

Nephronophthisis Type 12

NPHP12 (tetratricopeptide repeat domain 21B [TTC21B]) is a novel gene that has very recently been identified as the cause of NPHP type 12.[40] Because mutations in NPHP12 were identified in 5% of other ciliopathy cases, it was suggested that NPHP12 mutations may have a role as genetic modifier mutations in ciliopathies.[40]

Nephronophthisis-like 1

Mutations in the XPNEPEP3 (X-prolyl aminopeptidase 3) gene were shown to cause an NPHP-like 1 (NPHPL-1) nephropathy.[92] Unlike other NPHP proteins, the NPHPL-1 gene product does not localize to the primary cilia or centrosomes. Instead, the enzyme XPNPEP3 harbors a mitochondrial leader sequence and localizes to mitochondria.[92] Possible involvement of NPHPL-1 in ciliary function is suggested by the presence of putative XPNPEP target sequences on several centrosomal proteins, including NPHP6/CEP290.[92]

Nephronophthisis with Extrarenal Associations

With the exception of the occurrence of hyperuricemia and gout in MCKD, extrarenal disease manifestations have only been described in recessive forms of nephronophthisis (Tables 15.1B and 15.2). Ocular motor apraxia Cogan type is a transient inability of horizontal eye movements occurring in the first few years of life. This has been described in patients with mutations in NPHP1[26,27] or NPHP4.[33]

SLSN, represented by a concomitant occurrence of NPHP with retinitis pigmentosa, was first described by Contreras et al.,[93] Senior et al.,[94] and Løken et al.[95] The designation SLSN seems more appropriate than the term retinal-renal dysplasia, because both renal and retinal changes are degenerative rather than dysplastic.[96] In NPHP types 1 through 4 retinitis pigmentosa occurs in about 10% of all affected families. In NPHP type 5, all patients exhibited early onset retinitis pigmentosa,[20] whereas in NPHP type 10, nearly all patients display late onset retinitis pigmentosa.[37] Retinitis pigmentosa is diagnosed by its specific findings on an ophthalmoscopy including increased pigment, attenuation of retinal vessels, and pallor of the optic disc, and is coupled with the results of an electroretinography and electrooculography. Retinal degeneration is characterized by a constant and complete extinction of the electroretinogram, which precedes the development of visual and funduscopic signs of retinitis pigmentosa.[97,98] The early onset and the late onset type of SLSN have been distinguished. The early onset type seems to represent a form of a Leber congenital amaurosis because children exhibit coarse nystagmus and/or blindness at birth or within the first 2 years of life.[99] Funduscopic alterations are present in all SLSN patients by the age of 10 years. The late onset form is characterized by the development of blindness during the school age years after a preceding night blindness. Other eye symptoms besides tapetoretinal degeneration include nystagmus, myopia, and coloboma of the choroidea.[57] The age of onset, symptoms, and a histology of renal disease is identical to what is known from patients with juvenile nephronophthisis without ocular involvement.

The association of NPHP with the degenerative phenotype of liver fibrosis was first noted by Boichis et al.,[28] and was later also reported by others.[100–102] All patients had hepatomegaly and moderate portal fibrosis with mild bile duct proliferation. This pattern differs from that of classical congenital hepatic fibrosis, where biliary dysgenesis is prominent. Cases with skeletal changes, predominantly in the form of cone-shaped epiphyses (type 28 and 28A) are known as Mainzer-Saldino syndrome, and were first published by Mainzer et al.[29] in combination with cases of retinal degeneration and cerebellar ataxia. Recessive mutations in the NPHP3, NPHP4, NPHP6, NPHP8, and NPHP11 genes have been described in patients with NPHP and liver degenerative phenotypes[25,78] where NPHP11 mutations seem to be the most frequently associated.[39]

In Joubert syndrome type B (JBTS), a developmental disorder with multiple organ involvement, NPHP occurs in association with coloboma of the eye or retinal degeneration, aplasia of the cerebellar vermis with ataxia, the facultative symptoms of psychomotor retardation, and neonatal tachy/dyspnea.[30,103,104] A diagnostic feature of Joubert syndrome on an axial magnetic resonance imaging (MRI) of the brain is prominent superior cerebellar peduncles, termed the molar tooth sign (MTS).[104] Thirteen genes have now been shown to cause Joubert syndrome. NPHP1 gene defects are a rare cause of Joubert syndrome in a subset of patients with NPHP.[105] Additionally, patients with mutations in NPHP3, NPHP6, NPHP8, NPHP11, and NPHP12 genes display JBTS.[25,35,39,40,81] A homozygous deletion of NPHP1 was found in two siblings and in a third patient with mild features of Joubert syndrome type B. The second gene defect was found in the Abelson Helper Integration Site (AHI1) gene, and its protein product has been termed Jouberin. The Jouberin protein has three known isoforms and possesses a coiled coil domain, at least six WD40 domains, and an SH3 domain. It is thus likely to be part of the nephrocystin complex of proteins. In the initial reports of AHI1 mutations, the phenotype included cerebellar abnormalities, but no renal phenotype was reported. Recently, Jouberin mutations were detected in patients with NPHP and JBTS.[106]

Additional phenotypes have been described in association with NPHP. These include Jeune syndrome (asphyxiating thoracic dysplasia)[107–109]; Meckel-Gruber syndrome[25,35,91]; Ellis van Creveld syndrome[110]; ulcerative colitis[111]; retinitis pigmentosa, hypopituitarism, nephronophthisis, and mild skeletal dysplasia (RHYNS) syndrome[112]; Alstrom syndrome[113]; Sensenbrenner syndrome[114–117]; and Arima syndrome.[118,119]

BBS[120,121] has been reported to exhibit renal histology findings reminiscent of NPHP. Recently, it was shown by using candidate exome capture and massively parallel sequencing that mutations in SDCCAG8/NPHP10 cause BBS-like phenotype (without polydactyly) in NPHP type 10 patients.[37] Gene identification of NPHP genes has revealed that the molecular relation between these diseases may lie in the expression of the respective gene products in primary cilia, basal bodies, or centrosomes of renal epithelial cells.[2]

Animal Models of NPHP

Genetic animal models resembling NPHP have been fruitful in the identification of underlying gene defects, and more recently in the experimental treatment of cystic kidney disease.

The Invs gene, when mutated, gives rise to renal cysts as well as left–right asymmetry, cardiovascular defects, hepatobiliary defects, and premature death in inv/inv knockout mice.[72,122] Collecting ducts of newborn inv/inv mice demonstrate diffuse cystic dilatation.[123] Mutations in INVS give rise to human NPHP type 2, with and without situs inversus. The pcy mouse model[123] demonstrates interstitial fibrosis and cystic kidneys. The underlying defect was shown to be a missense mutation in the Nphp3 gene.[78] Recently, mouse

models of Nphp1,[124] Nphp4,[125] Nphp7/Glis2,[86] and Nphp9/jck[126] have been reported. Unexpectedly, the phenotype of Nphp1$^{-/-}$ mice is relatively mild, affecting only spermatogenesis.[124] Another study, with a different Nphp1 knockout design, uncovered an epistatic relationship between Nphp1 and Ahi in regulating the severity of retinal degeneration phenotype first in mice and then in humans,[127] underlining the strength of the animal models in studying the pathomechanisms of NPHP. Similarly to Nphp1 knockout mice, homozygous mutant Nphp4 mice do not display renal phenotype, but present a severe retinal degeneration and male infertility phenotype.[125] The Nphp7 knockout mouse model has been instrumental in deciphering the underlying molecular defects causing NPHP7 by showing that the derepression of Sonic hedgehog (Shh) signaling in the adult kidney leads to epithelial to mesenchymal transition and, ultimately, interstitial fibrosis—the disease phenotype in NPHP7 patients.[84,86] The juvenile cystic kidney (jck) mouse model has been used extensively as a model for PKD, and its renal phenotype is caused by a recessive missense mutation in the Nphp9 gene.[126] This model has been fruitful for testing different modalities to ameliorate renal cystic disease progression. It was shown that cyst formation in jck mice can be suppressed by treatment with the CDK inhibitor roscovitine[128] or the glycosylceramide synthase inhibitor.[129]

The kd (kidney disease) mouse strain has also been reported as a genetic animal model of NPHP.[130,131] It shares several clinical and histologic[131] features with human NPHP. The mice are born healthy, but by 8 weeks of age, they develop severe interstitial nephritis that progresses to ESRD by 4 to 8 months of age. The defect is caused by a mutation of a gene that encodes a mitochondrial protein, namely prenyltransferaselike mitochondrial protein (PLMP).[132] Kd/kd mice were shown to have dysmorphic mitochondria within renal tubular epithelia.[132] Additional transgenic mouse models for NPHP, such as the tensin knockout mouse,[132] the bcl-2 knockout mouse,[133–135] and the Ace knockout mouse[136] will hopefully aid our understanding of the pathophysiology of NPHP.[137] A canine model of NPHP has also been reported.[31,138–140]

The Pathogenic Hypotheses of Nephronophthisis

The identification of mutations in the inversin gene, which cause NPHP type 2, established a link between the pathogenesis of NPHP to disease mechanisms of PKD.[31] The knockdown of invs in the zebra fish embryo causes a renal cystic phenotype. In addition, the positional cloning of the novel gene NPHP3, mutated in adolescent NPHP (type 3) and in the renal cystic mouse model pcy,[123] confirmed this paradigm. Nephrocystin interacts with both inversin and with b-tubulin, with colocalization of all three proteins in the primary renal cilia of epithelial cells.[74] Inversin was also shown to be localized to mitotic spindles and centrioles.[74] The IQ calmodulin-binding motif containing protein-1 (IQCB1), also known as nephrocystin-5, also reveals a ciliary and basal body colocalization.[20] All NPHP proteins identified so far share the localization to cilia, centrosomes, or the basal body, with the exception of mitochondrial NPHPL1. The finding that such nephrocystins colocalize to primary cilia, basal bodies, or centrioles together with other proteins that, if defective, cause renal cystic diseases, suggests a role within a functional module shared with other proteins (Fig. 15.5). Therefore, recently, a unifying hypothesis of renal cystogenesis has been established, thus characterizing renal cystic diseases as ciliopathies.[141] This hypothesis states that proteins, which, if mutated, cause renal cystic disease in humans, mice, or zebra fish, are part of a functional module, as defined by their subcellular localization to primary cilia, basal bodies, or centrioles.[2] This applies to polycystin-1 and -2, fibrocystin/polyductin, nephrocystin-1, -2 (inversin), -3, -4, -5, BBS-associated proteins, cystin, polaris, ALMS1, oral-facial-digital syndrome type 1 (OFD1), and others. The existence of such functional modules in ciliopathies was recently demonstrated by proteomic studies, showing that NPHP-JBTS-MKS proteins function in distinct modules that are mechanistically connected.[142]

A model of evolutionary conserved proteins involved in cilia has also recently added weight to the "cystogenes" hypothesis. Following identification the NPHP1, 2, and 4 genes, orthologs of these genes in the nematode Caenorhabditis elegans have been identified.[19,60,69] This strong evolutionary conservation of genes that, if defective, cause NPHP in humans, suggests that their products may be part of a functional module conserved in C. elegans. This assumption was also supported by the finding of cell-specific GFP expression under the nephrocystin-1 and -4 promoters in the same cell types of head and tail ciliated neurons, in which the C. elegans orthologs of other renal cyst-causing genes are expressed, such as pkd-1 (lov-1), pkd-2, and polaris (osm 5).[143]

In addition to the ciliary hypothesis, an adherens junction/focal adhesion hypothesis has also been suggested on the basis that nephrocystin-1 contains an SH3 domain.[60,144] This theory is based on the fact that most SH3 domains are found in adapter proteins, which have a function in focal adhesion signaling complexes of cell-matrix contacts.[145,146] Several findings support this hypothesis, such as:

1. Nephrocystin was shown to bind to the protein p130Cas ("crk-associated substrate"),[147–149] which is a major mediator of focal adhesion assembly[145] and to compete for binding with Src and Fyn.[147]
2. In children with NPHP, Rahilly and Fleming[150] described strong $\alpha 5\beta 1$ integrin expression in proximal tubules, from which $\alpha 5$ integrin is normally absent, which most likely results from defective $\alpha 6$ integrin expression. The $\alpha 5\beta 6$ complex is an important receptor for focal adhesion signaling in renal tubular cells.
3. The knockout mouse models for tensin[132] and for the Rho GDIa gene[151] both exhibit an NPHP-like phenotype, thereby implicating proteins of the focal adhesion signal transduction cascade in the pathogenesis of NPHP-like diseases.

Together, these findings may point to a pathogenesis of NPHP, which involves focal adhesion and/or adherens junction signaling processes. Data from Mollet et al.[152] demonstrated, in addition to ciliary and centrosomal localization, that NPHP4 was part of a subplasmalemmal protein complex which included NPHP1, p130Cas, and Pyk2. These data confirm the role of the nephrocystin proteins within both a cilial/centrosomal hypothesis and an adherens junction/focal adhesion hypothesis.

Medullary Cystic Kidney Disease

The first large kindreds of autosomal dominant medullary cystic kidney disease (MCKD) were reported by Goldman and by Gardner.[10,153,154] Dominant MCKD by a renal macroscopic pathology and histology is indistinguishable from recessive NPHP. In MCKD, terminal renal failure develops later than in NPHP, within the seventh decade of life (Fig. 15.4). The only extrarenal associations known to occur with MCKD are hyperuricemia and gouty arthritis, which have been described in the majority of the kindred reported.

Medullary Cystic Kidney Disease Type 1 (MCKD1)

A gene locus for MCKD1 was mapped to chromosome 1q21 in large pedigrees from Cyprus.[21] Further refinement of this locus has been possible using an observed recombinant from within a Belgian kindred,[155] reducing the critical genetic region to 2.1 Mb (Table 15.2). This disease form was associated with hyperuricemia and gout.[23] ESRD occurred at a median age of 62 years (Fig. 15.4).

Medullary Cystic Kidney Disease Type 2 (MCKD2)

A second locus (MCKD2) for medullary cystic kidney disease was localized to chromosome 16p12 (Table15.2).[22,156,157] In this variant, ESRD develops much earlier, at a median age of 32 years (Fig. 15.4). MCKD2 and an autosomal dominant disease formerly known as familial juvenile hyperuricemic nephropathy (FJHN)[158] have been shown to map to the same chromosomal region and suggest that they represent the same disease entity.[159,160] This was confirmed with the identification of mutations within the uromodulin (UMOD) gene in affected patients with phenotypes of FJHN and MCKD2.[161] UMOD encodes the Tamm-Horsfall protein, which is a GPI-anchored glycoprotein and is present abundantly in normal urine. It has been suggested that mutations within UMOD may disrupt the tertiary structure of UMOD.[161] A clustering of UMOD mutations was noted within the highly conserved exon 4 of the encoded sequence of UMOD.[162] An investigation of UMOD mutations in the urine of affected individuals and renal biopsies revealed an abnormal accumulation of uromodulin within tubular cells and reduced urinary excretion of wild-type uromodulin.[163] Glomerulocystic kidney disease (GCKD), characterized by dilatation of the Bowman space and the collapse of the glomerular tuft, is a renal disorder distinct from MCKD/FJHN, although some clinical features are shared. A clinical variant of GCKD demonstrates a reduced fractional excretion of uric acid, resulting in hyperuricemia. A mutation in UMOD was recently described in one family (three patients) with this condition, thus broadening the phenotype associated with UMOM mutations further.[164] Finally, there is evidence for at least one additional locus for MCKD.[53,54]

MOLECULAR GENETIC DIAGNOSIS, IMAGING, AND LABORATORY STUDIES

Molecular Genetic Diagnosis in Nephronophthisis

Nephronophthisis types 1 through 12 can now be unequivocally diagnosed, because direct molecular genetic diagnosis has become available through the identification of the responsible genes (www.renalgenes.org). Molecular genetic analysis is the only diagnostic procedure by which the diagnosis of NPHP can be made with certainty. It should be initiated to noninvasively prove or exclude NPHP before the invasive procedure of renal biopsy is performed. However, due to the presence of additional genes for NPHP, the lack of detection of mutations in NPHP1–12 and NPHPL-1 genes does not exclude the diagnosis of NPHP. In a similar manner, UMOD mutational analysis will allow a precise genetic diagnosis of MCKD2, but a lack of any mutations will not exclude MCKD. Molecular genetic testing should be performed only in the context of genetic counseling and within the guidelines of the National and International Societies for Human Genetics (www.ethics.ubc.ca). Prior to genetic counseling, a thorough pedigree analysis to distinguish recessive (early onset) from dominant (late onset) disease is mandatory, and extrarenal organ involvement should be sought.

Imaging Techniques

Renal ultrasound is a very useful imaging technique in the NPHP-MCKD complex. Kidneys are normal or moderately reduced in size and exhibit, typically, a loss of corticomedullary differentiation and an increased echogenicity. Later in the course of the disease, mostly when patients have reached ESRD, cysts can be detected at the corticomedullary junction (Fig. 15.6).[165–167] Garel and associates[168] have seen medullary cysts in 13 out of 15 children studied at the time of renal failure (mean age: 9.7 years).

Magnetic resonance tomography and computed tomography demonstrate the presence of cysts in MCKD.[169–173] The invasive procedure of renal arteriography is not indicated to demonstrate the presence of medullary cysts,[174] and caution must be exercised when performing contrast studies in patients with renal failure.

Laboratory Studies and Urinary Concentrating Ability

Besides a molecular genetic diagnosis of NPHP1-12, NPHPL-1, and UMOD, there are no chemical laboratory tests in

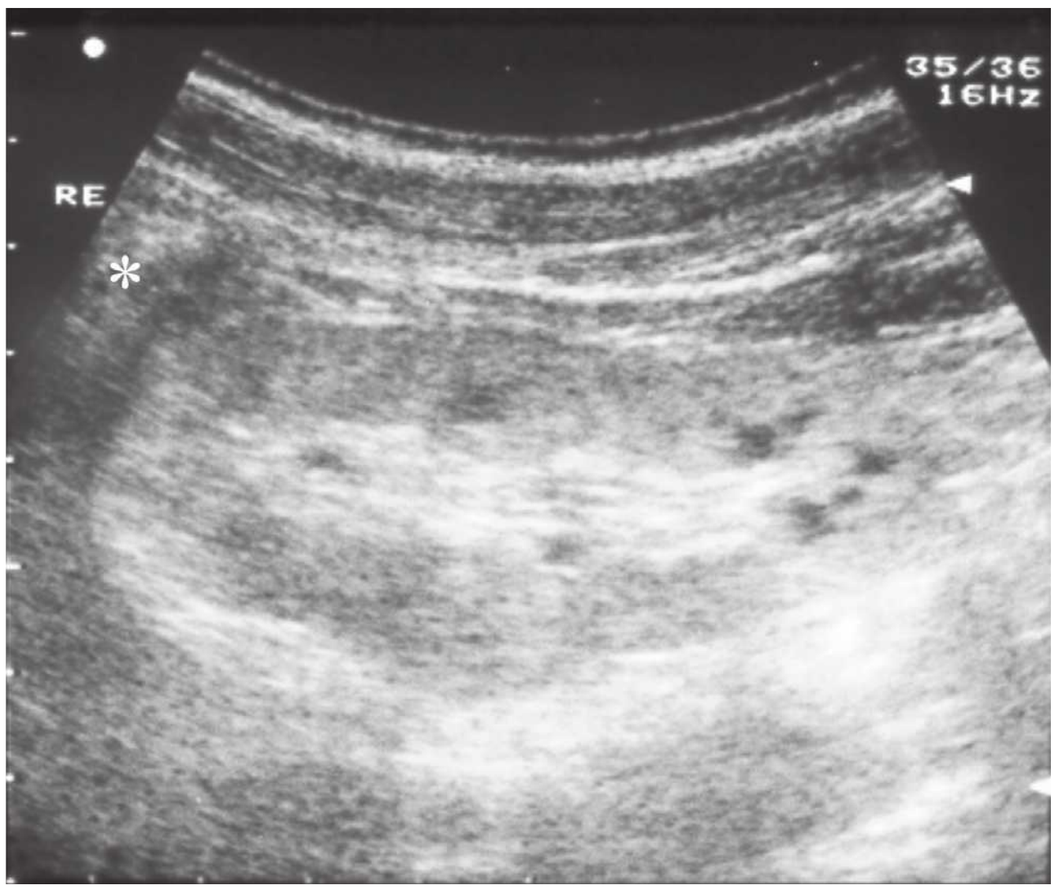


FIGURE 15.6 Characteristic renal ultrasound findings in juvenile nephronophthisis (NPHP1). Note the normal kidney size, the loss of corticomedullary differentiation, and the increased echogenicity, which renders the pattern of the kidney similar to that of the liver (*), together with the presence of cysts at the corticomedullary border of the kidney. (Courtesy of Prof. J. Dippel, Frankfurt, Germany.)

the NPHP-MCKD complex that specifically establish the diagnosis. Hematuria, proteinuria, and bacteriuria are typically absent in NPHP. In rare cases where proteinuria is present, it is usually mild and of the tubular type. Laboratory studies are needed to assess the severity of renal failure and generally demonstrate elevated serum creatinine, blood urea nitrogen (BUN), phosphorus, a metabolic acidosis, and anemia at the characteristic ages of the onset of ESRD for the different disease entities. Ophthalmoscopy should be performed in any patient to exclude SLSN. Liver function and hepatic ultrasonography should also be performed to facilitate the detection of patients with hepatic fibrosis.

A characteristic early finding in NPHP is the decreased ability to concentrate the urine following a water deprivation test.[41] An impairment of tubular function, with the constant finding of a renal concentration defect, usually precedes any documentable reduction in the glomerular filtration rate[10] and may be present with minimal histologic abnormalities.[175]

An intermediate defect of urinary concentration ability has been inconsistently demonstrated in the parents and some siblings of children with NPHP, and has been suggested to reflect the heterozygous state of the disease.[176] An 8-hour water deprivation test or vasopressin administration can be used to demonstrate a tubular concentration defect. Such tests should be performed with caution because dehydration may precipitate acute renal failure in patients with the disease or in unrecognized affected family members. In affected individuals, urine osmolality after 8 hours of water deprivation or vasopressin administration is $<$800 mOsm per kilogram of water. The diseases of the complex have also become known as salt losing nephritis. Poor renal uptake of 99^{m}-technetium-DMSA has been proposed as diagnostic of NPHP.[177]

Differential Diagnosis of Nephronophthisis-Medullary Cystic Kidney Disease

On histopathology, the NPHP-MCKD complex has to be differentiated from other forms of interstitial nephropathies like chronic pyelonephritis or drug injury. In oligomeganephronic dysplasia[178] kidney size is reduced and histology is distinct from NPHP. The paucity of urinary abnormalities, the frequent lack of hypertension, and the localization of renal cysts (if present) readily differentiate variants of the NPHP-MCKD complex from recessive or dominant polycystic kidney disease. Finally, a medullary sponge kidney[179] (see the subsequent text) does usually not lead to chronic renal failure and shows calcifications and calculi on renal ultrasound, and is, therefore, readily distinguishable from the complex.

PROGNOSIS, THERAPY, AND COUNSELING

Therapy of NPHP and MCKD is symptomatic and will pertain to the treatment of hypertension, if present, as well as the correction of disturbances of electrolyte, acid–base, and water balance. Hypokalemia may contribute to the polyuria, so that oral potassium supplementation may alleviate this symptom. Metabolic acidosis should be corrected, and osteodystrophy and secondary hyperparathyroidism should be treated with adequate calcium supplementation, phosphorus restriction or binders, and vitamin D therapy. Anemia can be treated with erythropoietin and growth retardation may require the administration of growth hormone if the diagnosis is made early enough for an intervention. Adequate nutrition (caloric and amino-acid supplementation) should be maintained with the help of a dietician. Salt wasting seems to be more frequent in the phase just preceding the development of end-stage renal disease. Patients are at risk for sudden water and electrolyte disturbances due to the high urinary output and salt loss. In some cases, an event of severe dehydration with acute renal failure can abruptly precipitate chronic renal failure. Sufficient salt and water supplementation is important at this stage, but may have to be restricted because hypertension develops late in the course of renal failure. Psychological counseling of the patients is an integral part of therapy because of the poor self-image associated with growth retardation and to alleviate pressures resulting from the need to comply with complicated medications and dietary prescriptions. All patients will require renal replacement therapy during childhood, adolescence, or in dominant disease, in adulthood.

At present, renal transplantation is the treatment of choice for ESRF associated with both NPHP and MCDK. Stavrou et al.[179] recently reported the outcomes of renal transplantation for 19 patients with MCKD type 1. Five-year graft survival was 90% with no evidence of recurrence of disease or specific complications.

Prior to genetic counseling, a thorough pedigree analysis to distinguish recessive (early onset) from dominant (late onset) disease is mandatory, and diseases other than renal organ involvement should be excluded. Siblings below 13 years of age should be reevaluated yearly by maximal urinary concentrating ability to allow for early detection and early prevention of complications. If a transplant recipient's renal histology suggests NPHP or MCKD and a living related donor is considered, an extensive search should be made to exclude or detect renal disease within the family.

Future therapeutic strategies targeted at renal cyst expansion may lead to the successful delay of ESRD. Vasopressin, a major adenyl cyclase agonist, acts via V2 receptors in the collecting duct. Recently, an antagonist of the V2 receptor (OPC31260) has been shown to inhibit renal cystogenesis in the pcy mouse, which is the murine equivalent of human NPHP3.[180] Clinical trials in patients with NPHP are eagerly awaited. Similarly, the antiproliferative agent rapamycin has been used in the Han:SPRD rat model of polycystic kidney disease, where a reduction in cyst volume density and a preservation of renal function was observed.[181] Thus, additional studies into therapeutic interventions in animal models are necessary to enable the development of therapeutic approaches to NPHP-MCKD.

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