

Cystic Diseases of the Kidneys: From Bench to Bedside

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Abstract

Exploration into the causes of hereditary renal cystic diseases demonstrates a deep-rooted connection with the proteomic components of the cellular organelle cilia. Cilia are essential to the signaling cascades and their dysfunction has been tied to a range of renal cystic diseases initiating with studies on the orpk mouse model.^{1,2} Here we delve into renal cystic pathologies that have been tied with ciliary proteasome and highlight the genetics associated with each. The pathologies are grouped based on the mode of inheritance where inherited causes that result in cystic kidney disease phenotypes include autosomal dominant and autosomal recessive polycystic kidney disease, nephronophthisis (Bardet-Biedl Syndrome and Joubert Syndrome), and autosomal dominant tubulointerstitial kidney disease. Alternatively, ciliopathy associated cystic kidney diseases include tuberous sclerosis, Zellweger syndrome, and Von Hoppel-Lindau disease. Additionally, we group the pathologies by the mode of inheritance to discuss variations in recommendations for genetic testing for biological relatives of a diagnosed individual.

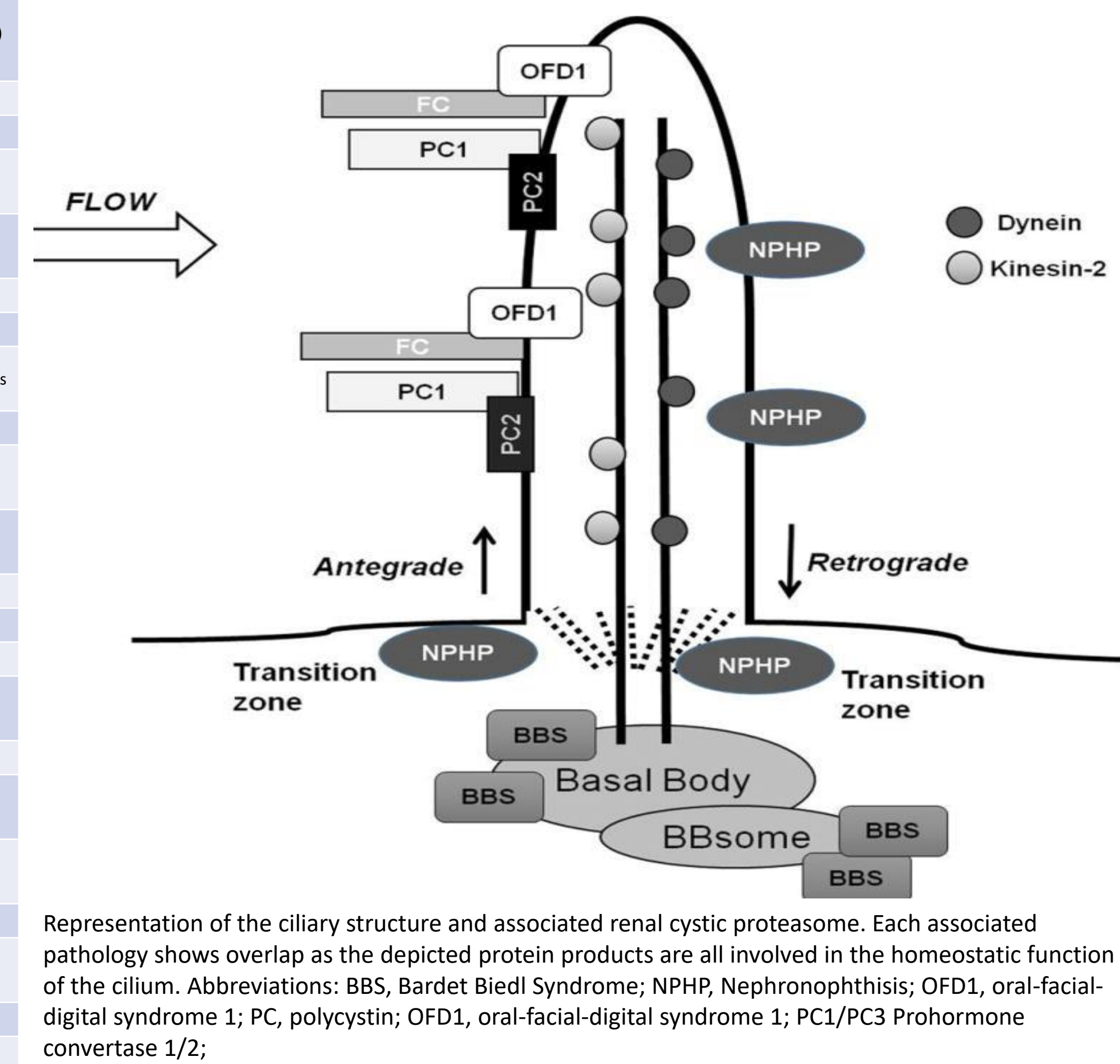
Cystic Kidney Disease as a Ciliopathy

- Recent data provides compelling evidence that inherited cystic disease is linked to alterations in different genes involved in the formation and function of both the cilia of the embryonic node and cilia in epithelial renal tubes³
- Kidney function depends on flow through nephrons to create a GFR, this flow is sensed by the primary cilia of the nephrons and deflected by the fluid passing to increase intracellular calcium. Normally, this increase causes regulation of a calcium-dependent channel, however, disruption of cilia formation is proposed to result in both defects in the channel and ultimately, polycystic kidney disease⁴
- Signaling pathway connecting cilia to cell proliferation is largely unknown; polycystin-1 and polycystin-2 have been implicated in numerous pathways including JAK-STAT, Wnt, β -catenin, protein kinase C, cAMP, G-protein, and Ca^{2+} signaling pathways⁵
- Models using nonbiased forward genetic screening for cystic kidney mutants in non-human models found defects in cilia associated with abnormal cytogenesis^{6,7}
- Analyzing mutant phenotypes suggests that cilia link extracellular signals to intracellular events such as cell proliferation; further research will be paramount in dissecting the signaling network of cilia's role in coordinated cellular responses

Genetic Counseling

- Prenatal and preimplantation genetic testing plans should be highly considered for families with high-risk pregnancies that are predisposed to pathogenic gene mutations for cystic diseases
- Autosomal dominant ciliopathies (ADPKD, HNF1B, BORSD, VHL):
Assuming one parent has the proband, all offspring have a 50% chance of inheriting the pathogenic gene mutation, increasing to 75% if both parents are afflicted. Assessing parental predisposition can be done on macroscale with MRI or CT scan (ADPKD) or microscale with genetic testing of both parents for the proband
- Autosomal recessive ciliopathies (isolated/syndromic nephronophthisis, ARPKD, BBS, Zellweger):
Siblings of the proband have 25% chance of inheriting both genotypes resulting in pathology, 50% chance of becoming a carrier, and 25% of not being a carrier. Siblings of the proband's parents are at 50% risk of being carriers of the pathogenic gene mutation. For high-risk pregnancies (> 25% chance of autosomal recessive ciliopathy), if mutant genes have been identified in the family member, prenatal testing is available. For low-risk pregnancies (no family history of ARPKD, but enlarged cystic kidneys on prenatal ultrasound), there are multiple testing options including karyotyping or array with fetal ultrasonography, molecular genetic testing, and renal ultrasound (ARPKD) of both parents assessing predisposition
- Simple Mendelian inheritance patterns cannot always be attributed to the transmittance of these pathologies – rather, oligogenic inheritance plays a role

Classification of Cystic Kidney Diseases		
Genetic	Autosomal Dominant	Autosomal dominant polycystic kidney disease (ADPKD)
		Glomerulocystic kidney disease (GCKD)
	Autosomal Recessive	Autosomal recessive polycystic kidney disease (ARPKD)
		Juvenile nephronophthisis
		Bardet-Biedl syndrome
		Beckwith-Wiedemann syndrome
		Glomerulocystic kidney disease (GCKD)
		Hajdu-Cheney syndrome
		Ivemark Syndrome
		Jeune syndrome and other chondrodysplasia syndrome
		Meckel-Gruber syndrome
		Orofaciodigital syndrome, Type I
		Short-rib polydactyly syndrome
		Trisomy 9 and 13
		Tuberous sclerosis complex
		Von Hippel-Lindau syndrome
Sporadic		Zellweger cerebrohepatorenal syndrome
		Calyceal diverticulum
		Isolated diffuse cystic dysplasia
		Multicystic Dysplastic Kidney (MCDK)
		Simple renal cyst
Miscellaneous		Unilateral/localized cystic kidney disease
		Acquired cystic kidney disease
		Bilateral renal vein thrombosis
		Bilateral Wilms' tumor
		Congenital nephrotic syndrome
		Glomerulonephritis
		Glycogen storage disease
		Leukemia or lymphoma
		Nephroblastomatosis
		Pyelonephritis
	Radiocontrast nephropathy	
	Transient ephremegaly	



Causes of Hepatorenal Fibrocystic Diseases

Fibrocystic Disease	Gene and Protein	Renal Impairment	Hepatic Association	Extra hepatorenal Implications
Autosomal Dominant Polycystic Kidney Disease	PKD (Polycystin-1) PKD2 (Polycystin-2)	Cysts over whole nephron	Nodular hepatomegaly, Pancreatic cysts	Hypertension, Retinal dysplasia, Aneurysm
Autosomal Recessive Polycystic Kidney Disease	PKHD1 (Fibrocystin)	Cysts towards collecting ducts	Congenital hepatic fibrosis, Portal hypertension	Hypoplastic lung, Splenomegaly, Hypersplenism, Cholangitis
Bardet-Biedl Syndrome	BBS1-21 (BBSome)	Structural impairment, Cyst formation, Urinary tract malformation	Non-alcoholic Steatohepatitis	Retinal dystrophy, Obesity, Polydactyly, Hypogonadism, Mental retardation
Joubert Syndrome	INPP5E (PtdIns Phosphatase)	Cystic dysplasia	Congenital hepatic fibrosis	Muscle control (Ataxia), Coloboma, Polydactyly, Encephalocele
Zellweger Syndrome	PEX1 (Pex1p)	Cortical microcysts	Fibrosis, Cirrhosis, Hepatomegaly	Craniofacial abnormality, Hypomyelination, Chondrodysplasia
Von Hippel-Lindau	VHL (pVHL)	Clear cell RCC	Tumor	PNET, Pancreatic cysts, Pheochromocytoma, Hemangioblastoma, Ovarian cysts
Jeune Syndrome	Several Implicated Genes	Cystic dysplasia	Fibrosis	Skeletal dysplasia (Small Thorax), Pancreatic cysts, Retinal Abnormality
Nephronophthisis	NPHP1-18	Hyperechogenic kidneys, reduced size, and corticomedullary cysts	-	Tapetoretinal degeneration, ocular motor apraxia, and cone-shaped epiphysis

Conclusion

Ciliopathies are an emerging conceptual framework to tie in the clinically relevant renal cystic diseases with the emerging cellular research into ciliopathies. By combining forays with animal (particularly mouse models) with clinically oriented research, new insights can further the molecular basis of understanding the cystic kidney diseases and provide novel understanding into the role of cilia in pathologic manifestations. The quintessential example is the creation of double knockout mice lacking *Pkd* genes and *Kif3a* or *Ift20* which reduced the burden of polycystic kidney disease. Clinical trials can further employ these basic science trials further progress bedside-oriented research.

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