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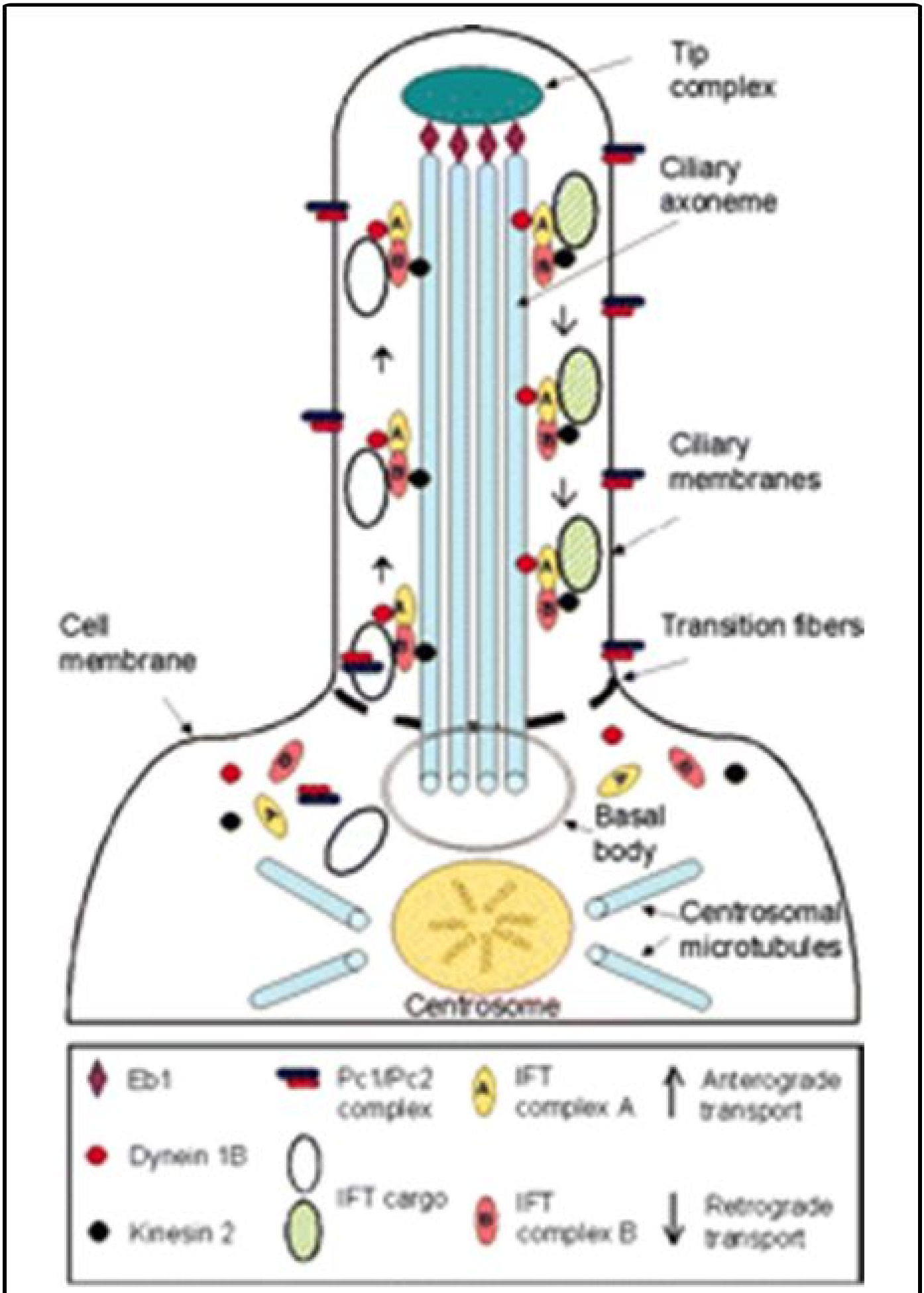
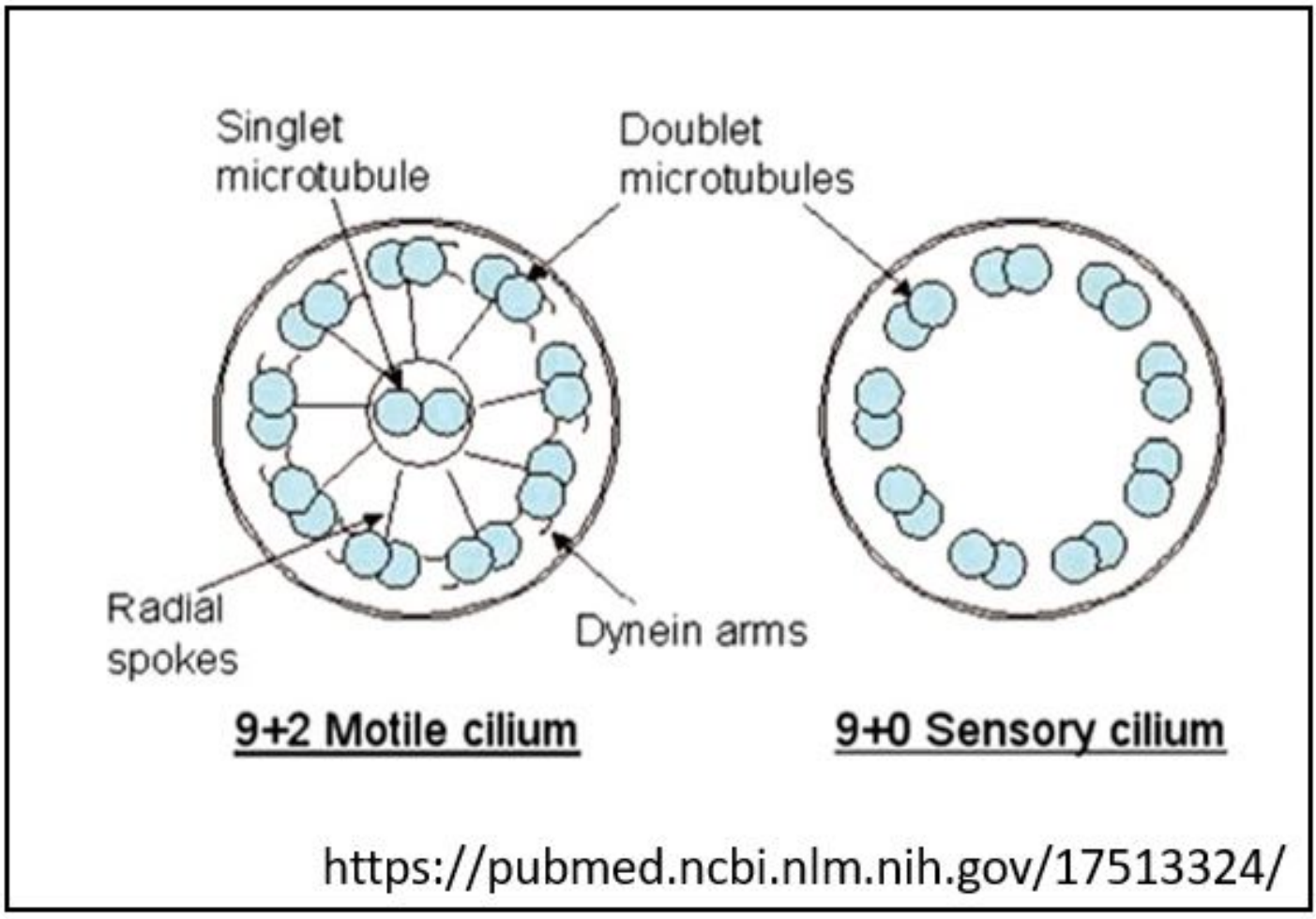
1/ 💥Hello, #Nephtwitter 💥
⚡Let's talk a little bit about #ciliopathies today.
⚡How are Nephronophthisis (NPHP), polycystic kidney disease (PKD), & in fact many cystic diseases (aka #ciliopathies) related?!
Join me in the exploration-
#tweetorial #MedTwitter #ASPNeph #NSMC

2/ 💥Let's begin with Cilia-
📌Motile cilia- generate flow of mucus & CSF
📌Non-motile/sensory cilia (inner ear, retina, & olfactory epithelium)
- plays a part in important pathways [Hedgehog, Wnt (wingless-Int-1), & PCP (planar cell polarity) signaling]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588048/



https://pubmed.ncbi.nlm.nih.gov/17513324/

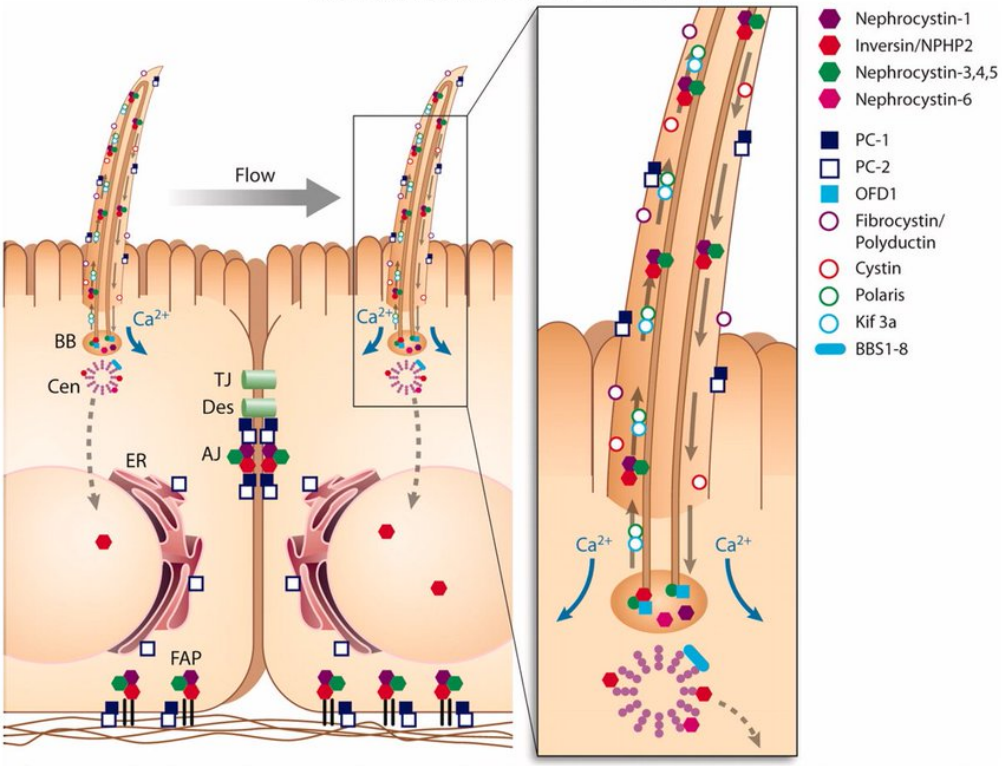


3/Now let's move on to💥Cystoproteins💥

📌These are proteins in cilia when mutated → cystic kidney diseases in humans, mice, or zebrafish

📌expressed in primary cilia, basal bodies or centrosomes

Cystoproteins are proteins of genes that are mutated in cystic kidney diseases of humans, mice, or zebrafish

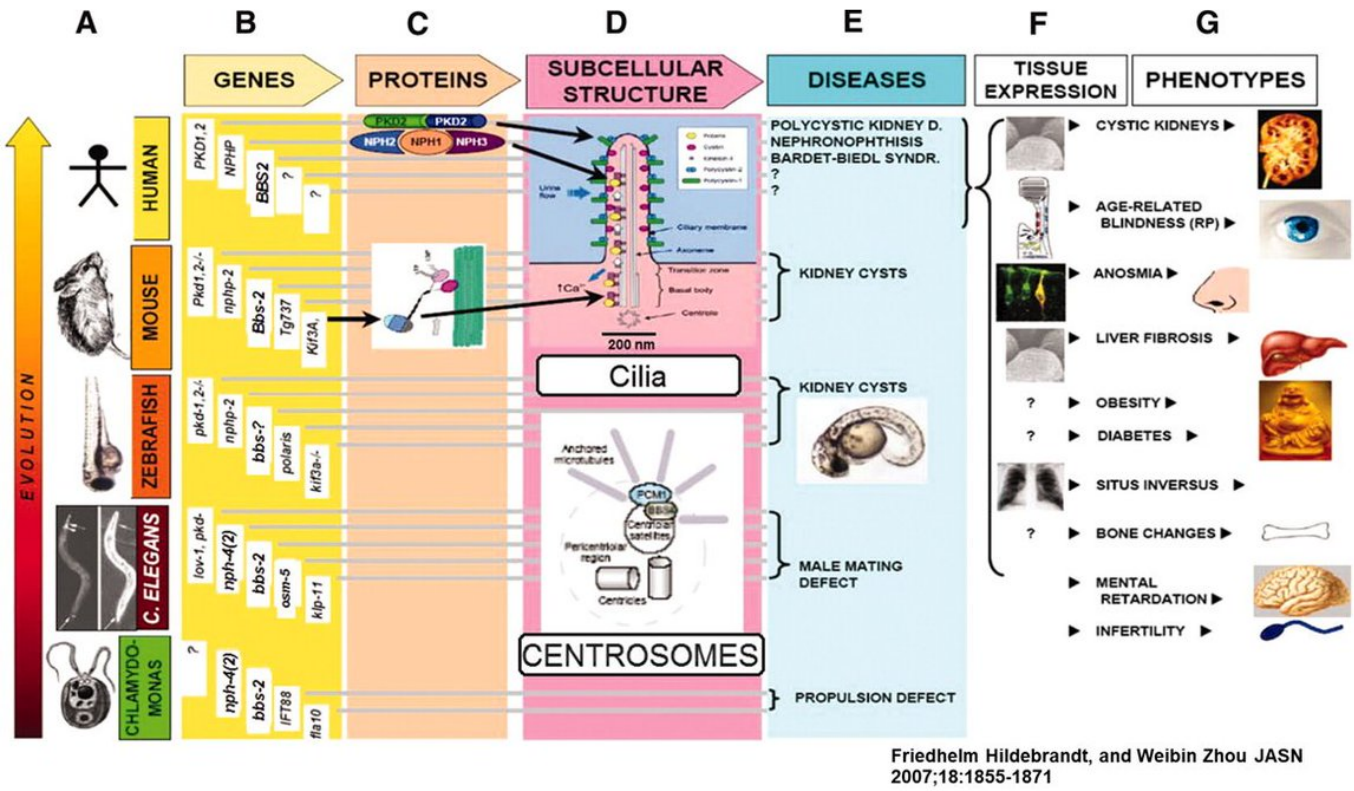


The speckled arrow in the primary cilium indicates the direction of anterograde transport along the microtubule system mediated by kinesin 2, a heterotrimeric protein that is composed of two motor units (Kif3a and Kif3b) and one nonmotor unit (KAP3). AJ, adherens junction; BB, basal body; Cen, centriole; ER, endoplasmic reticulum; FAP, focal adhesion plaque; TJ, tight junction; PC-1, polycystin-1; PC-2, polycystin-2.

Friedhelm Hildebrandt, and Weibin Zhou
JASN 2007;18:1855-1871

4/ 💥Did you know that these cystoproteins were conserved for over >1.5 billion years of evolution from the unicellular organism to vertebrates!

⚡Fascinating isn’t it ?!⚡



Friedhelm Hildebrandt, and Weibin Zhou JASN 2007;18:1855-1871

5/ 💥Cystoproteins💥

📌participate in protein-protein interaction complexes

📌share certain domains with each other

These interactions may partially explain the cause of similar phenotypes

6/ 💥Some examples of cystoprotein related diseases-

Cystoproteins	Disease
Nephrocystin1-6, Inversin	NPHP / Nephronophthisis
Polycystin 1,2	ADPKD
Fibrocystin/ Polyductin	ARPKD
OFD1	Orofaciodigital syndrome

7/ Defects in cytsoproteins➡️ affects cilia formation, maintenance, or function (signaling mechanisms)➡️ impaired processing of extracellular cues➡️defects in tissue differentiation & maintenance
➡️#ciliopathies & #pleiotropy

Organ	manifestation	Ciliary pathology
Kidney	Cystic Kidney Disease	Involvement of primary cilia of kidney epithelial cells
Brain	Mental retardation, Cerebellar vermis hypoplasia, Oculomotor apraxia	Defects in microtubule-associated functions during neurite outgrowth and axonal guidance
Retina	Retinal degeneration and blindness	connecting cilium of photoreceptor cells in the retina
Liver	Liver fibrosis and bile duct atresia	Primary cilia of cholangiocytes (cells lining bile ducts)

8/ Some more examples and characteristics of 💥 ciliopathies💥

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588048/

https://pubmed.ncbi.nlm.nih.gov/25266212/

Ciliopathy or related disease	Genes	Affected Tissues	Presentation
Alstorm Syndrome	*ALMS1*		Blindness, hearing loss, obesity
Bardet Biedel Syndrome	*BBS1- BBS16*		Blindness, anosmia, kidney dysfunction, polydactyly, obesity, mental retardation
Joubert Syndrome	*JBTS1- JBTS15*		Blindness, anosmia, Kidney and liver dysfunction, uncoordinated movements, mental retardation
Mainzer-Saldino syndrome	*IFT 140*		Blindness, phalangeal cone shaped epiphyses, abnormality of the proximal femur, kidney dysfunction
MOPD II and Seckel syndrome	*PCNT* *POC1A*		Anosmia, Developmental defects, dwarfism
Senior-Loken Syndrome	*NPHP 1,4,6*		Blindness, male infertility
Usher Syndrome	*USHA1A-G* *USH2A-C* *USH3A-B*		Blindness, Hearing loss, infertility, movement disorders

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Syndrome	Renal manifestations	Extrarenal manifestations	Genetic basis
ADPKD	Urine-concentrating defects, enlarged kidneys with continuous growth of cysts throughout, haematuria, hypertension, decline in glomerular filtration rate with advancing age9,[16,19,37]	Liver and pancreatic cysts, intracranial aneurysms, arachnoid cysts, abdominal hernias, cardiac complications (valve abnormalities, left ventricular hypertrophy), male infertility, intestinal diverticulosis, bronchiectasis[10,15]	Mutations in *PKD1* and *PKD2* account for 91% of all cases[10,12]
ARPKD	Chronic renal insufficiency, multiple renal cysts[65,66,67]	Biliary dysgenesis, congenital hepatic fibrosis, hepatosplenomegaly, hepatic complications, cholangitis, cholangiocarcinomas[65,66,67]	Mutations in *PKHD1*[145,146]
NPHP	Polydipsia, polyuria, urine-concentrating defects and secondary enuresis in childhood;[74] tubulointerstitial nephropathy, corticomedullary cysts, tubular basement membrane thickening and disruption	Numerous possible extrarenal complications, largely depending upon the exact mutation[74] Many extrarenal complications of NPHP are described as separate syndromes	18 known subtypes (NPHP1–18), accounting for 40% of cases[72,76,77]
MCKD	Tubulointerstitial nephritis, renal cysts, hyperuricaemia, gout, small-sized kidneys[96,97,98]	None identified to date	*MUC1* mutations are associated with type 1 disease;[100,101,102] mutations in *UMOD1* account for 17.8% of type 2 disease
Senior–Løken syndrome	Similar to NPHP	Retinitis pigmentosa[73]	Always observed in NPHP5 and NPHP6, can also occur in most other subtypes of NPHP except NPHP7[74]
Joubert syndrome	Similar to NPHP	Cerebellar vermis hypoplasia or aplasia, liver fibrosis, retinitis pigmentosa, coloboma of the eye, altered neonatal respiration[73,86,87]	Mutations in 21 different genes[153]
Meckel–Gruber syndrome	Similar to NPHP	Bilateral postaxial hexadactyly, hepatobiliary ductal dysgenesis causing fibrocystic liver disease, CNS malformations, usually occipital encephalocele[82]	Mutations in 11 different genes[154]
Bardet–Biedl syndrome	Similar to NPHP	Polydactyly, juvenile obesity, mental retardation, retinal defects, anosmia, hypogonadism[93]	BBS1–19 account for 80% of cases[95]
VHL syndrome	Renal cell carcinoma, multiple renal cysts, resembling ADPKD[127]	Haemangioblastomas in the CNS (retina, brain and spinal cord); possible phaeochromocytomas, pancreatic cysts, pancreatic neuroendocrine tumours, endolymphatic sac tumours of the inner ear, cystadenomas of the epididymis and broad ligament[127]	Autosomal dominant mutations in *VHL*[128,129,131]
Tuberous sclerosis complex	Renal cell carcinoma, angiomyolipoma, sometimes multiple renal cysts	Hypomelanotic macules, epilepsy, cognitive dysfunction, behavioural disturbances, developmental disorders	Mainly sporadic *TSC1* or *TSC2* germ line mutations[125]

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BBS, Bardet–Biedl syndrome; CNS, central nervous system; MCKD, medullary cystic kidney disease; NPHP, nephronophthisis; VHL, von Hippel–Lindau syndrome.

9/ That's All Folks!

To learn more about #Nephronophthisis case-based discussion, logon to #ASPNeph October medical education #webinar Thank you @amyaimei @DrFlashHeart @RoshanPGeorgeMD @priti899 @pedsnephrology