Experimental Models of Polycystic Kidney Disease: Applications and Therapeutic Testing

Cynthia J. Sieben, Ph.D.[1] and Peter C. Harris, Ph.D.[1]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

Supplemental Information

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Supplemental Table 1. Summary of Available PKD Models *(ARPKD and syndromic PKDs only)*

				Phenotypes			
Model	**Mutation mechanism**	**Human Gene**	**Disease (stage)**	**Kidney**	**Extrarenal**	**Survival**	**Ref(s)**
Zebrafish							
dzip1l$^{-/-}$	Knockout, CRISPR	*DZIP1L*	ARPKD (Early?)	Pronephric cysts	Body curvature, hydrocephalus, and otolith defects	ND	1,2
cc2d2a$^{-/-}$	Konckout, ENU	*CC2D2A*	JBTS (Early?)	Pronephric cysts	Pericardial edema, and body curvature	ND	2,3
inpp5e$^{-/-}$	Knockout, CRISPR	*INPP5E*	JBTS (Early?)	Pronephric cysts	Pericardial effusion, and body curvature	ND	2,4,5
arl13b$^{-/-}$	Knockout, retroviral insertion	*ARL13B*	JBTS (Early?)	Pronephric cysts	Body curvature	ND	2,6
tmem67$^{e3/e3}$	Hypomorphic, TALENs (~10% TMEM67)	*TMEM67*	MKS, JBTS, NPHP, RHYNS, CHF (Early?)	Pronephric and mesonephric cysts; more prominent in adult male fish	Body curvature in embryos and adults	Viable to at least 15m	7
ift172$^{-/-}$	Knockout, retroviral insertion	*IFT172*	Short-rib thoracic dysplasia (Early?)	Renal cysts	Body curvature, and cartilage defects	ND	2,8-10
tsc2$^{-/-}$	Knockout, ENU	*TSC2*	TSC (Early?)	No phenotype	Brain defects and enlarged liver	Increased embryonic mortality	2,11
Mice							
Pkhd1$^{del2/del2}$	Knockout, deletion of exon 2	*PKHD1*	ARPKD (Early)	Dilation of PT at advanced age; phenotypes more severe in females?	Severe PLD; occasional pancreatic cysts; phenotypes more severe in females?	ND	12,13
Pkhd1$^{lsl/lsl}$	Knockout, insertion of lox-stop-lox (lsl) cassette in IVS2	*PKHD1*	ARPKD (Early)	Dilation of PT at advanced age; phenotypes more severe in females?	Severe PLD; occasional pancreatic cysts; phenotypes more severe in females?	ND	13,14

Pkhd1$^{C642X/+}$	Truncation, C642X (c.1926_1932delTGATTGG, in exon 20)	*PKHD1*	ARPKD (Early)	Dilation of PT at advanced age (1.5y); phenotypes more severe in females?	Biliary cysts and increased number of bile ducts	ND	13,15
Pkhd1$^{del3-4/del3-4}$	Knockout, deletion of exons 3-4	*PKHD1*	ARPKD (Early)	Dilation of CD and TALH (6m or older, ~55%)	Abnormalities of the biliary tract; subset of animals exhibit pancreatic cysts, perinatal respiratory failure, or growth retardation	ND	13,16
Pkhd1$^{lacZ/lacZ}$	Knockout, replacement of exons 1-3 with a LacZ reporter gene	*PKHD1*	ARPKD (Early)	Dilation of PT, CD, and glomeruli at 9m	Dilatation of the bile ducts and periportal fibrosis; dilatation of the pancreatic exocrine ducts, with less frequent pancreatic cysts	ND	13,17
Pkhd1$^{del15-16\ GFP/del15-16\ GFP}$	Knockout, deletion of exon 16 and disruption of exon 15 by insertion of GFP/Neomycin cassette	*PKHD1*	ARPKD (Early)	Mild to severe tubule dilation or cyst formation (~10% early onset [4m] and ~60% late onset [after 1 yr]	Cysts, fibrosis, and necrosis in the liver (4m); dilation of pancreatic ducts with interstitial fibrosis (6m)	Median ~10m	13,18
Bbs2$^{-/-}$	Knockout, deletion of exons 5-14	*BBS2*	BBS (Early)	Inflammatory infiltration and multiple cysts (5m)	Obesity; retinal degeneration; accumulation of lipids in the liver; male infertility	ND	19
Bbs4$^{-/-}$	Knockout, gene trap IVS1	*BBS4*	BBS (Early)	Tubular cystic lesions (6m); inflammatory infiltration; later onset of glomerular cysts	Obesity; metabolic syndrome; anosmia; male infertility; hydrometrocolpos; neural tube defects; retinal degeneration; hypertension; perinatal lethality	ND	20,21
Bbs8$^{-/-}$	Knockout, deletion of exons 1-2	*BBS8*	BBS (Early)	Mild dilation (8m)	Reduced olfactory response	ND	22

Cys1$^{cpk/cpk}$	Spontaneous deletion of 2 portions of exon 1, premature stop codon	*CYS1*	Boichis disease (Early & Late)	Bilateral cysts	Liver inflammation; pancreatic cysts	3-4w	13,23,24
Bicc1$^{bpk/bpk}$	Spontaneous insertion of 2 bases in exon 22	*BICC1*	CYSRD (Early & Late)	Bilateral cysts	Liver cysts	ND	13,25-29
Bicc1$^{jcpk/jcpk}$	Splicing mutation, premature stop codon	*BICC1*	CYSRD (Early & Late)	Bilateral cysts	Bile duct defects	ND	13,27,30-35
Arl3$^{Gt(neo)1Lex/Gt(neo)1Lex}$	Aberrant splicing (IVS1 insertion of neomycin cassette)	*ARL3*	JBTS (Late)	Defective development and cysts	Bile duct and gall bladder defects; pancreatic cysts	Maximum P21	13,36
Tmem218$^{-/-}$	Knockout, gene trap IVS1	*TMEM218*	JBTS, MKS (Early & Late)	Bilateral cysts, inflammation, and fibrosis (14w)	Retinal degeneration	ND	37
Cep290$^{-/-}$	Knockout, deletion of exons 1-4	*CEP290*	MKS, JBTS, NPHP, BBS (Late)	Bilateral cysts (12m- small number of survivors without hydrocephalus)	Early vision loss; hydrocephalus	80% death by P21	38
Cep290$^{Gt/Gt}$	Truncation, gene trap IVS25	*CEP290*	MKS, JBTS, NPHP, BBS (Late)	Severe cystic disease (P19)	Majority of mice die mid-gestation; occasional survivors have hydrocephalus and severe cystic kidneys	E13-14	38
Tmem67$^{Bpck/Bpck}$	Knockout, large deletion including *Tmem67* and 5 other genes	*TMEM67*	MKS, JBTS, NPHP, RHYNS, CHF (Late)	Bilateral cysts (E16.5)	Retinal degeneration; skeletal defects; cochlea defects; occasional hydrocephalus	P16/P13	39,40
Tmem67$^{-/-}$	Knockout, deletion of exons 2-3	*TMEM67*	MKS, JBTS, NPHP, RHYNS, CHF (Late)	Bilateral cysts (E18.5)	Early postnatal lethality	ND	41
Anks6$^{I747N/I747N}$	Missense mutation (p.I747N; induced by ENU)	*ANKS6*	NPHP (Early & Late)	Slowly progressive cyst formation from birth to 12m (peak %KW/BW and renal dysfunction)	None described	18m	42

Anks6$^{Strkr/Strkr}$	Missense mutation (p.M187K; induced by ENU)	*ANKS6*	NPHP (Early & Late)	Glomerular cysts (at birth) and cystic dilatation (first several wks); inflammation (9-10m)	Heterotaxy and *situs inversus*; cardiopulmonary malformations	Perinatal lethality in mice with CHD; those without CHD survive long term (evaluated up to 10m)	43
Nek8$^{jck/jck}$	Spontaneous missense mutation (p.G448V)	*NEK8*	NPHP, Renal-hepatic-pancreatic dysplasia 2 (Early & Late)	Enlarged kidneys with cysts at 4w	No other abnormalities described	~20-25w	13,44-46
Nek8$^{Roc/Roc}$	Missense mutation (p.I124T; induced by ENU)	*NEK8*	NPHP, Renal-hepatic-pancreatic dysplasia 2 (Early & Late)	Glomerular cysts (at birth) and cystic dilatation (first several wks); occasional hydroureter, hyrdonephrosis, and duplex kidneys	Heterotaxy and *situs inversus*; cardiopulmonary malformations	Perinatal lethality in mice with CHD; those without CHD are postnatally viable	43
Nphp2$^{-/-}$	Knockout, deletion exons 3-11 (transgenic insertion)	*NPHP2*	NPHP (Late)	Bilateral cysts (E15)	Altered left-right laterality; bile duct malformations; postnatal death	P7	47
Nphp3$^{pcy/pcy}$	Spontaneous missense mutation (p.I1614S)	*NPHP3*	NPHP (Early & Late)	Inflammation, fibrosis, and cysts	Occasional intracranial aneurysm; craniofacial and skeletal defects	~40w, but 2y in C57BL6 background	13,48,49
Nek1$^{kat-2J/kat-2J}$	Spontaneous insertion (c.966insG), resulting a frameshift and premature stop	*NEK1*	Short rib-polydactyly syndrome type II (Early & Late)	Progressive bilateral cysts (3m)	Runted; hydrocephalus; anemia; nervous system and craniofacial defects; male sterility; portal bile duct dilation in older mice	Median 211d	13,50,51
Rats							

Pkhd1$^{PCK/PCK}$	Spontaneous missense mutation in IVS35, resulting in frameshift	*PKHD1*	ARPKD (Early & Late)	Progressive PKD starting from 20d; more severe in males	Progressive PLD, more prominent in females	18m	13,52,53
Tmem67$^{wpk/wpk}$	Spontaneous missense mutation (p.P394L)	*TMEM67*	MKS, JBTS, NPHP, RHYNS, CHF (Late)	Severe cystic disease, enlargement, and uremia at P21	Brain, retinal, and fertility defects (males)	ND	13,54-57
Anks6$^{+/Cy}$ (Han:SPRD)	Spontaneous missense mutation (p.R823W)	*ANKS6*	NPHP (Early & Late)	Progressive PKD, fibrosis, inflammation; uremia and proteinuria in males after 10m	Liver and pancreatic cysts in females after 17m; hyperlipidemia and hypertension in males after 10m	12-18m *Anks6*$^{+/Cy}$ (3w in *Anks6*$^{Cy/Cy}$)	13,58-61
Nek8$^{LPK/LPK}$	Spontaneous missense mutation (p.R650C)	*NEK8*	NPHP, Renal-hepatic-pancreatic dysplasia 2 (Early & Late?)	Cyst formation	Hypertension	ND	13,62,63

ARPKD, autosomal recessive polycystic kidney disease; ND, not determined; TSC, tuburous sclerosis complex; MKS, meckel syndrome; JBTS, joubert syndrome; NPHP, nephronophthisis; RHYNS, retinitis pigmentosa-hypopituitarism-nephronophthisis-skeletal dysplasia syndrome; CHF, congenital hepatic fibrosis; VEO, very early-onset; CYSRD: cystic renal dysplasia; BBS, bardet-biedl syndrome

Supplemental Table 2. Summary of Clinical and Preclinical Trials *(ADPKD only; no preclinical results)*

		Clinical Trials		Preclinical Trials		Clinical/ Preclinical Trials Consistent	Preclinical Trials Consistent	Ref(s)
Intervention	**Target/Pathway (PKD Relevance)**	**Number, Status**	**Results**	**Species**	**Results**			
Lisinopril, Telmisartan, placebo	ACEI, ARB (inhibits ACE & ARB, lowers BP)	2, C	ACEI controlled BP; ARB did not impact eGFR	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT01885559, NCT00283686
Candesartan, Clinidipine, and non-calcium channel blocker (CCB) agents	ARB, CCB, and other antihypertensive drugs (inhibits ARB and voltage-dependent calcium channels, lowers BP)	1, U	NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT00541853
Clinidipine, Imidapril	CCB, ACEI (inhibits voltage-dependent calcium channels and ACE, lowers BP)	1, U	NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT00890279
Tetracosactin	Adrenocorticotropic hormone (ACTH) peptide (increases aldosterone, counteracting hyponatremia, hyperkalemia, and metabolic acidosis)	1, C	NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT00598377
Spironolactone	Aldosterone Receptor Antagonist (endothelial cell dysfunction & arterial stiffness)	1, C	Vascular endothelial cell function not improved, despite ↓ BP	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT01853553
AL01211	Glucosylceramide Synthase (GCS) Inhibitor (reduces glycosphingolipid formation; regulate proliferation, apoptosis, and cell signaling)	1, R	NA	NA	NA	Unknown	NA	ClinicalTrials.gov: NCT04908462

Bardoxolone	Nrf2 pathway activator/NFkB inhibitor (activates Nrf2 antioxidant pathway & inhibits pro-inflammatory & pro-apoptotic NFkB pathway)	3, C/R	NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT03918447, NCT03749447, NCT03366337; [64]
Ng-monomethyl-L-arginine (L-NMMA)	Nitric oxide (NO) synthase inhibitor (inhibits natriuresis & diuresis)	1, C	NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT00345137
Lanreotide	Somatostatin (growth hormone [GH] inhibiting hormone) analogue; Somatostatin receptors, inhibits GH, insulin, & glucagon secretion (targets proliferation & cAMP)	4, C/U	↓ TKV, TLV, no improvement in KF, & ↑ incidence of gallstones; ↓ TKV, TLV, & eGFR only after start; & NA	N/A	N/A	Unknown	N/A	ClinicalTrials.gov: NCT01616927, NCT01354405, NCT02127437, NCT00565097

ACEI, ACE inhibitor; ARB, Angiotensin Receptor Blocker; BP, blood pressure; eGFR, estimated GFR; C, Completed; R, Recruiting; U, Unknown; NA, not available; N/A, not applicable; TKV, total kidney volume; TLV, total liver volume; KF, kidney function

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