Chapter 2
Genetic Mechanisms of ADPKD

Do Yeon Kim and Jong Hoon Park

Abstract Autosomal dominant polycystic kidney disease is caused by mutation of PKD1 (polycystic kidney disease-1) or PKD2 (polycystic kidney disease-2). PKD1 and PKD2 encode PC1 (polycystin-1) and PC2 (polycystin-2), respectively. In addition, the mutation of cilia-associated proteins is also a recognized major factor of pathogenesis, since PC1 and PC2 are located in primary cilium. Abnormalities of PC1 or PC2 lead to aberrant signaling through downstream pathways, such as the negative growth regulation, G protein activation, and canonical and non-canonical Wnt pathways. According to the "second hit" model, an additional somatic mutation results in the expansion of cyst growth. In this chapter we discuss the genetic mechanisms and signaling pathways involved in ADPKD.

Keywords Genetic mechanism • PKD • Mutation • PKD1 • PKD2 • Polycystin-1 • Polycystin-2 • Signaling pathways

2.1 Polycystin-1 and Polycystin-2

Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations of two genes, namely PKD1 (polycystic kidney disease-1) and PKD2 (polycystic kidney disease-2), which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Approximately 85 % of ADPKD cases result from mutations in PKD1. PC1 is a 450-kD receptor-like protein with a large extracellular N terminus, 11 membrane-spanning domains, and a short cytoplasmic C terminus. The expression of PC1 was evaluated in epithelial cells during development (Ward et al. 1996), but its expression level is high in fetal renal tissue only and low in adult tissue (Chauvet et al.

D.Y. Kim
Molecular Medicine Laboratory, Department of Life systems, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Youngsan-gu, Seoul 04310, South Korea
e-mail: doyeon42@sookmyung.ac.kr

J.H. Park (✉)
Department of Life systems, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Youngsan-gu, Seoul 04310, South Korea
e-mail: parkjh@sookmyung.ac.kr

J.H. Park, C. Ahn (eds.), *Cystogenesis*, Advances in Experimental Medicine and Biology 933, DOI 10.1007/978-981-10-2041-4_2

2002). PC1 localizes to the cilium, plasma membrane, and adhesion complex in polarized epithelial cells (Ibraghimov-Beskrovnaya et al. 1997; Huan and van Adelsberg 1999). PC1 and PC2 form a complex through their C-terminal tails (CTTs) to play a role in intracellular Ca^{2+} regulation (Tsiokas et al. 1997; Qian et al. 1997). The N terminus of PC1 consists of 15 PKD repeat motifs, two leucine-rich motifs, and a C-type lectin domain (Harris et al. 1995; Bycroft et al. 1999). These domains play an important role in mediating the subcellular localization of PC1 within the plasma membrane and junctional complexes (Streets et al. 2009; Babich et al. 2004). The CTT of PC1 includes a G protein-binding domain, a coiled-coil domain, and residues associated with ubiquitin-mediated degradation (Low et al. 2006). The N- and C-terminal domains of PC1 can be cleaved. The N-terminal domain is cleaved at the G protein-coupled receptor proteolysis site (GPS) in the early secretory pathway (Wei et al. 2007; Yu et al. 2007). Generally, PC1 exists as a heterogeneous population of the full-length and N-terminal cleaved forms (Wei et al. 2007). However, one study suggested that N-terminal cleavage is necessary for the complete functional activation of PC1 (Qian et al. 2002). One interesting study revealed that cleaved CTT, which is assembled in the nucleus during reduced fluid flow in mouse kidney, was increased in the cyst-lining cells in ADPKD (Low et al. 2006).

PC2 (968 aa; ~110 kDa) is a six-transmembrane protein with intracellular N and C termini (Mochizuki et al. 1996). PC2 acts as a Ca^{2+}–responsive cation channel of the transient receptor potential family (Gonzalez-Perrett et al. 2001). Although PC2 is co-localized with PC1 to the cilium and plasma membrane (Yoder et al. 2002; Yu et al. 2009), the major portion of cellular PC2 is observed in the intracellular compartment and functions to release calcium from the intracellular store (Vassilev et al. 2001). The channel formed by PC1 and PC2 in complex is activated in response to ciliary bending, and it leads to signal transduction by chemical or mechanical stimuli (Nauli et al. 2003). The calcium-conducting pore consists of the loop between the fifth and sixth transmembrane domains, and a missense mutation in the conducting pore was shown to cause ADPKD (Koulen et al. 2002). PC2 also functions as an indirect regulator of the cytoplasmic calcium level together with two other intracellular Ca^{2+} channels, namely the inositol 1, 4, 5-triphosphate receptor (IP3R) and ryanodine receptor. The C-terminus of PC2, which directly interacts with IP3R, results in IP3-induced Ca^{2+} flux. PC2 also binds to the ryanodine receptor channel and regulates calcium-induced calcium release (Anyatonwu et al. 2007; Li et al. 2009). The largest pools of PC2 appear in the ER and the early Golgi body among the subcellular compartments (Cai et al. 1999; Koulen et al. 2002). PC2's subcellular localization requires specific signal transduction and trafficking proteins that bind to PC2's C terminus (Chapin and Caplan 2010). The movement of PC2 from the ER to the Golgi is modulated by polycystin-2 interactor (PIGEA-14), which causes a redistribution of PC2 (Hidaka et al. 2004).

The PC1 and PC2 proteins are co-located in the primary cilium and ER (Yoder et al. 2002); however, they are also found in other locations depending on their functions (Hanaoka et al. 2000; Grimm et al. 2003). Especially, many studies have suggested that PC1 and PC2 reciprocally influence each other's localization. One study confirmed that impairing the function of PC1 prevents GPS cleavage in ADPKD

cyst cells, which leads to a decreased co-localization and amount of both PC1 and PC2 in primary cilia (Xu et al. 2007). The interaction between PC1 and PC2 has been recognized as an important factor for creating a functional ion channel through the intrinsic channel formed by activated PC2 alone or the emergent channel formed by the PC1-PC2 complex (Hanaoka et al. 2000). A physical connection between PC1 and PC2 is mediated by the CTTs of PC1 and PC2 (Qian et al. 1997; Tsiokas et al. 1997; Casuscelli et al. 2009). Through this interaction, PC2 prevents the ability of PC1 to activate G proteins (Delmas et al. 2002).

2.2 Signaling Pathways of PKD1 and PKD2

Although the complete pathologic mechanisms remain to be elucidated, the loss of function of the PC1 and/or PC2 proteins leads to ADPKD pathogenesis through a myriad of signaling pathways, including planar cell polarity (PCP), Wnt, mammalian target of rapamycin (mTOR), cyclic adenosine monophosphate (cAMP), G-protein coupled receptor (GPCR), cystic fibrosis transmembrane conductance regulator (CFTR), epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), cellular Ca^{2+}, and the cell cycle (Gallagher et al. 2010). As explained above, PC1 and PC2 form a complex that functions as a transient receptor potential channel to maintain intracellular calcium homeostasis (Vassilev et al. 2001; Anyatonwu and Ehrlich 2005) and as a calcium release channel (Koulen et al. 2002). Disruption of PC1/PC2 results in a decreased level of intracellular Ca^{2+}, leading to upregulated cAMP signaling and increased cell proliferation (Masyuk et al. 2006) (Fig. 2.1).

An increased level of cAMP has been identified in many animal models of polycystic kidney disease (PKD), not only in the kidney but also in other tissues, such as

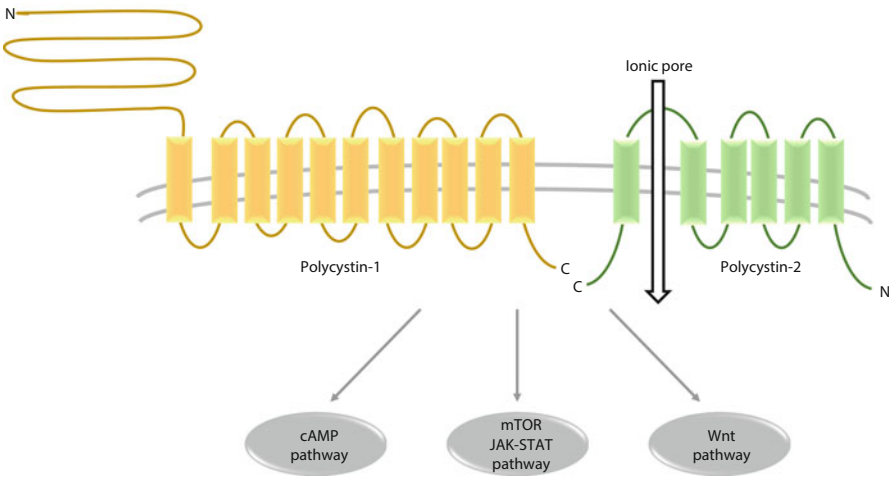

Fig. 2.1 Representative signaling pathways regulated by polycystin 1 and/or 2

cholangiocytes (Masyuk et al. 2007), vascular smooth muscle cells (Kip et al. 2005), and the choroid plexus (Banizs et al. 2007). cAMP levels are modulated by the activities of membrane-bound GPCRs, soluble adenylyl cyclases (ACs), and cAMP phosphodiesterases (PDEs). Several hypotheses have been proposed regarding the mechanisms by which the cAMP level is influenced in PKD. At first, reduced calcium directly inhibits PDE1, indirectly suppresses PDE3, and activates membrane bound AC6 (Gattone et al. 2003; Wang et al. 2010). Next, a defect in PC2-mediated calcium entry in the ciliary protein complex occurs, leading to the inhibition of AC5/6 and the activation of PDE4C (Choi et al. 2011). Also, depletion of the endoplasmic reticulum (ER) calcium store triggers the accumulation of stromal interaction molecule 1 to the plasma membrane and activates AC6 (Spirli et al. 2012). Likewise, several factors can contribute to an increase in the intracellular level of cAMP—disrupted PC1 binds to heterotrimeric G proteins (Parnell et al. 1998), vasopressin V2 receptor is upregulated, and circulating vasopressin, forskolin, ATP, or other adenylyl cyclase agonists are increased (Putnam et al. 2007; Hovater et al. 2008). Certain ACs and PDEs are recognized as being important in PKD progression because of their influence on compartmentalized pools of cAMP (Torres and Harris 2014).

One of the most evident characteristics of ADPKD pathogenesis is elevated cellular growth and division. Polycystin proteins inhibit cell growth through interactions with several pathways including the mTOR (Shillingford et al. 2006) and Janus kinase (JAK)-signal transducers and activators of transcription (STAT) (Bhunia et al. 2002) pathways. PC1 inhibits mTOR activity by stabilizing the tuberous sclerosis 1-tuberous sclerosis 2 (TSC1-TSC2) complex, which is known as a negative regulator of the mTOR complex (Huang and Manning 2008; Distefano et al. 2009; Dere et al. 2010). PC1 stabilizes the TSC1-TSC2 complex through two distinct mechanisms. PC1 suppresses the ERK-dependent phosphorylation of TSC2 at S664 (Distefano et al. 2009) and Akt-dependent phosphorylation of TSC2 at S939 by binding to TSC2 at the plasma membrane (Dere et al. 2010). The influence of the PC1-TSC2 interaction allows the TSC1-TSC2 complex to inhibit the mTOR signaling pathway. PC1 also functions as a positive regulator of p21 (cyclin-dependent kinase inhibitor) by binding and activating members of the JAK-STAT pathway (Bhunia et al. 2002). Following the PC2-JAK2 interaction and the formation of the intact C terminus of PC1, PC1 can activate STAT1 and STAT3 and it allow to increase p21 and decrease cell growth (Bhunia et al. 2002). PC2 also reduces cell proliferation by binding both eukaryotic translation elongation initiation factor 2a (eIF2a) and pancreatic ER-resident eIF2a kinase (Liang et al. 2008).

The Wnt signaling pathways regulate cell growth, differentiation, and planar cell polarity and are classified into the canonical (β-catenin dependent) and noncanonical (β-catenin independent) pathways. Both PC1 and PC2 affect the canonical Wnt pathway. In the case of PC1, the cleaved PC1 CTT directly or indirectly binds to β-catenin, translocates to the nucleus, and promotes T cell factor (TCF)-dependent transcription (Lal et al. 2008). PC2 also modulates the expression levels of some Wnt pathway components (Kim et al. 2009). In the noncanonical Wnt pathway, the function of PC1 is associated with the maintenance of planar cell polarity. Planar cell polarity is essential for oriented cell division and the establishment of kidney

tubule structure, and defects in this process trigger the expansion of renal tubules and cyst formation (Fischer et al. 2006).

2.3 Genetic Mechanisms of Pathogenesis

Approximately 85 % of ADPKD patients have mutations in PKD1; thus, it is supposed that mutations in PKD1 cause a more severe disease than mutations in PKD2 do (Rossetti et al. 2007). Generally, patients with PKD1 mutations develop ADPKD symptoms at younger ages relative to patients with PKD2 mutations, but their disease phenotypes are influenced by mutations in both genes (Hateboer et al. 1999). A myriad of mutation types that can cause ADPKD have been revealed, and the position of each mutation determines the severity of the disease (Rossetti et al. 2002; Rossetti and Harris 2013). Recent studies revealed that the type of mutation is more important, because patients with truncating mutations showed more severe disease phenotypes than did those with non-truncating mutations (Pei et al. 2012; Cornec-Le Gall et al. 2013).

ADPKD is genetically dominant at the organismal level, but recessive at the cellular level (Chapin and Caplan 2010). Although a germ line mutation in PKD1 or PKD2 is necessary to induce cyst formation in ADPKD, cysts form in only part of the kidney tubules and hepatic bile duct. However, in adult tissues, both copies of the mutated polycystic gene undergo recessive loss of function, causing cyst formation to be accelerated in a subset of tubular epithelial cells. This paradox is explained by the occurrence of an additional somatic "second hit" mutation (Qian et al. 1996; Watnick et al. 1998; Pei et al. 1999). Although the somatic second hit mutation mechanism is generally applicable to human ADPKD, additional factors contribute to determining the extent of cyst formation, including non-cell autonomous effects on polycystins-expressing cells (Nishio et al. 2005), the timing of PKD1 in the developmental stages (Piontek et al. 2007), and hypomorphic mutations of PC1 compared to complete loss of function mutations (Rossetti et al. 2009; Hopp et al. 2012). Especially, reduced PC1 dosage is suggested to explain autosomal recessive PKD phenotypes, in which the degree of PC1 dysregulation is associated with the extent of tubule dilation and cyst formation (Hopp et al. 2012).

ADPKD is characterized by the formation of multiple fluid-filled kidney cysts. Thus, we need to focus on the mechanisms of cyst expansion. In the patient's kidney, cells are organized in a circle and these lumens must fill with fluid. Subsequently, cysts increase by cell proliferation, leading to the dilation of the renal tubule and renal failure (Qian et al. 1996; Brasier and Henske 1997). One model involves a loss of oriented cell division in the cells of mouse models with kidney-specific PKD1 or PKD2 mutation, which does not initiate cyst formation. This model suggests that a defect of planar cell polarity is an important factor in the expansion of many cysts; however, this factor was not essential for the initiation of cyst formation (Nishio et al. 2010). According to other studies, ion absorption and secretion in cyst-lining epithelial cells are significant for cyst formation. cAMP can stimulate Cl^- transport,

resulting in the rapid and progressive dilation of tubules (Grantham 1996). In addition, one research group reported that tubule enlargement is prevented by inhibitors of $Na^+-K^+-2Cl^-$ cotransporters and CFTR (Montesano et al. 2009). Therefore, cAMP signaling plays a key role in renal cyst formation by promoting Cl^- driven fluid secretion. Furthermore, polycystin proteins also function as regulators of cAMP signaling by modulating the expression, localization, and activity of Cl^- channels (Chapin and Caplan 2010).

References

Anyatonwu GI, Ehrlich BE (2005) Organic cation permeation through the channel formed by polycystin-2. J Biol Chem 280(33):29488–29493. doi:10.1074/jbc.M504359200

Anyatonwu GI, Estrada M, Tian X, Somlo S, Ehrlich BE (2007) Regulation of ryanodine receptor-dependent calcium signaling by polycystin-2. Proc Natl Acad Sci U S A 104(15):6454–6459. doi:10.1073/pnas.0610324104

Babich V, Zeng WZ, Yeh BI, Ibraghimov-Beskrovnaya O, Cai Y, Somlo S, Huang CL (2004) The N-terminal extracellular domain is required for polycystin-1-dependent channel activity. J Biol Chem 279(24):25582–25589. doi:10.1074/jbc.M402829200

Banizs B, Komlosi P, Bevensee MO, Schwiebert EM, Bell PD, Yoder BK (2007) Altered pH(i) regulation and Na(+)/HCO3(−) transporter activity in choroid plexus of cilia-defective Tg737(orpk) mutant mouse. Am J Physiol Cell Physiol 292(4):C1409–C1416. doi:10.1152/ajpcell.00408.2006

Bhunia AK, Piontek K, Boletta A, Liu L, Qian F, Xu PN, Germino FJ, Germino GG (2002) PKD1 induces p21(waf1) and regulation of the cell cycle via direct activation of the JAK-STAT signaling pathway in a process requiring PKD2. Cell 109(2):157–168

Brasier JL, Henske EP (1997) Loss of the polycystic kidney disease (PKD1) region of chromosome 16p13 in renal cyst cells supports a loss-of-function model for cyst pathogenesis. J Clin Invest 99(2):194–199. doi:10.1172/JCI119147

Bycroft M, Bateman A, Clarke J, Hamill SJ, Sandford R, Thomas RL, Chothia C (1999) The structure of a PKD domain from polycystin-1: implications for polycystic kidney disease. EMBO J 18(2):297–305. doi:10.1093/emboj/18.2.297

Cai Y, Maeda Y, Cedzich A, Torres VE, Wu G, Hayashi T, Mochizuki T, Park JH, Witzgall R, Somlo S (1999) Identification and characterization of polycystin-2, the PKD2 gene product. J Biol Chem 274(40):28557–28565

Casuscelli J, Schmidt S, DeGray B, Petri ET, Celic A, Folta-Stogniew E, Ehrlich BE, Boggon TJ (2009) Analysis of the cytoplasmic interaction between polycystin-1 and polycystin-2. Am J Physiol Renal Physiol 297(5):F1310–F1315. doi:10.1152/ajprenal.00412.2009

Chapin HC, Caplan MJ (2010) The cell biology of polycystic kidney disease. J Cell Biol 191(4):701–710. doi:10.1083/jcb.201006173

Chauvet V, Qian F, Boute N, Cai Y, Phakdeekitacharoen B, Onuchic LF, Attie-Bitach T, Guicharnaud L, Devuyst O, Germino GG, Gubler MC (2002) Expression of PKD1 and PKD2 transcripts and proteins in human embryo and during normal kidney development. Am J Pathol 160(3):973–983. doi:10.1016/S0002-9440(10)64919-X

Choi YH, Suzuki A, Hajarnis S, Ma Z, Chapin HC, Caplan MJ, Pontoglio M, Somlo S, Igarashi P (2011) Polycystin-2 and phosphodiesterase 4C are components of a ciliary A-kinase anchoring protein complex that is disrupted in cystic kidney diseases. Proc Natl Acad Sci U S A 108(26):10679–10684. doi:10.1073/pnas.1016214108

Cornec-Le Gall E, Audrezet MP, Chen JM, Hourmant M, Morin MP, Perrichot R, Charasse C, Whebe B, Renaudineau E, Jousset P, Guillodo MP, Grall-Jezequel A, Saliou P, Ferec C, Le

Meur Y (2013) Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol JASN 24(6):1006–1013. doi:10.1681/ASN.2012070650

Delmas P, Nomura H, Li X, Lakkis M, Luo Y, Segal Y, Fernandez-Fernandez JM, Harris P, Frischauf AM, Brown DA, Zhou J (2002) Constitutive activation of G-proteins by polycystin-1 is antagonized by polycystin-2. J Biol Chem 277(13):11276–11283. doi:10.1074/jbc.M110483200

Dere R, Wilson PD, Sandford RN, Walker CL (2010) Carboxy terminal tail of polycystin-1 regulates localization of TSC2 to repress mTOR. PLoS One 5(2):e9239. doi:10.1371/journal.pone.0009239

Distefano G, Boca M, Rowe I, Wodarczyk C, Ma L, Piontek KB, Germino GG, Pandolfi PP, Boletta A (2009) Polycystin-1 regulates extracellular signal-regulated kinase-dependent phosphorylation of tuberin to control cell size through mTOR and its downstream effectors S6K and 4EBP1. Mol Cell Biol 29(9):2359–2371. doi:10.1128/MCB.01259-08

Fischer E, Legue E, Doyen A, Nato F, Nicolas JF, Torres V, Yaniv M, Pontoglio M (2006) Defective planar cell polarity in polycystic kidney disease. Nat Genet 38(1):21–23. doi:10.1038/ng1701

Gallagher AR, Germino GG, Somlo S (2010) Molecular advances in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis 17(2):118–130. doi:10.1053/j.ackd.2010.01.002

Gattone VH 2nd, Wang X, Harris PC, Torres VE (2003) Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 9(10):1323–1326. doi:10.1038/nm935

Gonzalez-Perrett S, Kim K, Ibarra C, Damiano AE, Zotta E, Batelli M, Harris PC, Reisin IL, Arnaout MA, Cantiello HF (2001) Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca2 + −permeable nonselective cation channel. Proc Natl Acad Sci U S A 98(3):1182–1187

Grantham JJ (1996) The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: recent advances. Am J Kidney Dis Off J Nat Kidney Found 28(6):788–803

Grimm DH, Cai Y, Chauvet V, Rajendran V, Zeltner R, Geng L, Avner ED, Sweeney W, Somlo S, Caplan MJ (2003) Polycystin-1 distribution is modulated by polycystin-2 expression in mammalian cells. J Biol Chem 278(38):36786–36793. doi:10.1074/jbc.M306536200

Hanaoka K, Qian F, Boletta A, Bhunia AK, Piontek K, Tsiokas L, Sukhatme VP, Guggino WB, Germino GG (2000) Co-assembly of polycystin-1 and −2 produces unique cation-permeable currents. Nature 408(6815):990–994. doi:10.1038/35050128

Harris PC, Ward CJ, Peral B, Hughes J (1995) Polycystic kidney disease. 1: identification and analysis of the primary defect. J Am Soc Nephrol JASN 6(4):1125–1133

Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D (1999) Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet 353(9147):103–107

Hidaka S, Konecke V, Osten L, Witzgall R (2004) PIGEA-14, a novel coiled-coil protein affecting the intracellular distribution of polycystin-2. J Biol Chem 279(33):35009–35016. doi:10.1074/jbc.M314206200

Hopp K, Ward CJ, Hommerding CJ, Nasr SH, Tuan HF, Gainullin VG, Rossetti S, Torres VE, Harris PC (2012) Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. J Clin Invest 122(11):4257–4273. doi:10.1172/JCI64313

Hovater MB, Olteanu D, Welty EA, Schwiebert EM (2008) Purinergic signaling in the lumen of a normal nephron and in remodeled PKD encapsulated cysts. Purinergic Signal 4(2):109–124. doi:10.1007/s11302-008-9102-6

Huan Y, van Adelsberg J (1999) Polycystin-1, the PKD1 gene product, is in a complex containing E-cadherin and the catenins. J Clin Invest 104(10):1459–1468. doi:10.1172/JCI5111

Huang J, Manning BD (2008) The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. Biochem J 412(2):179–190. doi:10.1042/BJ20080281

Ibraghimov-Beskrovnaya O, Dackowski WR, Foggensteiner L, Coleman N, Thiru S, Petry LR, Burn TC, Connors TD, Van Raay T, Bradley J, Qian F, Onuchic LF, Watnick TJ, Piontek K, Hakim RM, Landes GM, Germino GG, Sandford R, Klinger KW (1997) Polycystin: in vitro

synthesis, in vivo tissue expression, and subcellular localization identifies a large membrane-associated protein. Proc Natl Acad Sci U S A 94(12):6397–6402

Kim I, Ding T, Fu Y, Li C, Cui L, Li A, Lian P, Liang D, Wang DW, Guo C, Ma J, Zhao P, Coffey RJ, Zhan Q, Wu G (2009) Conditional mutation of Pkd2 causes cystogenesis and upregulates beta-catenin. J Am Soc Nephrol JASN 20(12):2556–2569. doi:10.1681/ASN.2009030271

Kip SN, Hunter LW, Ren Q, Harris PC, Somlo S, Torres VE, Sieck GC, Qian Q (2005) [Ca2+]i reduction increases cellular proliferation and apoptosis in vascular smooth muscle cells: relevance to the ADPKD phenotype. Circ Res 96(8):873–880. doi:10.1161/01.RES.0000163278.68142.8a

Koulen P, Cai Y, Geng L, Maeda Y, Nishimura S, Witzgall R, Ehrlich BE, Somlo S (2002) Polycystin-2 is an intracellular calcium release channel. Nat Cell Biol 4(3):191–197. doi:10.1038/ncb754

Lal M, Song X, Pluznick JL, Di Giovanni V, Merrick DM, Rosenblum ND, Chauvet V, Gottardi CJ, Pei Y, Caplan MJ (2008) Polycystin-1 C-terminal tail associates with beta-catenin and inhibits canonical Wnt signaling. Hum Mol Genet 17(20):3105–3117. doi:10.1093/hmg/ddn208

Li Y, Santoso NG, Yu S, Woodward OM, Qian F, Guggino WB (2009) Polycystin-1 interacts with inositol 1,4,5-trisphosphate receptor to modulate intracellular Ca2+ signaling with implications for polycystic kidney disease. J Biol Chem 284(52):36431–36441. doi:10.1074/jbc.M109.068916

Liang G, Yang J, Wang Z, Li Q, Tang Y, Chen XZ (2008) Polycystin-2 down-regulates cell proliferation via promoting PERK-dependent phosphorylation of eIF2alpha. Hum Mol Genet 17(20):3254–3262. doi:10.1093/hmg/ddn221

Low SH, Vasanth S, Larson CH, Mukherjee S, Sharma N, Kinter MT, Kane ME, Obara T, Weimbs T (2006) Polycystin-1, STAT6, and P100 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease. Dev Cell 10(1):57–69. doi:10.1016/j.devcel.2005.12.005

Masyuk AI, Masyuk TV, Splinter PL, Huang BQ, Stroope AJ, LaRusso NF (2006) Cholangiocyte cilia detect changes in luminal fluid flow and transmit them into intracellular Ca2+ and cAMP signaling. Gastroenterology 131(3):911–920. doi:10.1053/j.gastro.2006.07.003

Masyuk TV, Masyuk AI, Torres VE, Harris PC, Larusso NF (2007) Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3′,5′-cyclic monophosphate. Gastroenterology 132(3):1104–1116. doi:10.1053/j.gastro.2006.12.039

Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ, Reynolds DM, Cai Y, Gabow PA, Pierides A, Kimberling WJ, Breuning MH, Deltas CC, Peters DJ, Somlo S (1996) PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 272(5266):1339–1342

Montesano R, Ghzili H, Carrozzino F, Rossier BC, Feraille E (2009) cAMP-dependent chloride secretion mediates tubule enlargement and cyst formation by cultured mammalian collecting duct cells. Am J Physiol Renal Physiol 296(2):F446–F457. doi:10.1152/ajprenal.90415.2008

Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J (2003) Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet 33(2):129–137. doi:10.1038/ng1076

Nishio S, Hatano M, Nagata M, Horie S, Koike T, Tokuhisa T, Mochizuki T (2005) Pkd1 regulates immortalized proliferation of renal tubular epithelial cells through p53 induction and JNK activation. J Clin Invest 115(4):910–918. doi:10.1172/JCI22850

Nishio S, Tian X, Gallagher AR, Yu Z, Patel V, Igarashi P, Somlo S (2010) Loss of oriented cell division does not initiate cyst formation. J Am Soc Nephrol JASN 21(2):295–302. doi:10.1681/ASN.2009060603

Parnell SC, Magenheimer BS, Maser RL, Rankin CA, Smine A, Okamoto T, Calvet JP (1998) The polycystic kidney disease-1 protein, polycystin-1, binds and activates heterotrimeric G-proteins in vitro. Biochem Biophys Res Commun 251(2):625–631. doi:10.1006/bbrc.1998.9514

Pei Y, Watnick T, He N, Wang K, Liang Y, Parfrey P, Germino G, St George-Hyslop P (1999) Somatic PKD2 mutations in individual kidney and liver cysts support a "two-hit" model of cystogenesis in type 2 autosomal dominant polycystic kidney disease. J Am Soc Nephrol JASN 10(7):1524–1529

Pei Y, Lan Z, Wang K, Garcia-Gonzalez M, He N, Dicks E, Parfrey P, Germino G, Watnick T (2012) A missense mutation in PKD1 attenuates the severity of renal disease. Kidney Int 81(4):412–417. doi:10.1038/ki.2011.370

Piontek K, Menezes LF, Garcia-Gonzalez MA, Huso DL, Germino GG (2007) A critical developmental switch defines the kinetics of kidney cyst formation after loss of Pkd1. Nat Med 13(12):1490–1495. doi:10.1038/nm1675

Putnam WC, Swenson SM, Reif GA, Wallace DP, Helmkamp GM Jr, Grantham JJ (2007) Identification of a forskolin-like molecule in human renal cysts. J Am Soc Nephrol JASN 18(3):934–943. doi:10.1681/ASN.2006111218

Qian F, Watnick TJ, Onuchic LF, Germino GG (1996) The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. Cell 87(6):979–987

Qian F, Germino FJ, Cai Y, Zhang X, Somlo S, Germino GG (1997) PKD1 interacts with PKD2 through a probable coiled-coil domain. Nat Genet 16(2):179–183. doi:10.1038/ng0697-179

Qian F, Boletta A, Bhunia AK, Xu H, Liu L, Ahrabi AK, Watnick TJ, Zhou F, Germino GG (2002) Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations. Proc Natl Acad Sci U S A 99(26):16981–16986. doi:10.1073/pnas.252484899

Rossetti S, Harris PC (2013) The genetics of vascular complications in autosomal dominant polycystic kidney disease (ADPKD). Curr Hypertens Rev 9(1):37–43

Rossetti S, Burton S, Strmecki L, Pond GR, San Millan JL, Zerres K, Barratt TM, Ozen S, Torres VE, Bergstralh EJ, Winearls CG, Harris PC (2002) The position of the polycystic kidney disease 1 (PKD1) gene mutation correlates with the severity of renal disease. J Am Soc Nephrol JASN 13(5):1230–1237

Rossetti S, Consugar MB, Chapman AB, Torres VE, Guay-Woodford LM, Grantham JJ, Bennett WM, Meyers CM, Walker DL, Bae K, Zhang QJ, Thompson PA, Miller JP, Harris PC, Consortium C (2007) Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol JASN 18(7):2143–2160. doi:10.1681/ASN.2006121387

Rossetti S, Kubly VJ, Consugar MB, Hopp K, Roy S, Horsley SW, Chauveau D, Rees L, Barratt TM, Van't Hoff WG, Niaudet P, Torres VE, Harris PC (2009) Incompletely penetrant PKD1 alleles suggest a role for gene dosage in cyst initiation in polycystic kidney disease. Kidney Int 75(8):848–855. doi:10.1038/ki.2008.686

Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, Flask CA, Novick AC, Goldfarb DA, Kramer-Zucker A, Walz G, Piontek KB, Germino GG, Weimbs T (2006) The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. Proc Natl Acad Sci U S A 103(14):5466–5471. doi:10.1073/pnas.0509694103

Spirli C, Locatelli L, Fiorotto R, Morell CM, Fabris L, Pozzan T, Strazzabosco M (2012) Altered store operated calcium entry increases cyclic 3′,5′-adenosine monophosphate production and extracellular signal-regulated kinases 1 and 2 phosphorylation in polycystin-2-defective cholangiocytes. Hepatology 55(3):856–868. doi:10.1002/hep.24723

Streets AJ, Wagner BE, Harris PC, Ward CJ, Ong AC (2009) Homophilic and heterophilic polycystin 1 interactions regulate E-cadherin recruitment and junction assembly in MDCK cells. J Cell Sci 122(Pt 9):1410–1417. doi:10.1242/jcs.045021

Torres VE, Harris PC (2014) Strategies targeting cAMP signaling in the treatment of polycystic kidney disease. J Am Soc Nephrol JASN 25(1):18–32. doi:10.1681/ASN.2013040398

Tsiokas L, Kim E, Arnould T, Sukhatme VP, Walz G (1997) Homo- and heterodimeric interactions between the gene products of PKD1 and PKD2. Proc Natl Acad Sci U S A 94(13):6965–6970

Vassilev PM, Guo L, Chen XZ, Segal Y, Peng JB, Basora N, Babakhanlou H, Cruger G, Kanazirska M, Ye C, Brown EM, Hediger MA, Zhou J (2001) Polycystin-2 is a novel cation channel

implicated in defective intracellular Ca(2+) homeostasis in polycystic kidney disease. Biochem Biophys Res Commun 282(1):341–350. doi:10.1006/bbrc.2001.4554

Wang X, Ward CJ, Harris PC, Torres VE (2010) Cyclic nucleotide signaling in polycystic kidney disease. Kidney Int 77(2):129–140. doi:10.1038/ki.2009.438

Ward CJ, Turley H, Ong AC, Comley M, Biddolph S, Chetty R, Ratcliffe PJ, Gattner K, Harris PC (1996) Polycystin, the polycystic kidney disease 1 protein, is expressed by epithelial cells in fetal, adult, and polycystic kidney. Proc Natl Acad Sci U S A 93(4):1524–1528

Watnick TJ, Torres VE, Gandolph MA, Qian F, Onuchic LF, Klinger KW, Landes G, Germino GG (1998) Somatic mutation in individual liver cysts supports a two-hit model of cystogenesis in autosomal dominant polycystic kidney disease. Mol Cell 2(2):247–251

Wei W, Hackmann K, Xu H, Germino G, Qian F (2007) Characterization of cis-autoproteolysis of polycystin-1, the product of human polycystic kidney disease 1 gene. J Biol Chem 282(30):21729–21737. doi:10.1074/jbc.M703218200

Xu C, Rossetti S, Jiang L, Harris PC, Brown-Glaberman U, Wandinger-Ness A, Bacallao R, Alper SL (2007) Human ADPKD primary cyst epithelial cells with a novel, single codon deletion in the PKD1 gene exhibit defective ciliary polycystin localization and loss of flow-induced Ca2+ signaling. Am J Physiol Renal Physiol 292(3):F930–F945. doi:10.1152/ajprenal.00285.2006

Yoder BK, Hou X, Guay-Woodford LM (2002) The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris, and cystin, are co-localized in renal cilia. J Am Soc Nephrol JASN 13(10):2508–2516

Yu S, Hackmann K, Gao J, He X, Piontek K, Garcia-Gonzalez MA, Menezes LF, Xu H, Germino GG, Zuo J, Qian F (2007) Essential role of cleavage of Polycystin-1 at G protein-coupled receptor proteolytic site for kidney tubular structure. Proc Natl Acad Sci U S A 104(47):18688–18693. doi:10.1073/pnas.0708217104

Yu Y, Ulbrich MH, Li MH, Buraei Z, Chen XZ, Ong AC, Tong L, Isacoff EY, Yang J (2009) Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. Proc Natl Acad Sci U S A 106(28):11558–11563. doi:10.1073/pnas.0903684106