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Nephronophthisis

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NPHP is the most common monogenic cause of CKD in children or adolescents. Extra-renal symptoms often accompany, therefore examination of retina, hearing, and skeleton is necessary in patients with CKD with insidious onset. Genes involved in NPHP-RC are mostly related in primary cilia. While genetic diagnosis is necessary for definitive diagnosis, there is no curative treatment.

Key words: Nephronophthisis, Chronic kidney disease, Genetic disease, Ciliopathy

Nephronophthisis (NPHP), meaning 'disappearance of nephrons', is the most common monogenic cause of chronic renal failure (CRF) in children or adolescents[1-4]. For instance, among 160 end-stage renal disease (ESRD) patients of our center, one fourth had clinical diagnosis of NPHP.

Symptoms

NPHP typically has insidious onset, therefore when the diagnosis is made, most of the patients have advanced chronic kidney disease (CKD) with decreased renal function. Advanced CRF is accompanied by anemia and growth retardation, thus most of NPHP patients present with general weakness, pallor, and poor growth. History taking commonly reveals recent onset polyuria/nocturia and polydipsia, which is considered as resulting from decreased renal concentrating ability. Urinalysis is often normal[5], and the blood pressure is usually not high in early stage. Contrast to autosomal recessive or autosomal dominant polycystic kidney disease (ARPKD or ADPKD), kidney size of NPHP is usually normal or relatively small[6]. On ultrasonography, corticomedullary differentiation of the kidney is lost. Case 1 describes a typical case of juvenile NPHP.

1. Case 1

A 14 years old boy presented with both lower leg pain. He had suffered from general weakness, pallor, nocturia for some time. Laboratory test revealed anemia and azotemia. USG showed small kidneys with increased echogenicity and impaired perfusion (Fig. 1). He denied history of UTI, and his VCUG was normal.

NPHP is often accompanied by extra-renal symptoms, such as retinitis

pigmentosa (RP) or Leber's congenital amaurosis (LCA) in Senior-Løken syndrome (SLSN), hypo-/ a-plasia of cerebellar vermis in Joubert syndrome (JBTS), hepatic fibrosis in Meckel Gruber syndrome (MKS), and COACH (cerebellar vermis hypoplasia/ aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis) syndrome with multiple problem[7], listing a few. Because most of the causative genes in these disorders encode proteins that play a role in the cilium[8-10], a collective term NPHP-related ciliopathy (NPHP-RC) is used to describe this group of diseases. Case 2 describes a case of COACH syndrome.

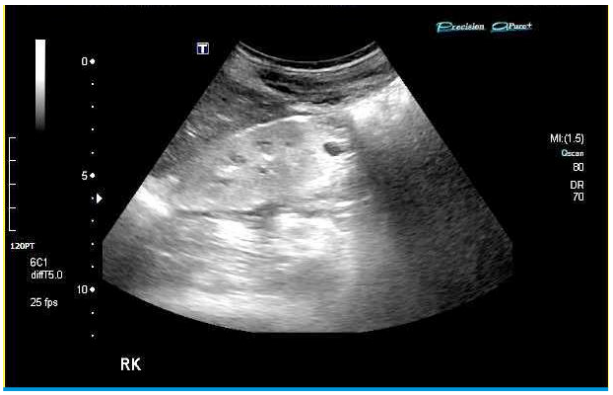

Fig. 1. Ultrasonography of the kidney in Case 1 showing typical finding of NPHP. Kidney size of NPHP is usually normal or relatively small, and corticomedullary differentiation of the kidney is lost.

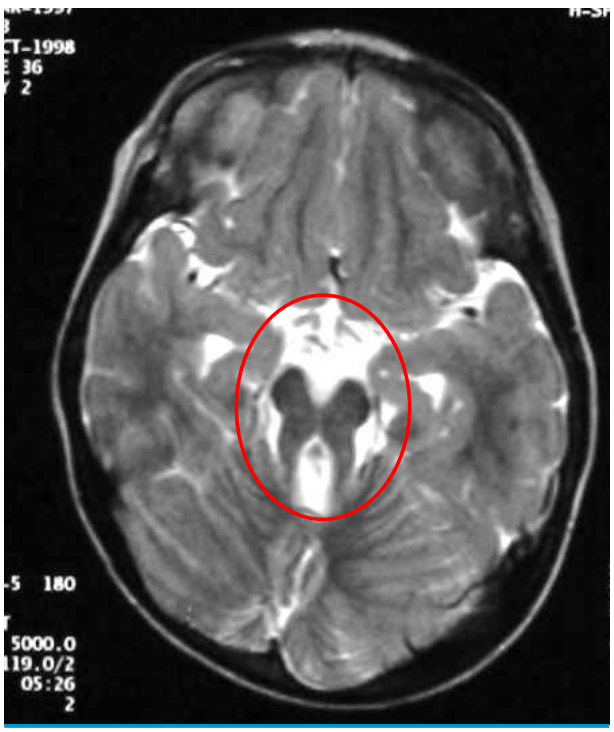

Fig. 2. Brain MRI of Case 2 showing 'molar tooth' sign.

Case 2

A one year old girl presented with developmental delay and apraxia. Imaging studies revealed molar tooth sign' in brain stem (Fig. 2), multiple cysts in the kidneys and hepatic fibrosis. She lost her kidney function when she was 11 years old.

Diagnosis

Diagnostic criteria of NPHP are as follows[11].

Clinical diagnostic criteria of NPHP
Insidious onset of CRF the first thirty years, without identifiable cause.
Patients often presents with <30 years, idiopathic
Anemia, growth retardation
Polyuria, nocturia, polydipsia from Decreased concentrating ability of the kidneys.

Histological findings are non-specific showing chronic tubulointerstitial nephropathy (Fig. 3), therefore pathologic diagnosis is not mandatory for NPHP. Furthermore, since most of the patients present at their advanced stage, renal biopsy can be risky of bleeding complication. On electron microscopy, tubular basement membrane change is , similar to glomerular basement membrane change in Alport syndrome[12].

Since the clinical features of patients with NPHP-RC are rather non-specific, a genetic diagnosis is required for a definitive diagnosis of NPHP-RC. In addition, multiple syndromes of NPHP-RC share their phenotype in various degrees, which requires clarification of genetic aberration for appropriate diagnosis[10]. Inheritance pattern of NPHP-RC is commonly autosomal recessive (AR), and currently more than 20 causative genes of NPHP are known, with 'NPHP' as part of their names[13-15]. Table 1 shows list of genes searched with term 'NPHP', 'SLSN', 'JBTS', 'MKS' and 'Bardet-Biedl syndrome (BBS, syndrome of NPHP, RP, obesity, polydactyly, cognitive impairment, and male infertility)', representatives of NPHP-RC.

Among the known genes causing NPHP, a large deletion of *NPHP1* is the most common, accounting for approximately one fifth of NPHP cases[16-20]. It is the first gene dis-

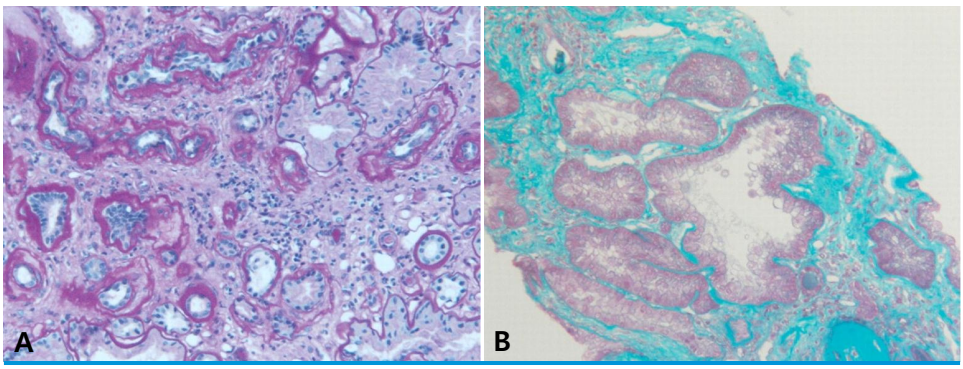

Fig. 3. Kidney biopsy of a patient with NPHP, showing interstitial inflammatory fibrosis with tubular basement membranes thickening (A, PAS staining) and cystic tubular enlargement (B, Masson's trichrome staining). Reprint with permission[12].

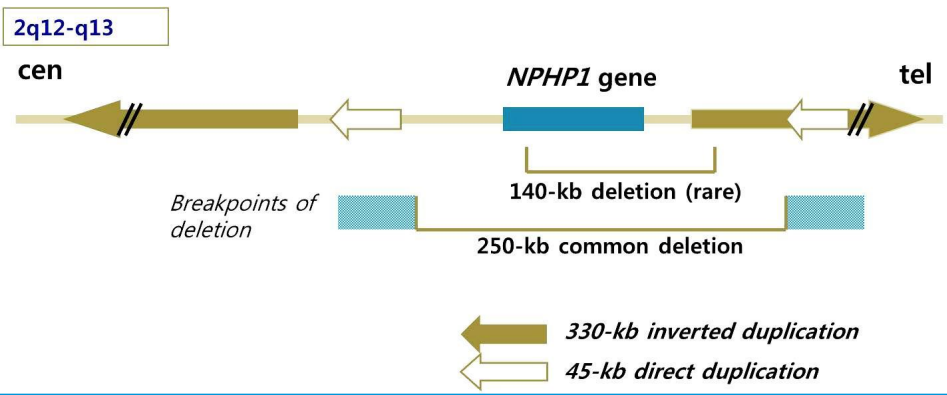

Fig. 4. NPHP1 with nearby homologous segments, rendering this gene prone to large deletion. Courtesy from Dr. Hae Il Cheong.

covered as cause of NPHP, and it has homologous segments nearby, rendering this gene prone to large deletion (Fig. 4). Those with *NPHP1* total deletion mostly have juvenile NPHP, whose onset of CRF is later than 5 years of age, with of ESRD about 13 yrs. Diagnosis of *NPHP1* total deletion is rather straightforward, because multiplex PCR of *NPHP1* exons does not produce band in *NPHP1* total deletion. Recently, Korean patients with total *NPHP1* deletion were reported to have unexpected findings of retinopathy with large or small flecks, compatible with Stargardt disease or albipunctatus retinopathy[21] (Fig. 5, 6); the authors suggested that children with impaired renal function of unknown cause should be screened for retinopathy, and retinopathy warrants screening for a homozygous deletion of *NPHP1*.

Other genes contribute less than 2-3%[9]. Some of them are strongly associated to certain phenotype, *NPHP5* or *NPHP6* mutation lead to RP, *WDR19* (*NPHP13*) is associated with Caroli disease[22] (Fig. 7). On the other hand many of them share phenotypes, demonstrated by the number

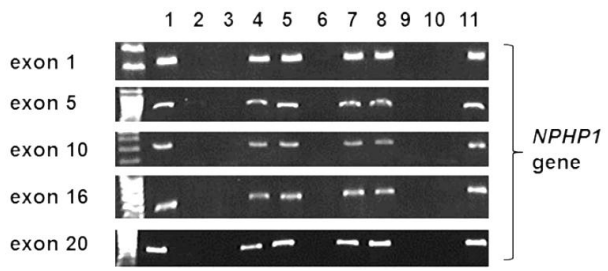

Fig. 5. The results of amplification of the exons of *NPHP1* by polymerase chain reaction, which revealed a failure of amplification (homozygous deletion) of all exons of NPHP1 in patients. (Lanes 1 and 11, control subjects; lanes 2, 3, 6, 9, and 10, patients with total deletion of NPHP1; lanes 4, 5, 7, and 8, family members of patients). Reprint with permission[21].

of genes associated with each syndrome (Table 1). Due to the large number of genes to test, recently. next-generation sequencing (NGS) is often applied, and about 1/3 patients obtain genetic diagnosis, implying that there are yet many genes to discover[23].

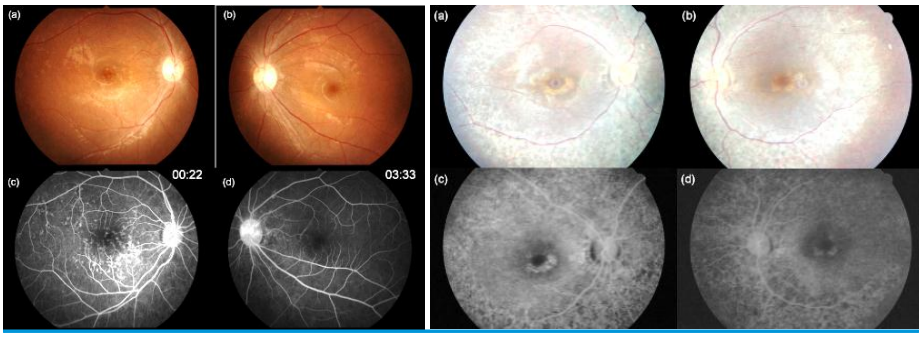

Fig. 6. A fundus photograph and fundus fluorescein angiograms of the eyes of two Korean patients with total deletion of NPHP1. Left) (a) The fundus photograph shows a normal disc and yellow flecks on the posterior pole in the right and (b) left eyes. (c) A fluorescein angiogram 22 s after dye injection shows multiple hyperfluorescent lesions corresponding to the flecks on the fundus photograph of the right eye. (d) A fluorescein angiogram 3.5 min after dye injection shows no definite hyperfluorescence and choroidal silence in the left eye.
Right) (a) The fundus photograph shows a normal disc, a yellow fleck at the parafovea, and retinal pigment epithelium (RPE) degeneration along the major arcades without involvement of the far peripheral retinal area in the right (b) and left eyes. (c) A fluorescein angiogram 2 min after dye injection shows a bull's eye appearance in the right eye. Maculopathy is shown with a foveal decrease in fluorescence surrounded by a continuous ring of increased fluorescence. Discrete areas of RPE atrophy (transmission window defect) surrounding the fovea (d). Reprint with permission[21].

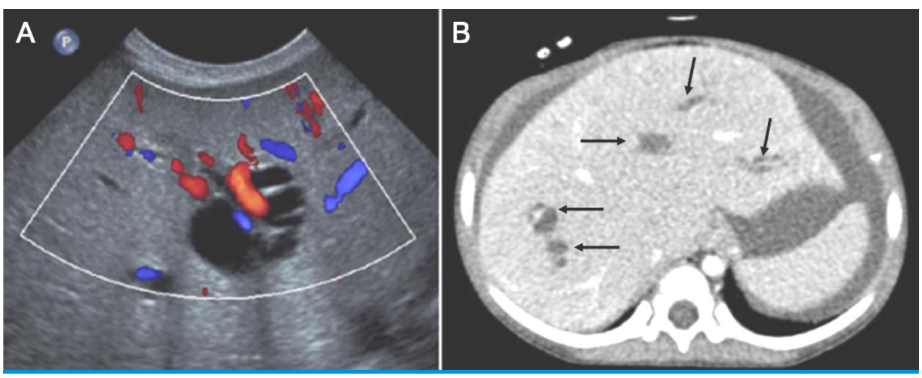

Fig. 7. Liver images of patients with *WDR19* mutations. (A) Abdominal Doppler ultrasonography reveals variable dilatation of the intrahepatic bile ducts in patient III-1. Red or blue tubular structures indicate hepatic vessels. (B) Axial computed tomography image of patient IV-1 shows globular enlargement of the liver and dilatation of the intrahepatic bile ducts (arrows), which are consistent with Caroli syndrome. Reprint with permission[22].

Table 1. NPHP-RC Genes

Gene	Description	MIM	NPHPs (ESRD Age)	JBTS	MKS	SLSN	BBS	IFT	LF	Comment
*NPHP1**	nephronophthisis 1	607100	NPHP1 (13yr)	JBTS4		SLSN1				Most common
*INVS**	inversin	243305	NPHP2 (<4yr)			SLSN			+	Situs inversus
*NPHP3**	nephronophthisis 3	608002	NPHP3		MKS7	SLSN3			+	Situs inversus
*NPHP4**	nephronophthisis 4	607215	NPHP4 (21yr)			SLSN4			+	
IQCB1	IQ motif containing B1	609237	NPHP5 (13yr)			SLSN5				LCA 100%
CEP290	centrosomal protein 290kDa	610142	NPHP6	JBTS5	MKS4	SLSN6	BBS14			20% of LCA
GLIS2	GLIS family zinc finger 2	608539	NPHP7			LCA				
*RPGRIP1L**	RPGRIP1-like	610937	NPHP8	JBTS7	MKS5					
NEK8	NIMA-related kinase 8	609799	NPHP9							
SDCCAG8	serologically defined colon cancer antigen 8	613524	NPHP10			SLSN7	BBS16			LCA 80%
TMEM67	transmembrane protein 67	609884	NPHP11	JBTS6	MKS3		BBS		+	
*TTC21B**	tetratricopeptide repeat domain 21B	612014	NPHP12	JBTS11			BBS	IFT139		Jeune
WDR19	WD repeat domain 19	608151	NPHP13			SLSN	BBS	IFT144		Jeune

Table 1. NPHP-RC Genes (Continues)

Gene	Description	MIM	NPHPs (ESRD Age)	JBTS	MKS	SLSN	BBS	IFT	LF	Comment
ZNF423	zinc finger protein 423	604557	NPHP14, PKD	JBTS19						Situs inversus
CEP164	centrosomal protein 164kDa	614848	NPHP15 (8yr)	JBTS		RP			+	
ANKS6	ankyrin repeat and sterile a motif domain containing 6	615370	NPHP16, PKD						+	Situs inversus
IFT172	intraflagellar transport 172	607386	NPHP17	JBTS				IFT172		
CEP83	centrosomal protein 83kDa	615847	NPHP18 (3yr)						+	
DCDC2	doublecortin domain containing 2	605755	NPHP19							
XPNPEP3	X-prolyl aminopeptidase 3, mitochondrial	613553	NPHP1L							CMP, Seizure
SLC41A1	solute carrier family 41, member 1	610801	NPHP2L							Bronchiectasis
INPP5E	inositol polyphosphate-5-phosphatase, 72 kDa	613037		JBTS1						
TMEM216	transmembrane protein 216	613277		JBTS2	MKS2					
*AHI1**	Abelson helper integration site 1	608894		JBTS3						
ARL13B	ADP-ribosylation factor-like 13B	608922		JBTS8						
CC2D2A	coiled-coil & C2 domain containing 2A	612013		JBTS9	MKS6					
OFD1	oral-facial-digital syndrome 1	300170		JBTS10						
KIF7	kinesin family member 7	611254		JBTS12						
TCTN1	tectonic family member 1	609863		JBTS13						
TMEM237	transmembrane protein 237	614423		JBTS14						
CEP41	centrosomal protein 41kDa	610523		JBTS15						
TMEM138	transmembrane protein 138	614459		JBTS16						
C5orf42	Chr.5 open reading frame 42	614 571		JBTS17						
TCTN3	tectonic family member 3	613847		JBTS18						
TMEM231	transmembrane protein 231	614949		JBTS20	MKS11					
CSPP1	centrosome and spindle pole associated protein 1	611654		JBTS21						
PDE6D	phosphodiesterase 6D, cGMP-specific, rod, delta	602676		JBTS22						
MKS1	Meckel syndrome, type 1	609883			MKS1		BBS13			
TCTN2	tectonic family member 2	613846			MKS8					
B9D1	B9 protein domain 1	27077			MKS9					
B9D2	B9 protein domain 2	80776			MKS10					
BBS1	Bardet-Biedl syndrome 1	209901					BBS1			
BBS2	Bardet-Biedl syndrome 2	606151					BBS2			
ARL6	ADP-ribosylation factor-like 6	608845					BBS3			
*BBS4**	Bardet-Biedl syndrome 4	600374					BBS4			
BBS5	Bardet-Biedl syndrome 5	603650					BBS5			
MKKS	McKusick-Kaufman syndrome	604896					BBS6			
BBS7	Bardet-Biedl syndrome 7	607590					BBS7			
TTC8	tetratricopeptide repeat domain 8	608132					BBS8			
BBS9	Bardet-Biedl syndrome 9	607968					BBS9			
BBS10	Bardet-Biedl syndrome 10	610148					BBS10			
TRIM32	tripartite motif containing 32	602290					BBS11			
BBS12	Bardet-Biedl syndrome 12	610683					BBS12			
WDPCP	WD repeat containing planar cell polarity effector	613580					BBS15			LZTFL1
BBIP1	BBSome interacting protein 1	613605					BBS18			
IFT27	intraflagellar transport 27	615870					BBS19			
CCDC28B	coiled-coil domain containing 28B	610162					BBS			
WDR35	WD repeat domain 35	613602						IFT121		
IFT122	intraflagellar transport 122	606045						IFT122		
IFT140	intraflagellar transport 140							IFT140		
IFT43	intraflagellar transport 43	614068						IFT43		

Abbreviations: MIM, Mendelian inheritance in Men. NPHP, nephronophthisis. ESRD, end stage renal disease. JBTS, Joubert syndrome. MKS, Meckel Gruber syndrome. SLSN, Senior-Løken syndrome. BBS, Bardet-Biedl syndrome. IFT, intraflagella transport. LCA, Leber's congenital amaurosis. LF, liver fibrosis.

Pathogenesis

Primary cilia (Fig. 8) is present in almost all mammalian cells, functioning as sensory organelles, responding to flow, optic, osmotic, chemo or olfactory stimuli[24, 25], linking to various cellular function such as polarity, cell-cycle control [10]. Therefore defect of primary cilia of renal tubular cells results in cystic disease. Extra-renal symptoms are explained by presence of primary cilia in respective cells; Primary cilia at retina are photoreceptors, whose defect can cause retinopathy, oculomotor apraxia, nystagmus, and coloboma [10, 15, 26, 27]. Primary cilia in choangiocytes explain hepatic fibrosis in NPHP-RC[28]; Primary cilia in chondrocytes explains skeletal abnormalities such as short ribs, cone-shaped epiphysis, and postaxial polydactyly in Jeune syndomre and JBTS or BBS[29, 30], especially with defect in genes of intra-flagella transport (IFT)[29].

Location, interacting molecules, and involved signaling pathway of respective causative genes are linked to the phenotype of various NPHP-RC. In addition, effect of additional mutations in another NPHP-RC genes or genetic modifiers has been suggested[9, 24, 31-33].

Treatment

There is no curative treatment for NPHP. Conservative management of CKD is necessary. There is no risk of recurrence after kidney transplantation; extra-renal symptoms progress irrespective of kidney transplantation.

Summary

NPHP is the most common monogenic cause of CKD in children or adolescents. Extra-renal symptoms often accompany, therefore examination of retina, hearing, and skeleton is necessary in patients with CKD with insidious onset. Genes involved in NPHP-RC are mostly related in primary cilia. While genetic diagnosis is necessary for definitive diagnosis, there is no curative treatment.

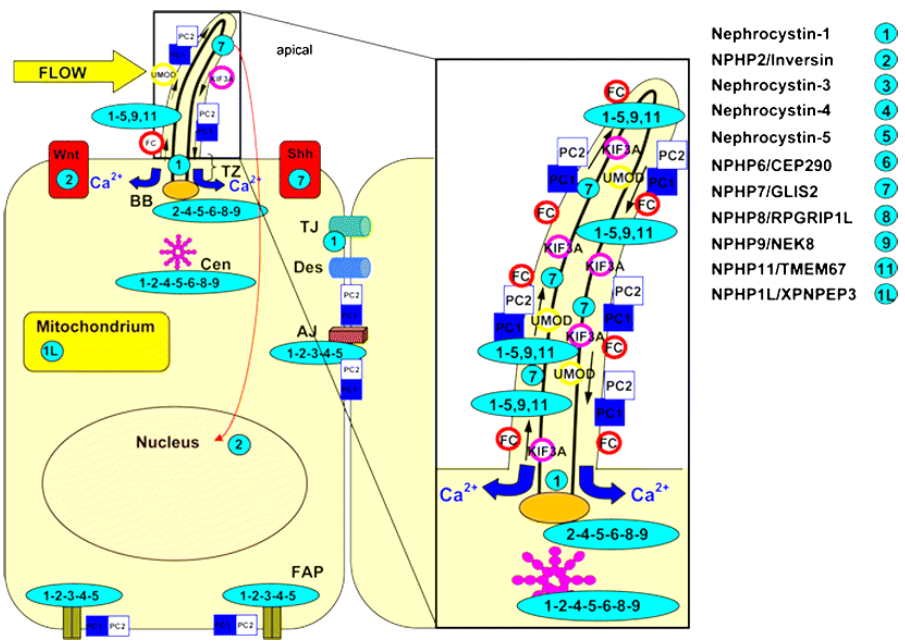

Fig. 8. Subcellular localization of the NPHP molecules nephrocystins. Nephrocystins are detected in the primary cilia, basal bodies, the mitotic spindle, focal adhesions, and adherens junctions. Most nephrocystins are expressed in the primary cilium (PC, enlarged box), the basal body (BB), and centrosomes (Cen) in a cell cycle-dependent manner. NPHP1 is expressed in the transition zone (TZ), focal adhesion plaques (FAP), adherens junctions (AJ), and tight junctions (TJ). Arrows in the cilium show the directions of the anterograde and retrograde transport along the microtubule transport. The intraflagellar transport is mediated by kinesin 2, a heterotrimeric protein that is composed of two motor units (Kif3a and Kif3b) and one nonmotor unit (KAP3). Sensory cilia transfer external stimuli. Wnt and hedgehog (Shh) signaling interfere with planar cell polarity by affecting the orientation of the centrosomes and mitotic spindles. Reprint with permission[34].

Acknowledgement

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