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Review Article

Nephronophthisis: A review of genotype–phenotype correlation

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ABSTRACT:

Nephronophthisis is an autosomal recessive cystic kidney disease and one of the most common genetic disorders causing end-stage renal disease in children. Nephronophthisis is a genetically heterogenous disorder with more than 25 identified genes. In 10%–20% of cases, there are additional features of a ciliopathy syndrome, such as retinal defects, liver fibrosis, skeletal abnormalities, and brain developmental disorders. This review provides an update of the recent advances in the clinical features and related gene mutations of nephronophthisis, and novel approaches for therapy in nephronophthisis patients may be needed.

SUMMARY AT A GLANCE

Nephronophthisis (NPHP) is a renal ciliopathy affecting children and young adults. This review gives an update on the recent advances in the clinical features and related gene mutations of NPHP.

Nephronophthisis (NPHP), the most common monogenic cause of end-stage renal disease (ESRD) during the first three decades of life, is responsible for 2.4%–15% of ESRD in this population. The estimated incidence varies from 1:50 000 live births in Finland to 1:1 000 000 in the United States.[1] It is caused by mutations in many genes that encode nephrocystin protein, which is involved in the function of primary cilia, basal bodies, and centrosomes. These mutations result in renal disease and extra-renal manifestations.[2] This review provides an update about the recent advances in the field of NPHP.

CLINICAL MANIFESTATIONS OF NPHP

Nephronophthisis is characterized by reduced ability of the kidneys to concentrate solutes, chronic tubulointerstitial nephritis, cystic renal disease, and progression to ESRD before age 30. The typical clinical symptoms of NPHP include polyuria, polydipsia with regular fluid intake at night, secondary enuresis, anaemia, and growth retardation. Patients with NPHP typically have a "bland" urinalysis without evidence of proteinuria, hematuria, or cellular elements until the late stage, when proteinuria may develop into secondary glomerulosclerosis.

Clinically, three clinical subtypes of NPHP have been recognized based on the median age of onset of ESRD: infantile, juvenile, and adolescent/adult.[3] The main characteristics of these three subtypes of NPHP are summarized in Table 1. However, there have been several case reports of patients with NPHP who progressed to ESRD between the ages of 27 and 56 years.[4–6] These cases of NPHP extend the age of ESRD from birth to the sixth decade of life.

Extra-renal manifestations occur in approximately 10%–20% of patients, including retinitis pigmentosa,[7] skeletal defects,[8] hepatic fibrosis,[9] neurologic abnormalities,[10] and

Table 1 Main features of three clinical subtypes of nephronophthisis (NPHP)

Item	Infantile NPHP	Juvenile NPHP	Adolescent/ adult NPHP
Onset of ESRD (median in years)	1 year	13 years	19 years
Clinical manifestations	Oligohydramnios sequence in utero (limb contractures, pulmonary hypoplasia, and facial dysmorphisms), severe renal failure in the first years of life, severe hypertension	Impaired urinary concentrating ability (polyuria and polydipsia), impaired sodium reabsorption (hypovolaemia, hyponatraemia, chronic kidney disease (severe anaemia, growth retardation), proteinuria (late stage), normal blood pressure	Similar to juvenile NPHP
Renal ultrasound	Enlarged kidneys, large cortical microcysts, absent medullary cysts	Normal-sized or smaller hyperechogenic kidneys with corticomedullary cysts and poor corticomedullary differentiation	Similar to juvenile NPHP
Renal histology	Tubular atrophy, usually lack tubular basement membrane change, interstitial fibrosis, collecting tubule cystic dilatation, enlarged kidneys	Tubular atrophy, tubular basement membrane disruption, cysts at the corticomedullary border, diffuse interstitial fibrosis with chronic inflammation	Similar to juvenile NPHP
Extra-renal association	Liver fibrosis, severe cardiac valve or septal defects, recurrent bronchial infections	Retinal degeneration, cerebellar vermis aplasia, gaze palsy, liver fibrosis, skeletal defects	Similar to juvenile NPHP
Typical gene	*NPHP2/INVS, NPHP3, NPHP12/ TTC21B/JBTS11, NPHP14 /ZNF423, NPHP18 /CEP83*	All NPHP genes except *NPHP2/ INVS*	*NPHP3, NPHP4, NPHP9/ NEK8*

cardiac defects.[11] NPHP is also a major clinical finding in several syndromes, including Senior-Loken, Joubert, Meckel-Gruber, Cogan, and Sensenbrenner syndromes, and asphyxiating thoracic dystrophy (ATD, also known as Jeune syndrome). A summary of the main extra-renal manifestations associated with NPHP is described in Table 2.

GENOTYPE–PHENOTYPE CORRELATION OF NPHP

To date, more than 25 different genes have been found to be associated with NPHP (Table 3).[2,12–51] Mutations in the *NPHP1* gene are the most common, being reported in approximately 20% of cases. Each of the remaining *NPHP* genes probably account for 1% or fewer of all cases of NPHP, and around two-thirds of cases remain genetically unknown.[41]

Most nephrocystins are located in the transition zone, inversin compartment, or subunits of intraflagellar transport (IFT) complexes.[6] However, genome-wide homozygosity mapping identified pathogenic mutations in *NPHP1L* and *NPHP2L* of which the protein product localizes to mitochondria.[52] Currently, at least four distinct nephrocystin modules have been found: the NPHP1-4-8 module, NPHP2-3-9-ANKS6 module, NPHP5-6 module, and MKS module (Fig. 1). These nephrocystin modules are related to different signalling pathways, including the Wnt pathway, Hedgehog pathway, DNA damage response (DDR) pathway, Hippo pathway, intracellular calcium signalling pathway, cAMP signalling pathway, and mTOR pathway.

NPHP shows genetic and phenotypic heterogeneity. Mutations in single ciliary genes are often associated with multiple phenotypes (Table 1 and Table 3). Single locus allelism is insufficient to explain the variability in phenotypic heterogeneity in NPHP. Digenic and triallelic inheritance may provide an explanation. Triallelic inheritance was first demonstrated for BBS.[53]To date, oligogenic inheritance has been noted in some patients with mutations in *NPHP1*, *NPHP5*, *NPHP6*, *NPHP8*, *NPHP9*, *NPHP11*, and *TTC21B* genes.[12,54–56]

APPROACH TO CLINICAL DIAGNOSIS OF NPHP

The diagnosis of NPHP is suggested by clinical features and confirmed by a positive genetic test (Fig. 2). The role of renal biopsy in diagnosis is controversial. Renal biopsy should be limited to cases in which tissue diagnosis can be used to distinguish it from other differential diagnoses. Molecular genetic analysis is currently the only method available to diagnose NPHP and thus provide patients and families with an unequivocal diagnosis. Due to an increasing number of potentially causative monogenic genes and to advances in next-generation sequencing, whole-exome sequencing has mostly replaced targeted-sequencing panels in the diagnosis of NPHP.[57] Using this method, a causative single-gene mutation can be detected in up to 60% of cases depending on the composition of the cohort. However, the absence of mutation is not sufficient to exclude the diagnosis of NPHP. Most importantly, genetic testing should always be combined with thorough phenotyping and genetic counseling.

Table 2 Extra-renal manifestations associated with nephronophthisis (NPHP)

Involved organ	Manifestations	Associated syndrome
Eye	Retinitis pigmentosa	Senior-Løken syndrome (retinitis pigmentosa)
	Alstrom	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
		Alstrom syndrome (early cone-rod retinal dystrophy and blindness, hearing loss, childhood obesity, type 2 diabetes mellitus, cardiomyopathy, fibrosis, and multiple organ failure)
		RHYNS (retinitis pigmentosa, hypopituitarism, skeletal dysplasia)
		Joubert syndrome (cerebellar vermis hypoplasia)
	Oculomotor apraxia	Cogan syndrome (congenital oculomotor apraxia (absence or impairment of controlled, voluntary, and retinitis pigmentosa horizontal eye movement)
		Joubert syndrome
	Nystagmus	Joubert syndrome
	Coloboma	Joubert syndrome
		COACH (cerebellar vermis hypo/aplasia, oligophrenia, ataxia, ocular coloboma and hepatic fibrosis)
Central nervous system	Encephalocele	Meckel-Gruber syndrome (central nervous system malformation, bilateral renal cystic dysplasia, cleft palate, polydactyly, ductal proliferation in the portal area of the liver, pulmonary hypoplasia, and situs inversus)
	Vermis aplasia	Joubert syndrome
		COACH
	Hypopituitarism	RHYNS
Liver	Liver fibrosis	Boichis syndrome (progressive kidney dysfunction, liver fibrosis, excessive urination, excessive thirst, failure to thrive, retarded growth, progressive kidney insufficiency, anaemia, metabolic acidosis, weakness)
		Meckel-Gruber syndrome
		Arima syndrome
		Joubert syndrome
		COACH
Bone	Cone-shaped epiphysis	Mainzer-Saldino syndrome (phalangeal cone-shaped epiphyses, chronic renal failure, and early-onset, severe retinal dystrophy)
	Polydactyly	Joubert syndrome
		Meckel-Gruber syndrome
		Bardet-Biedl syndrome (retinitis pigmentosa, obesity, deafness)
		Ellis van Creveld syndrome (short limbs, short ribs, postaxial polydactyly, dysplastic nails and teeth)
		Jeune syndrome (asphyxiating thoracic dystrophy)
		Sensenbrenner syndrome (craniosynostosis, short limbs, brachydactyly, narrow thorax, and facial anomalies)
	Skeletal abnormalities	Sensenbrenner syndrome
		Ellis van Creveld syndrome
Heart	Cardiac malformation	
	Situs inversus	Meckel-Gruber syndrome
Lung	Bronchiectasis	
Other	Ulcerative colitis	

Early onset autosomal dominant polycystic kidney disease and autosomal recessive polycystic kidney disease are often in the main differential diagnosis for patients with NPHP. Renal imaging may be useful in differential diagnosis. But genetic testing is required to make a definite diagnosis.

TREATMENT OF NPHP

There is no specific therapy for NPHP. Management is supportive, focusing on slowing the progression of CKD, controlling complications, and maintaining the promotion of growth. This disease does not recur after transplantation, so renal transplantation is the preferred renal replacement therapy.

Some potential therapeutic interventions have arisen from several lines of investigation into the pathogenesis of NPHP. Various personalized drugs include isosorbide dinitrate and tolvaptan (vasopressin V2 receptor antagonist),[58] dimethyl fumarate,[59] rapamycin (mTOR inhibitor),[60] roscovitine and its analog S-CR8 (cyclin-dependent kinases inhibitor),[61] purmorphamine (Shh signalling pathway agonist),[62] paclitaxel,[63] regulation of transcription factor Glis2/NPHP7 by SUMOylation,[64] and FR167653 (p38 MAPK pathway inhibitor).[65] Despite the many promising interventions that have arisen from preclinical studies, no clinical trials have

Table 3 Genes mutated in isolated nephronophthisis (NPHP)- and NPHP-associated syndromes

Gene	Chromosome	Protein	Location	Interaction partners	Functionary mechanism	Disorders associated with mutations	Reference
NPHP1	2q12.3	Nephrocystin-1	Adherens junction, focal adhesion, transition zone	Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B, p130 Cas, focal adhesion kinase 2	Maintains the cellular scaffolding or cytoskeleton, role in cell–cell adhesion and cell signalling	NPHP, SLSN, JBTS	12
NPHP2/ INVS	9q21-22	Inversin	Inversin compartment	Nephrocystin-1, nephrocystin-3, calmodulin, catenins, β-tubulin, APC2	Acts in Wnt pathway and planar cell polarity	Infantile NPHP, SLSN, *Situs inversus*, congenital heart defects	13
NPHP3	3q22.1	Nephrocystin-3	Inversin compartment, axoneme	Nephrocystin-1, inversin, NEK8, ANKS6, PTK2B, BCAR1	Inhibits Wnt pathway	NPHP, liver fibrosis, RP, *Situs inversus*, MKS, SLSN, congenital heart defects	14–16
NPHP4	1p36.31	Nephrocystin-4	Transition zone	Nephrocystin-1, BCAR1, PTK2B, p130Cas, filamin, tensin	Inhibits Wnt and Hippo pathways	Juvenile NPHP, RP, OMA, SLSN, liver fibrosis	17
NPHP5/ IQCB1	3q13.33	Nephrocystin-5/IQ motif containing B1	Transition zone, basal body	Calmodulin, RPGR, nephrocystin-1, nehrocystin-4, nephrocystin-6	Forms complexes with RPGR	Juvenile NPHP, early-onset RP, LCA	18
NPHP6/ CEP290	12q21.32	Nephrocystin-6/ centrosomal protein 290	Transition zone, centrosome	ATF4, nephrocystin-5, CC2D2A, TMEM67	Regulates activity of transcription factor ATF4/CREB2, role in cAMP-dependent renal cyst formation, cell signalling, DNA damage response (DDR), and renal cystogenesis	NPHP, RP, LCA, JBTS, MKS	19–23
NPHP7/ GLIS2	16p13.3	Nephrocystin-7/ GLI similar 2	Nucleus	N/A	Regulates Hedgehog signalling	NPHP	24,25
NPHP8/ RPGRIP1L/ MKS5	16q12.2	Nephrocystin-8/ RPGRIP1-like	Transition zone	Nephrocystin-1, nephrocystin-4	Involved in Shh signalling	Juvenile NPHP, JBTS, MKS, RP, LCA, COACH	26
NPHP9/ NEK8	17q11.2	Nephrocystin-9/ NIMA-related kinase 8	Inversin compartment	ANKS6	Regulates cell cycle, involved in Hippo and DDR signalling	Infantile NPHP	27,28
NPHP10/ SDCCAG8/ SLSN7	1q43-q44	Nephrocystin-10/ Serologically defined colon cancer antigen 8	Basal body	Nephrocystin-5, OFD1	Involved in DDR signalling	Juvenile NPHP, RP, SLSN, BBS	29,30
NPHP11/ TMEM67/ MKS3	8q22.1	Nephrocystin-11/ Transmembrane protein 67	Transition zone	Nephrocystin-1, nephrocystin-4, nephrocystin-6, CEP290, MKS1, TMEM216, nesprin-2	Maintains cellular structure and mitigates centrosome migration	NPHP, JBTS, MKS, liver fibrosis, COACH	31,32
NPHP12/ TTC21B/ JBTS11	2q24.3	Nephrocystin-12/ Intraflagellar transport protein 139	IFT-A	Ciliopathy modifier	Regulates retrograde trafficking in the primary cilium,	Juvenile NPHP, JS, MKS, JBTS	33

(*Continues*)

Table 3 (Continued)

Gene	Chromosome	Protein	Location	Interaction partners	Functionary mechanism	Disorders associated with mutations	Reference
					regulates Hedgehog signalling		
NPHP13/ WDR19	4p14	Nephrocystin-13/ WD repeat domain 19/IFT protein 144	IFT-A	N/A	Participates in retrograde IFT; acts in ciliogenesis	NPHP, JS, RP, Caroli, Sensenbrenner syndrome	34,35
NPHP14 /ZNF423	16q12.1	Nephrocystin-14/ Zinc finger protein 423	Nucleus	DDR protein PARP1, nephrocystin-6	Involved in DDR signalling	Infantile NPHP, JBTS, *Situs inversus*	36
NPHP15/ CEP164	11q23.3	Nephrocystin-15 centrosomal protein 164	Basal body	Nephrocystin-3, nephrocystin-4, TTBK2, ATRIP, CCDC92, CEP83, Dvl3	Involved in DDR signalling, regulates ciliogenesis	NPHP, liver fibrosis, RP, JBTS	37
NPHP16/ ANKS6	9q22.33	Nephrocystin-16/ ANKS6	Axoneme, inversin compartment	INVS, nephrocystin-3, NEK8, ANKS3, NEK7, BICC1, HIF1AN	Connects key components of NEK8, INVS, and NPHP3	NPHP, liver fibrosis, *Situs inversus*	38–40
NPHP17/ IFT172	2p23.3	Nephrocystin-17/ IFT protein 172	IFT-B	IFT80, IFT140	Involved in intraflagellar transport	NPHP, JS, JBTS, MZSDS	41
NPHP18 /CEP83	12q22	Nephrocystin-18/ centrosomal protein 83	Basal body	IFT20, CEP164	N/A	NPHP, liver fibrosis, mental retardation, hydrocephalus	42
NPHP19/ DCDC2	6p22.3	Doublecortin domain-containing protein 2	Axoneme	DVL	Involved in Wnt signalling	NPHP, renal-hepatic ciliopathy	43
NPHP20/ MAPKBP1	15q15.1	Mitogen-activated protein kinase binding protein 1	Cytoplasm	N/A	Involved in DDR signalling and JNK signalling	NPHP	2
NPHP1L /XPNPEP3	22q13	X-prolyl aminopeptidase 3	Mitochondria	Cleaves LRRC50, ALMS1, nephrocystin-6	Interferes with cilia function by cleaving certain cilial proteins	NPHP, myocardiosis, epilepsy	44,45
NPHP2L /SLC41A1	1q32.1	Solute carrier family 41 member 1	Tubules at the borders of the cortex and medulla	N/A	Affects Mg^{2+} transport	NPHP, bronchiectasia	46
TRAF3IP1	2q37.3	TRAF3 interacting protein 1	Axonemes, basal bodies	N/A	Affects microtubule stabilization by IFT54	NPHP, SLSN, RP	47
AH11/ JBTS3	6q23.3	Jouberin	Basal bodies	N/A	Affects cerebellar and cortical development	JBTS, RP	48,49
CC2D2A/ MKS6	4p15.32	Coiled coil and C2 domain containing 2A	Basal bodies	CEP290	Acts in ciliogenesis	MKS, COACH, JBST	50,51

ALMS1, Alstrom Syndrome 1; APC2, anaphase-promoting complex 2; ATF4, activating transcription factor 4; ATRIP, ATR interacting protein; BBS, Bardet-Biedl syndrome; BCAR1, breast cancer anti-estrogen resistance 1; BICC1, Bicaudal-C1; CAD, cranioectodermal dysplasia; CCDC92, coiled-coil domain containing 92; CC2D2A, coiled-coil and C2 domain containing 2A; CEP290, centrosomal protein 290; CHD, congenital heart disease; COACH, cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, ocular coloboma and hepatic fibrosis; DVL3, dishevelled 3; HIF1AN, hypoxia inducible factor 1 alpha subunit inhibitor; IFT, intraflagellar transport; JATD, Jeune asphyxiating thoracic dysplasia; JBTS, Joubert syndrome; JS, Jeune syndrome; LCA, Leber congenital amaurosis; LRRC50, leucine-rich repeat containing protein 50; MKS, Meckel-Gruber syndrome; MZSDS, Mainzer-Saldino syndrome; OFD1, oral-facial-digital protein1; OMA, oculomotor apraxia; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; SBS, Sensenbrenner syndrome; SLSN, Senior-Loken syndrome; TMEM67,transmembrane protein 67; TTBK2, Tau-tubulin kinase 2.

yet been conducted in NPHP patients. Furthermore, large numbers of compounds which may be potential therapies are being screened in the zebrafish models of NPHP.[66]

The lack of a clear-cut genotype–phenotype correlation remains a major challenge for physicians treating children with NPHP, even though the development of a single

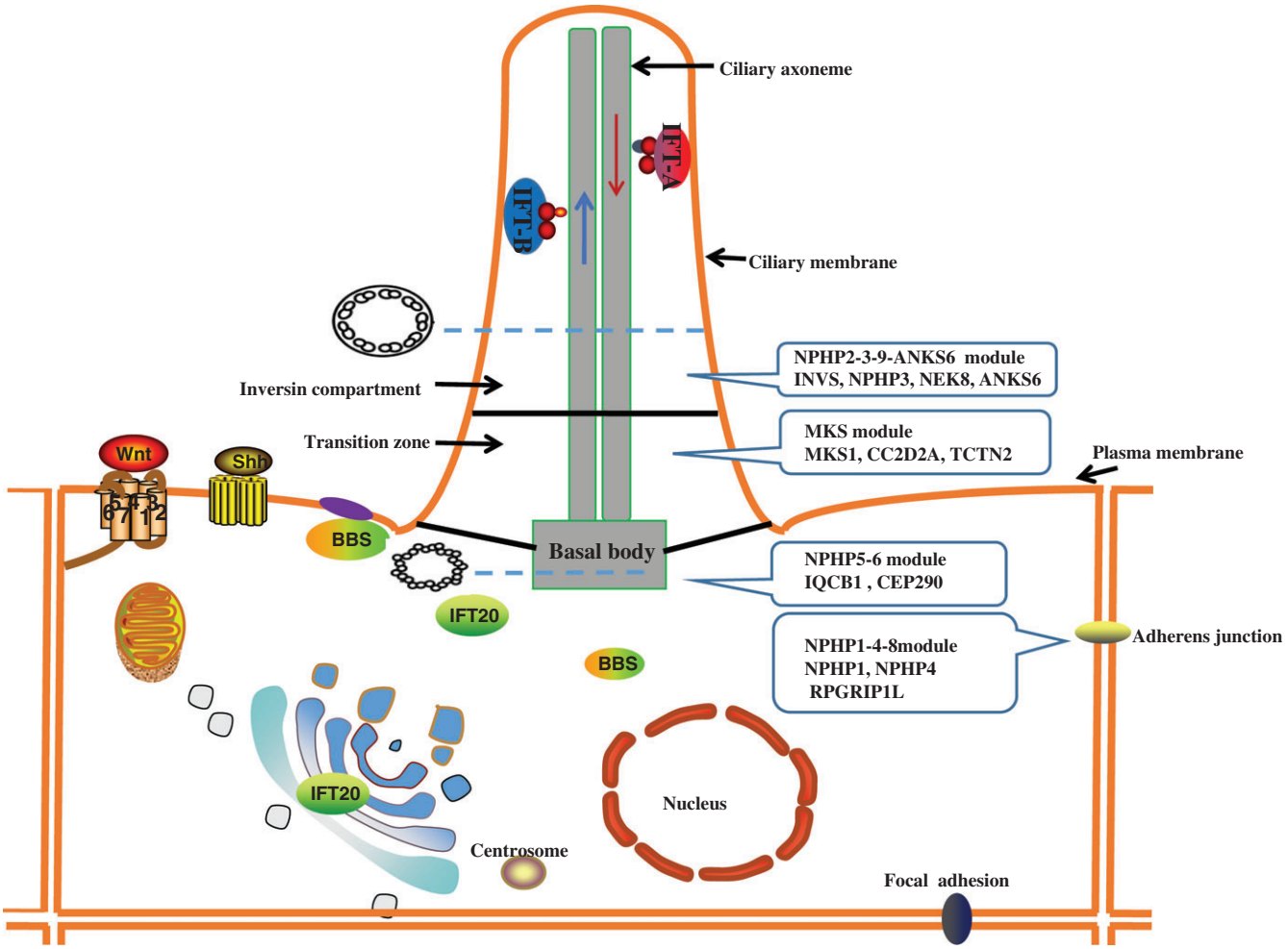

Fig. 1 Subcellular localization of different nephrocystin module.

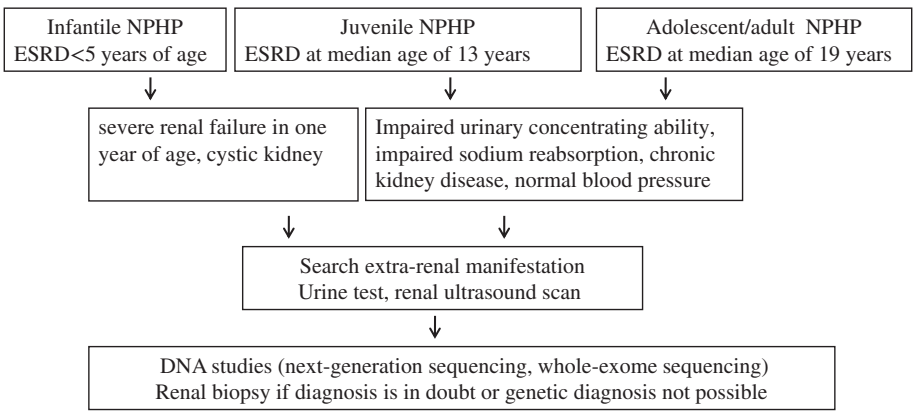

Fig. 2 Approach to clinical diagnosis of nephronophthisis (NPHP).

comprehensive histopathology and the discovery of specific disease genes and molecular mechanisms have significantly improved our understanding of NPHP. Only about 30% of NPHP patients have clear genetic mutations, suggesting that more NPHP genes have yet to be discovered. Novel genes will enable us to better understand the pathogenesis and relationship between cilia and cystic diseases. It is necessary to find new therapeutic strategies and develop alternative treatments other than conservative approaches and renal replacement therapy.

CONFLICTS OF INTEREST

There authors declare that they have no potential or actual competing interests.

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No.

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