Journal of Pediatric Genetics 3 (2014) 103–114
DOI 10.3233/PGE-14086
IOS Press

Nephronophthisis

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Received 2 May 2014
Revised 7 June 2014
Accepted 9 June 2014

Abstract. Nephronophthisis (NPHP) is a childhood cystic kidney disease, which almost invariably leads to end-stage renal disease in those affected. Recognition and diagnosis requires clinical suspicion, biochemical evaluation, renal imaging and historically, renal biopsy. Modern molecular genetics now allows a diagnosis to be made in a significant proportion of cases. Mutations in *NPHP1* account for 20% of cases, but the disease is genetically heterogeneous with at least 20 different genes associated with NPHP. Recent developments in the fields of genetics and proteomics have led to increased understanding of the underlying pathogenetic defects. Almost all NPHP genes encode proteins, which localize to the primary cilia, basal body and centrosome. NPHP is a therefore considered to be a ciliopathy, and can be part of a broad spectrum of clinical disease that includes extra-renal manifestations including retinal degeneration, cerebellar ataxia, liver fibrosis and situs inversus. In this review, we discuss the historical descriptions of NPHP in the context of more recent developments in our understanding of this disease.

Keywords: Nephronophthisis, ciliopathy, cystic kidney disease, end-stage renal disease

1. Introduction

Nephronophthisis (NPHP) is an autosomal recessive kidney disease and is a leading genetic cause of end-stage renal disease (ESRD) in the pediatric population [1]. The features of nephronophthisis were first described histologically by Smith and Graham [2] in 1945 in the post mortem examination of an 8-year-old girl presenting with refractory anemia and renal failure. The term familial juvenile nephronophthisis was later coined by Fanconi et al. [3] in 1951. Subsequently, infantile [4], adolescent [5] and late onset (with age of ESRD beyond the third decade) [6, 7] forms of NPHP have been described in the literature. The division of infantile versus other subtypes, based on the age of presentation, is still helpful to a degree, as it gives an indication of the most likely molecular defect. There are sometimes significant and important extra renal phenotypes that allow NPHP to be distinguished from its histopathological mimic medullary cystic kidney disease, which is autosomal dominantly inherited and where the only known extra renal manifestation is gout [8]. Also the differential diagnosis may include other ciliopathies associated with cystic kidney disease (CKD) (Table 1).

Since the original descriptions of NPHP, where the pathogenesis was completely unknown there have been significant advances in our knowledge concerning the molecular pathogenesis of this disease [9]. We now realize that this condition is genetically very heterogeneous. There are more than 20 genetic causes of NPHP, with *NPHP1* mutations being the most frequent form of NPHP and explaining 20% of cases [10]. As genetic analysis becomes more easily available, this list of known genetic causes of NPHP is likely to grow

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Table 1
Comparison of NPHP with MCKD and other ciliopathies

Diagnosis	NPHP	MCKD	ARPKD	ADPKD	OFD1
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal recessive	Autosomal dominant	X-linked dominant
Gene(s)	*NPHP* genes	*MUC1* (MCKD1) *UMOD* (MCKD2)	*PKHD1*	*PKD1 PKD2*	*OFD1*
Extrarenal associations	Retinal degeneration, cerebellar vermis aplasia, gaze palsy, liver fibrosis, situs inversus, skeletal defects	Gout	Congenital hepatic fibrosis	Polycystic liver, subarachnoid hemorrhage, cysts in pancreas/ spleen, diverticulosis	Face, oral cavity and digit abnormalities
Radiological features	Small or normal sized hyperechogenic kidneys, corticomedullary cysts (except infantile variant)	Small or normal sized hyperechogenic kidneys, corticomedullary cysts	Polycystic kidneys	Polycystic kidneys (1% may present antenatally)	Polycystic kidneys
Median age of ESRD	Usually under 30 yr	16–80 yr (*MUC1*) 30–50 yr (*UMOD*)	Variable	54 yr (*PKD1*) and 74 yr(*PKD2*)	Lethal in males and variable in females (11–70 yr)

NPHP = Nephronophthisis; MCKD = Medullary cystic kidney disease; ESRD = End-stage renal disease; ARPKD = Autosomal recessive polycystic kidney disease; ADPKD = Autosomal dominant polycystic kidney disease; OFD1 = Oral-facial-digital syndrome 1.

[11]. Both gene discovery and mechanistic insights have revealed that NPHP is a ciliopathy, given that the protein products of almost all mutated genes localize to the basal body complex, centrosome or cilium [9].

2. Clinical, histological and genetic classification of NPHP

NPHP is a slowly progressive form of renal failure, and literally means disappearance or disintegration of nephrons [12]. The clinical symptoms of NPHP, which reflect loss of tubular function [13] are typically polyuria, polydipsia, secondary enuresis and growth retardation. ESRD almost invariably occurs. Cases may be classified based on the age of onset of ESRD as infantile, juvenile, adolescent and late onset.

2.1. Infantile NPHP

Infantile NPHP is rare but is noteworthy due to its severe phenotype with ESRD typically occurring during the first year of life [4]. There may be antenatal presentation with oligohydramnios. It is usually caused by mutations in *INVS* [14] and *NPHP3* [15]. The kidney phenotype is markedly different from other varieties of NPHP, where characteristically large kidneys with large renal cysts (as opposed to micro and small corticomedullary cysts) are seen. Histologically, infantile NPHP lacks the tubular basement membrane changes seen in other NPHP phenotypes and may resemble autosomal dominant polycystic kidney disease. There may also be severe cardiac anomalies including situs inversus and ventricular septal defects [16]. There has been a recent report of an extremely severe phenotype presenting with enlarged cystic kidneys at a prenatal scan at 22 wk of gestation. The complex phenotype in this family was explained by a homozygous nonsense mutation in the *INVS* gene [17].

2.2. Juvenile NPHP

Juvenile NPHP is the classical form of NPHP and is characterized by symptoms in patients within the first decade of life and ESRD at a mean age of 13 yr [10]. The histological and molecular genetics features are discussed below.

2.3. Adolescent NPHP

The adolescent form of NPHP was originally described in a large Venezuelan pedigree, with a median age of ESRD of 19 yr [18]. Biallelic mutations in *NPHP3* were found in this family. In other families within this report, biallelic mutations in *NPHP3* resulted in ESRD between 7–11 yr of age [18]. It is

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now known that *NPHP3* mutations may lead to a broad range of phenotypes including perinatal lethal Meckel-Gruber syndrome (MKS) and infantile presentations. The term "adolescent NPHP" is thus somewhat arbitrary and merely extends the phenotypic spectrum from juvenile NPHP.

2.4. Late-onset NPHP

A number of case reports have highlighted the fact that NPHP may first present to adult nephrologists. Georges et al. [6], report three (genetically unsolved) families with retinal dystrophy, NPHP on renal biopsy and slowly progressive renal failure and ESRD between the ages of 42–56 yr. In another family with a homozygous *NPHP1* deletion [7], ESRD was reported between 27 and 43 yr of age for three of the affected patients. These cases of NPHP extend the age of ESRD from birth to up to the sixth decade of life.

3. Pathological and histological descriptions of NPHP

Kidneys affected by NPHP are grossly normal or have a shrunken appearance, typical of ESRD. There may be corticomedullary cysts, which are up to 1.5 cm in size and are fluid filled. If present, cysts often develop in later stages of the disease. The renal ultrasound scan appearances may display a loss of corticomedullary differentiation (Fig. 1A). In infantile NPHP, there may be bilateral large cystic kidneys reminiscent of autosomal dominant polycystic kidney disease (Table 1).

Where renal biopsies have been performed in NPHP patients, distinct histological features have been reported. The histological changes can be divided into early or late stages of disease. In the early stages of the NPHP, there is interstitial fibrosis (Fig. 1B) with sparse inflammation and lack of infiltration with neutrophils or monocytes. The tubules are tortuous and atrophic with segmented tubular basement membrane thickening [19]. The distal tubules have focal diverticulum like protrusions. The glomeruli are usually normal but there may be periglomerular fibrosis, which can extend into the glomerular tuft leading to focal or global collapse of the tuft and obsolescence of the glomeruli [4, 20]. In later stages of the disease, the tubules may demonstrate basement membrane abnormalities with both atrophy and thickening (Fig. 1C). There is often cystic dilatation of the distal tubules and the glomeruli may show collapse and severe periglomerular fibrosis [20, 21]. NPHP is not an immune-=mediated disease and consequently there is no immune or complement deposition [19, 20]. Electron microscopy may reveal tubular basement membrane duplication, thickening and folding [19, 20].

4. Extra-renal manifestations of NPHP

There are several important additional phenotypes that may be associated with NPHP. These multisystem features are consistent with the fact that NPHP results from cilium dysfunction and that these cell organelles occur widespread throughout the human body. Extra-renal manifestations are seen in approximately 20% of cases [22]. Important syndromes associated with NPHP are listed in Table 2 and are briefly described below.

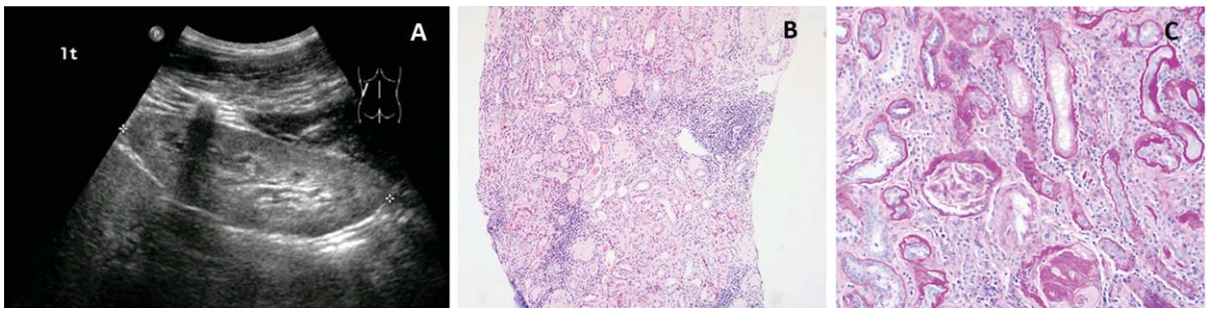

Fig. 1. Diagnostic features of nephronophthisis; (A) Renal ultrasound scan of a patient with nephronophthisis showing absence of corticomedullary differentiation, normal renal size and few corticomedullary cysts. (B) Haematoxylin and eosin stained renal biopsy demonstrating cyst formation, tubular atrophy and interstitial infiltrates. (C) Periodic acid-Schiff stained renal biopsy showing tubular basement membrane disruption.

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Table 2
Extra-renal manifestations of nephronophthisis and their associated syndromes

Extra renal manifestation associated with nephronophthisis	Syndrome
Retinitis pigmentosa/retinal dystrophy	Senior-Løken syndrome Alström syndrome Arima syndrome
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome and related disorders
Ocular coloboma	Joubert syndrome and related disorders
Posterior encephalocele	Meckel-Gruber syndrome
Cerebellar vermis aplasia/hypoplasia	Joubert syndrome and related disorders
Liver fibrosis	Joubert syndrome and related disorders Meckel-Gruber syndrome Arima syndrome
Postaxial polydactyly	Bardet-Biedl syndrome Joubert syndrome and related disorders
Skeletal dysplasia	Ellis-van Creveld syndrome Sensenbrenner syndrome Jeune syndrome Mainzer-Saldino syndrome
Situs inversus/cardiac malformation	Infantile nephronophthisis

4.1. NPHP with retinitis pigmentosa (Senior-Løken syndrome)

Retinal dysplasia and degeneration is seen in 10–15% of patients with NPHP and may lead to an early and severe visual loss resembling Leber's congenital amaurosis [23, 24]. Later onset forms such as retinitis pigmentosa present initially with night blindness, which then progresses to visual loss.

4.2. Cerebellar vermis aplasia/hypoplasia with NPHP (Joubert syndrome)

Joubert syndrome (JBTS) is a developmental disorder characterized by cerebellar vermis hypoplasia [25]. Brain magnetic resonance imaging reveals a pathognomonic appearance known as the "molar tooth sign". Clinical signs include hypotonia, cerebellar ataxia, neonatal tachypnea and developmental delay. There may also be ocular coloboma, polydactyly and hepatic fibrosis. NPHP is found in up to 27% of JBTS patients [26].

4.3. Oculomotor apraxia type Cogan

Oculomotor apraxia type Cogan is an eye movement disorder that is characterized by abnormal horizontal eye movements, which include nystagmus and difficulty with saccades (smooth visual pursuits) and has been associated with NPHP [9, 27]. Oculomotor apraxia may be a mild form of JBTS, as cerebellar vermis aplasia has been described in this condition [28].

4.4. Perinatal lethality in MKS

MKS is characterized by occipital encephalocele, polydactyly, bile duct proliferation and cystic kidney dysplasia. Typically, the condition is perinatally lethal. The syndrome is often associated with severe biallelic mutations in NPHP genes, which include *NPHP3*, *CEP290* and *RPGRIP1L* [29–33].

4.5. Skeletal defects (Jeune syndrome, Sensenbrenner syndrome, Saldino-Mainzer syndrome)

Various skeletal defects have been reported in association with NPHP. These include cone-shaped epiphyses [18, 34], shortening of limbs and ribs, scoliosis, polydactyly, brachydactyly and craniosynostosis. Mutations are in genes encoding intraflagellar transport proteins including *TTC21B* and *WDR19* [35–39].

5. Genetic classification of NPHP

There are now more than 20 genes that if mutated may lead to NPHP (Table 3). The most common genetic cause of NPHP is mutations in *NPHP1*, which account for around 20% of cases. The most common *NPHP1* gene defect is a large homozygous deletion of the whole gene [40, 41]. Each of the remaining NPHP genes probably account for 1% or less of all cases of NPHP, and around two-thirds of cases remain genetically unsolved [9]. It is noteworthy that mutations in a single NPHP gene may give an extremely wide spectrum of clinical phenotypes that may include isolated NPHP, NPHP with additional features (such as Senior-Løken syndrome and JBTS) and severe neonatal lethal forms (such as MKS). Linkage studies and painstaking mapping approaches led to the identification of *NPHP1* in 1997 [40]. Similar approaches for the next decade (sometimes combined with

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Table 3
Genetic causes of NPHP

HGNC Symbol	NPHP type	Disorders	Key insights	References
NPHP1	NPHP1	NPHP/SLSN/JBTS	Cell-cell junction and ciliary transition zone protein	[40, 91]
INVS	NPHP2	NPHP/SLSN	Role in Wnt signalling	[14]
NPHP3	NPHP3	NPHP/SLSN/MKS	Murine model *Pcy* has a hypomorphic *Nphp3* allele	[18]
NPHP4	NPHP4	NPHP/SLSN	Role in both cilia and cell-cell junctions	[92]
IQCB1	NPHP5	SLSN/LCA	Localises to connecting cilium of photoreceptor cells	[93]
CEP290	NPHP6	JBTS/BBS/MKS/LCA/SLSN	Centrosomal protein	[30, 62, 94]
GLIS2	NPHP7	NPHP	Increase in apoptosis and fibrosis in murine model of *Glis2*	[75]
RPGRIP1L	NPHP8	JBTS/MKS	Ciliary transition zone protein and facilitates vesicular docking of ciliary proteins	[33, 95]
NEK8	NPHP9	NPHP	Links cilia and cell cycle defects in NPHP	[96]
SDCCAG8	NPHP10	SLSN/BBS	Implicates DNA damage in NPHP	[44, 96]
TMEM67	NPHP11	NPHP/MKS/JBTS	Required for ciliogenesis	[97–99]
TTC21B	NPHP12	NPHP/JS	IFT protein	[35]
WDR19	NPHP13	NPHP/CED/JS	IFT protein	[36, 37]
ZNF423	NPHP14	JBTS	Centrosomal protein and role in DNA repair signalling	[49]
CEP164	NPHP15	NPHP/SLSN/JBTS	Centrosomal protein and role in DNA repair signalling	[49]
ANKS6	NPHP16	NPHP	Functional module with inversin and NPHP3	[51, 52]
AHI1	JBTS3	NPHP/JBTS	Important for cerebellar development	[100–102]
XPNPEP3	NPHP1	NPHP	Mitochondrial defect	[103]
ATXN10	N/A	NPHP/SCA	Interacts with IQCB1	[74]
SLC41A1	N/A	NPHP-like	Renal magnesium transport defect	[104]
CEP83	N/A	NPHP	Component of distal appendages of centrioles	[53]

HGNC = HUGO Gene Nomenclature Committee; NPHP = Nephronophthisis; SLSN = Senior-Løken syndrome; JBTS = Joubert syndrome; MKS = Meckel-Gruber syndrome; LCA = Leber's congenital amaurosis; BBS = Bardet-Biedl Syndrome; JS = Jeune syndrome; CED = Cranioectodermal dysplasia; SCA = Spinocerebellar ataxia; N/A = Not available.

candidate gene screens) allowed the discovery of eight genes (at a rate of around one new gene per year). Since 2010, next-generation sequencing approaches have been utilized [42] allowing the detection of NPHP genes at a much faster rate. We here review gene identifications from 2010 to date. The NPHP genes encoded proteins are almost all (except for *XPNPEP3* and *SLC41A1*) expressed in centrosomes and primary cilia; nephronophthisis is therefore considered to be part of the spectrum of disorders known as ciliopathies, a group of disorders resulting from ciliary disturbances. In the kidney, cilia project from the epithelial cell surface into the tubular lumen and act as flow sensors as well as signaling centers for inter- and intracellular communication [43].

5.1. SDCCAG8

SDCCAG8 was one of the first genes to be identified using next-generation sequencing approaches [44]. Patients with mutations in this gene were diagnosed with SLSN, but may also have features suggestive of Bardet-Biedl syndrome (BBS) including obesity and intellectual disability [45]. The encoded protein SDCCAG8 localizes to centrioles and directly interacts with the ciliopathy-associated protein OFD1. A recently described murine model of *SDCCAG8* has implicated elevated levels of DNA damage response signaling as a potential mechanism of kidney disease [46].

5.2. TTC21B

Davis et al. [35] reported the association of *TTC21B* mutations with both isolated NPHP and Jeune syndrome. *TTC21B* encodes the retrograde intraflagellar transport (IFT) protein IFT139, which has been shown to regulate Shh signaling [47].

5.3. WDR19

WDR19 mutations have been reported in patients with ciliopathy syndromes including Sensenbrenner syndrome, Jeune syndrome, SLSN and isolated NPHP [36, 39, 48]. *WDR19* encodes for IFT144, a protein, which participates in retrograde IFT and is important for ciliogenesis.

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5.4. ZNF423

ZNF423 mutations have shown to cause Joubert syndrome with NPHP [49]. The encoded protein ZNF423 interacts with DNA damage response protein PARP1 (poly (ADP-ribose) polymerase 1) and also CEP290 [49].

5.5. CEP164

Mutations in *CEP164* may cause NPHP and related ciliopathy syndromes including SLSN [49]. The CEP164 protein is a regulator of ciliogenesis and defines the mature centriole by formation of the distal appendage of the centriole [50]. Loss of *CEP164* induces DNA damage [49].

5.6. ANKS6

ANKS6 mutations lead to NPHP. ANKS6 localizes to the proximal cilium and links the NPHP proteins; inversin, NPHP3 and NEK8. This functional role of ANKS6 in a NPHP module may explain the phenotypic overlap, i.e. abnormalities in heart and liver, seen in the patients carrying individual mutations in these genes [51, 52].

5.7. CEP83

CEP83 mutations have recently been described to cause infantile NPHP [53]. The *CEP83* gene encodes a centriolar distal appendage protein, CEP83. In the seven families so far described, the NPHP phenotype was early-onset and in some was also associated with hydrocephalus and learning difficulties [53].

5.8. Mutational burden

Alongside the novel findings, relating to gene discovery in NPHP, there has been the continued theme of wide phenotypic variability, especially in extra-renal manifestations. The type of mutation may influence the phenotype in certain circumstances. Examples include *NPHP3*, *CEP290*, *RPGRIP1L* and *TMEM67* where two truncating mutations tend to lead to more severe phenotypes than missense mutations [16, 29, 33]. With the now frequent sequencing of NPHP cohorts [54, 55] and the use of high-throughput genetic sequencing platforms [56], the findings of oligogenicity within NPHP have been reported. In these cases, a third mutant allele is present and may modify the disease phenotype. Thus, biallelic mutations in one NPHP gene have been inherited in combination with a third allele in another NPHP or ciliopathy gene. As an example, a heterozygous *AHI1* mutation when inherited with biallelic *NPHP1* mutations seems to lead to a more severe brain phenotype [55]. Thus, a concept of mutation burden seems relevant to NPHP, like BBS [57]. It is important to report and to assess these variants in terms of their pathogenicity. Interestingly, *NPHP1* mutations and copy number variants, as well as causing NPHP and JBTS, may also contribute to the mutational burden of BBS [58].

6. Pathogenesis of the disease

There are various theories behind the pathogenesis of the NPHP disease process. The very early hypotheses were based entirely on the histopathological description of the disease and led to the widespread belief that this disease was caused by some unknown nephrotoxic agent or an enzyme defect [20]. The ubiquitous finding of tubular basement membrane thickening led to a basement membrane hypothesis for the pathogenesis of NPHP. It was observed that nephrocystin-1, the protein product of *NPHP1*, had a high degree of sequence conservation with CRK (a focal adhesion protein) [59] and contained an SH3 domain and interacted with other proteins including p130Cas and ACK1 [40, 60]. Nephrocystin-1 was shown to localize to adherens junctions and focal adhesions. This supported a hypothesis that nephrocystin-1 has an important role in the maintenance of the tubular epithelium and that abnormal cell-cell and cell-matrix interactions were the underlying defect in NPHP. Many years later, the debate of the initial pathogenic defect in NPHP continues, with the focus on NPHP as a ciliopathy [61]. As previously mentioned, this hypothesis is strongly supported by multiple gene discoveries in NPHP with nearly all the affected genes coding for the components of the cilia, basal body or centrosome. This link between NPHP and cilia was first established after the discovery that *INVS* mutations cause infantile NPHP and that the encoded protein inversin localizes to cilia and interacts with nephrocystin-1 and β-tubulin [14]. There is now almost universal agreement that the primary cilia are at the centre of the disease process although it should not be forgotten

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that nephrocystins may have multiple sub- cellular localizations [62] and may play different roles in different tissues [1].

The primary cilium is a sensory organelle, which is present on almost all cells of the body. It projects from the apical surface of the cell into the extracellular space like an antenna [63]. The cilium is a sensory organelle, which converts extracellular stimuli into intracellular signaling. The transition zone of the cilium, located at its base, separates it anatomically and functionally from the rest of the cell [64]. The transition zone controls the traffic of proteins into and out of the cilium, which is mediated by the intraflagellar transport (IFT) machinery. A primary cilium is present on all renal tubular cells, except alpha-intercalated cells [65]. Within the kidney, cilia project from the cell surface of individual epithelial cells into the tubular lumen and act as flow sensors as well as signaling hubs [43]. Cilia bend in response to mechanical stimuli (e.g. fluid flow) and regulate cell signaling pathways [66]. Primary cilia have been shown to play a role in many developmental signaling pathways including the Hedgehog (Hh), Wnt, planar cell polarity, platelet derived growth factor receptor alpha, fibroblast growth factor and Hippo pathways [67–69]. Some of these, if disrupted, may play fundamental roles in the development of CKD and will be briefly reviewed.

6.1. Hh signaling

Hh signaling pathway is a key developmental pathway and was first discovered in *Drosophila*. There are three mammalian Hh homologues, Desert, Indian and Sonic. The Sonic hedgehog (Shh) pathway is essential for development [70], patterning, organogenesis and cell signaling [71]. It acts as a morphogen and dysregulation of the pathway can lead to severe developmental defects and can give rise to various cancers [72]. Shh signaling is intimately related to the primary cilium [72]. Shh binds to Patched and regulates the translocation of Smoothened into the primary cilum [73]. Smoothened, when enriched in the primary cilium, activates GLI proteins that in turn regulate gene expression. An intact cilium is important for Hh signaling. The evidence implicating the defects of the Hh signaling in NPHP, renal development and cystogenesis is evolving [47, 74]. Loss of the transcription factor GLIS2, which is related to the GLI protein family, causes NPHP [75]. *Shh* knockout mouse embryos showed either renal agenesis or cystic dysplasia [76], while upregulated Indian hedgehog (Ihh) has been implicated in cystogenesis [77]. More recently, Hh signaling has been shown to be dysregulated in models of CKD including *Thm1*, *Pkd1*, *jck* [47] and *Cep290* [78]. These findings implicate abnormal Hh signaling in cystogenesis as well as ciliogenesis and opens the opportunity for therapeutic interventions [78].

6.2. Wnt signaling

The role of the Wnt signaling pathway in the pathogenesis of NPHP was originally described by Simons et al. [79]. Here defects in the primary ciliary protein inversin caused a switch from non-canonical to canonical Wnt signaling leading to disruption in apical-basolateral polarity. A mechanism of cystogenesis was then proposed whereby the normal tubular lengthening process, which occurs via cell division oriented along the tubular axis, is disrupted. Instead, defective renal tubular cilia leads to abnormal planar cell polarity signaling, misoriented cell division and tubular dilatation leading to cystic kidneys [80]. The Wnt signaling pathway has since been shown to be important in the brain development (hemisphere fusion) in *Ahi1* mutant mice, a model of JBTS [81]. Cilia regulate, via the *AHI1*-encoded protein Jouberin, the amplitude of canonical Wnt signaling [82]. The relationship between Wnt signaling and CKD has been recently reviewed [83].

7. Treatment and therapy development

NPHP is incurable at present. The options for treatment remain supportive with ideal control of blood pressure as a priority in children and young adults affected. Management of complications arising from progressive renal failure such as anemia, symptoms of uremia and fluid overload are important alongside preparation for future renal replacement therapy. This disease does not recur in a transplant, which remains the ideal mode of renal replacement therapy. Potential future therapies are still under investigation but could arise from several lines of investigation into the pathogenesis of NPHP. For example, murine models have been generated for almost all the NPHP-associated genes [84]. These are invaluable in evaluating various therapeutic agents for CKD. Vasopressin-2 receptor antagonists were able to rescue the CKD

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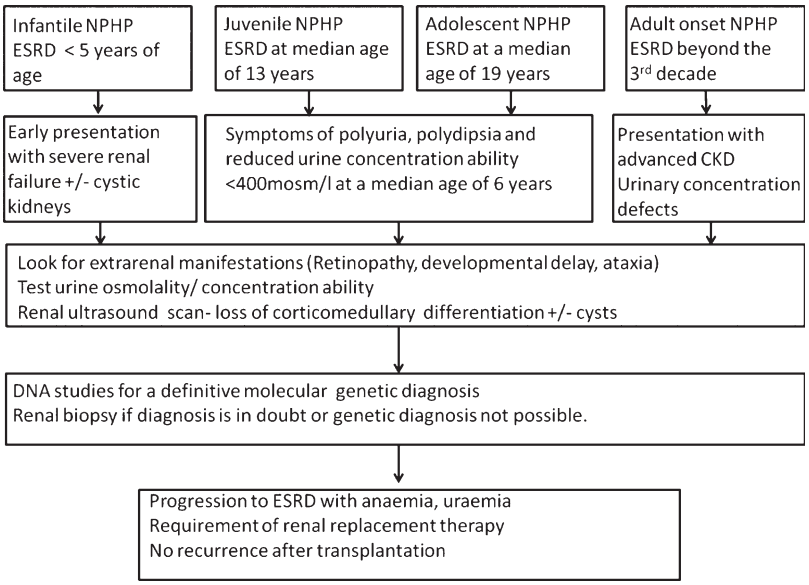

Fig. 2. Flow chart detailing clinical presentation, symptoms and investigation of suspected nephronophthisis.

phenotype in *Pcy* mice (a model of *NPHP3*) [85] whilst inhibitors of cell cycle (and therefore DNA damage) such as roscovitine rescued the phenotype of *Jck* mice (a model of *NEK8*) [86]. Kidney explants from *Ttc21b* null animals showed that modulation of Shh signaling pathways may also be a future strategy [47]. Indeed, modulation of Shh was shown to rescue cilia and cellular phenotypes in both murine *Cep290*-deficient cells and human urine-derived epithelial cells from a patient with *CEP290* mutations [78]. There is hope therefore that these and other animal models of NPHP will provide valuable insights for future treatments of NPHP in affected patients. Indeed, the zebrafish is proving to be useful for high-throughput drug screens to determine their effect on kidney development [87].

8. Conclusions: An approach to the clinical diagnosis of NPHP

Recognition of NPHP as an inherited ciliopathy is important. Renal and extra-renal features may allow a clinical diagnosis to be made. A detailed history with specific emphasis on the family history and extra-renal features known to be associated with NPHP is therefore an essential prerequisite to an exact diagnosis (Fig. 2). NPHP is characterized by a urinary concentrating defect early on in life, which leads to polyuria and polydipsia. Infantile NPHP, as we have discussed presents much earlier. Clinical spectrums of disease are wide and widening. Besides extensive investigations of renal functions, clinical phenotyping should also encompass a full neurological screening to assess for cerebellar signs and fundoscopy to assess for retinal degeneration. A formal ophthalmological examination is advised. The role of renal biopsy in diagnosing NPHP is contentious and should be limited to cases where a tissue diagnosis will serve to distinguish it from other differential diagnoses. We believe that in most cases a histopathological diagnosis should be superseded by a molecular genetic diagnostic approach, because genetic screening allows for early diagnosis and prevents complications of renal biopsy. *NPHP1* mutations and deletions are the most frequent genetic cause of NPHP and may be screened for using standard PCR assays [87]. Given the large numbers of other NPHP genes involved, multiplex PCR [88, 89], targeted exon capture or whole-exome sequencing approaches are recommended [90]. Treatment options are limited, but there is significant hope that therapies for NPHP will be available in the future.

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