International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (1781-1787), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Polycystic Kidney Disease, Pathogenesis, Diagnosis, Treatment: Review

[1]Mohammed aqeel Jaafari, [2]Mousa Mohammed Hadi, [3]Faisal Mohammed Ali Gasmi, [4]Ali shaya kaabi, [5]Ahmad Mosa Ali Faqeeh, [6]Anas Mohammed Alnahari

Abstract: **The objective of this review was to discuss the pathogenesis of Polycystic kidney disease (PKD), as well as the diagnosis and treatments approaches, through reviewing the evidence based on this manner. Databases; PubMed, and Embase were computerized searched for relevant studies concerning the Polycystic kidney disease (PKD), published in English language until the end of 2016. more relevant articles were extracted through searching the literature included in references of selected studies. Autosomal dominant polycystic kidney disease (ADPKD) is a common, acquired condition for which there is presently no effective specific medical therapy, pathologic accumulation of fluid in epithelium lined cavities causing the damage of adjacent regular parenchyma. Acquired cystic diseases, consisting of the most prevalent form, ADPKD, kidney ultrasonography is commonly utilized for the medical diagnosis of ADPKD and age-dependent criteria have been specified for subjects at-risk of PKD1. The utility of the PKD1 ultrasound criteria in the center setting is uncertain considering that their efficiency qualities have not been specified for the milder PKD2 and the gene type for a lot of test topics is unknown.**

Keywords: **Polycystic kidney disease (PKD), Diagnosis, treatments approaches.**

1. INTRODUCTION

Polycystic kidney disease (PKD) is a group of monogenic conditions that lead to renal cyst development. The morbidity connected with the most common kinds, autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), is mainly restricted to the kidney and liver (and, in ADPKD, vasculature) and extends from neonates to old age [(1,2)]. In a rarer group of mainly recessively acquired pleiotropic disorders, cystic kidneys or cystic dysplasia are part of a set of developmental phenotypes. Over the past 15 years, positional cloning techniques have actually identified more than 20 genes triggering these conditions. The typical forms of PKD are connected with a low level of genic heterogeneity but severe allelic heterogeneity, whereas marked genic heterogeneity is discovered in syndromic kinds of PKD. Novel protein households have actually been recognized, the functions which are just now coming to light. A factor that joins all these disorders is the involvement of the primary cilium and the base of the cilium, the basal body, in their pathogenesis. PKD proteins, and orthologs in other types, have been localized to cilia/basal body, and loss or irregularities of cilia in the kidney are connected with cyst development. Rapid development toward understanding the etiology and pathogenesis of these diseases is exposing possible restorative targets that are now being examined [(3,4)]. ADPKD is generally identified in adults and, with an incidence of 1:400 - 1000, is one of the most typical monogenic disorders. The disease is characterized by the progressive, bilateral advancement and augmentation of focal cysts that in most cases ultimately lead to end-stage renal disease (ESRD) [(1,4)]. In the United States, 4.4% of patients needing kidney replacement therapy (dialysis or transplant) have ADPKD. There is considerable phenotypic variability, however, from rare infantile cases with big cystic kidneys to patients in their tenth decade with adequate kidney function [(2)]. ADPKD is a systemic disease, with cyst development likewise taking place in the liver, pancreas, critical vesicles, and arachnoid. In the liver, it can (hardly ever; regularly in females) lead to extreme polycystic liver disease (PLD) requiring surgical intervention. Other significant phenotypes in ADPKD involve the vasculature, with intracranial aneurysms approximately five times more common than in the basic population and considerable morbidity/mortality associated with aneurysmal rupture [(1)]. Normal presenting signs include flank pain, hematuria, renal colic, urinary tract infections, and hypertension [(3)]. ADPKD can normally be detected in at-risk grownups by imaging of the kidney by ultrasound, CT, or MRI with numerous cysts usually noticeable

that boost in size and number with age. Current MRI data from an observational trial of ADPKD showed that kidneys increase typically 5.27% per year, however with a wide variety of variability, and that renal volume can be utilized to monitor disease progression prior to a measurable decrease in function [4].

The objective of this review was to discuss the pathogenesis of Polycystic kidney disease (PKD), as well as the diagnosis and treatments approaches, through reviewing the evidence based on this manner.

2. METHODOLOGY

Databases; PubMed, and Embase were computerized searched for relevant studies concerning the Polycystic kidney disease (PKD), published in English language until the end of 2016. more relevant articles were extracted through searching the literature included in references of selected studies.

3. RESULTS

- **Roles of Genetics in pathogenesis of PKD:**

PKD can be inherited as an autosomal dominant quality (ADPKD) or an autosomal recessive trait (ARPKD) (**Table 1**). ADPKD is a common disease that happens in both children and adults, whereas ARPKD is unusual and takes place mostly in neonates and children. ADPKD is triggered by anomalies of either the PKD1 gene on chromosome 16 or the PKD2 gene on chromosome 4. The gene responsible for ARPKD (PKHD1) has actually recently been identified on chromosome 6. ADPKD is genetically heterogeneous with two genes identified, PKD1 (16p13.3) and PKD2 (4q21), plus a couple of unlinked families explained [5,6,7,8]. PKD1 accounts for ~ 85% of cases in medically recognized populations [9] and is a substantially more extreme disease; the typical age at start of ESRD is 20 years younger in PKD1 than in PKD2 [54.3 years versus 74.0 years [10]. The higher severity of PKD1 seems due to the advancement of more cysts at an early age, not to faster growth [11]. Both PKD1 and PKD2 can be related to severe PLD and vascular irregularities. A separate, genetically heterogeneous disease, autosomal dominant polycystic liver disease (ADPLD), causes severe PLD but with no or very little renal cysts [12, 13].

The PKD1 gene (46 exons; genomic level, 50 kb) encodes a big record with an open reading frame (ORF) of 12,909 bp [6, 7]. The 5 ′ 33 exons of PKD1 lie in an area that is duplicated 6 times in other places on chromosome 16, complicating molecular diagnostics. PKD2 (15 exons; 68 kb) has an ORF of 2904 bp [8]. Screening of ADPKD patients shows that a large range of mutations trigger this disease; 314 different truncating anomalies (in 400 households) to PKD1 and 91 truncating anomalies (in 166 households) to PKD2 have actually been described. An additional one quarter of mutations are missense. Most likely mutations are discovered in ~ 90% of patients, making molecular diagnostics an option when diagnostics by kidney imaging is equivocal [9]. This is especially practical for getting a definite diagnosis in a young adult who is a prospective living associated donor. The type of mutation (truncating or missense) does not seem to be highly related to the phenotype [14, 15], but mutation position in PKD1 has actually been weakly related to intensity of kidney disease and to the advancement of intracranial aneurysms [14, 16]. The majority of patients have an affected parent, however > 10% of households can be traced to a new anomaly; two cases of mosaicism have actually just recently been explained [17, 18].

Table 1: Characteristics of autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD)

	ADPKD	ARPKD
Inheritance	Autosomal dominant	Autosomal recessive
Incidence	1/500 to 1/1000	1/6000 to 1/40000
Gene (chromosome)	*PKD1* (Chr 16); *PKD2* (Chr 4)	PKHD1 (Chr 6)
Age of onset of ESRD	53 yr (*PKD1*); 69 yr (*PKD2*)	Infancy/childhood usually
Location of renal cysts	All nephron segments	Collecting ducts
Extrarenal manifestations	Hepatic cysts/pancreatic cysts	Biliary dysgenesis
	Cerebral & aortic aneurysms	Hepatic fibrosis
	Cardiac valvular abnormalities	Portal hypertension
	Systemic hypertension	Systemic hypertension

	ADPKD	ARPKD
Protein name	Polycystin-1; Polycystin-2	Fibrocystin/Polyductin
Protein size	Polycystin-1: 4302 amino acids	4074 amino acids and alternative shorter forms
	Polycystin-2: 968 amino acids	
Protein structure	Polycystin-1: Integral membrane protein, multiple Ig-like domains, similar to egg jelly receptor	Transmembrane protein (and possible secreted forms), multiple TIG/IPT domains, as occur in hepatocyte growth factor receptor and plexins
	Polycystin-2: Integral membrane protein, similar to TRP channel	
Tissue distribution	Polycystin-1 and -2: Widespread	Kidney, pancreas, and liver
Subcellular localization	Polycystin-1: Plasma membrane, cilia	Unknown
	Polycystin-2: Endoplasmic reticulum, cilia	

- **Diagnostic procedures of PKD:**

Imagining techniques:

Ultrasound is the most typically used imaging method for screening individuals at risk for ADPKD. This is based on its safety and modest cost in contrast with CT and MRI. In the majority of moderate to innovative cases, ultrasound easily spots the classic finding of ADPKD including several, bilateral kidney cysts and liver cysts. In younger patients with early stage PKD, nevertheless, the medical diagnosis may not be obvious given that smaller cysts are more likely to leave sonographic detection, particularly for patients with milder PKD2 (**Figure 1**) [(19)].

Research studies released in the 1990's by Ravine and coworkers developed age graded ultrasound criteria for PKD1 (20). The basic concept, considered that erratic cysts occur more often with age, was that more cysts were needed to make a medical diagnosis of ADPKD in older individuals. Therefore, the presence of "2 bilateral or unilateral cysts" sufficed to verify the diagnosis in at-risk topics between 15-29 years, however at least "2 cysts per kidney" and "4 cysts per kidney" were required for diagnosis of at-risk subjects aged 30-59 years and 60 years of age or older, respectively [(20)]. To resolve this concern, Pei et al [(21)] and partners have actually just recently completed a multicenter research study of 577 people from 58 PKD1 households and 371 people from 39 PKD2 households who underwent ultrasound screening [(21)]. In addition, the authors used either DNA linkage or anomaly analysis to identify the gene type and disease status of each research study topic. The performance characteristics of numerous requirements were re-examined for people from both PKD1 and PKD2 households (**Table 2**). As anticipated, the Ravine requirements led to a greater rate of incorrect negative outcomes when applied to people at risk for PKD2. Surprisingly, although incidental basic kidney cysts were thought to be vanishingly uncommon in young people, they discovered that 2.1% of the genetically unaffected population younger than 30 years of age had 1-2 renal cysts. These latter findings recommended that a more stringent criterion might be beneficial in this group of patients [(21)].

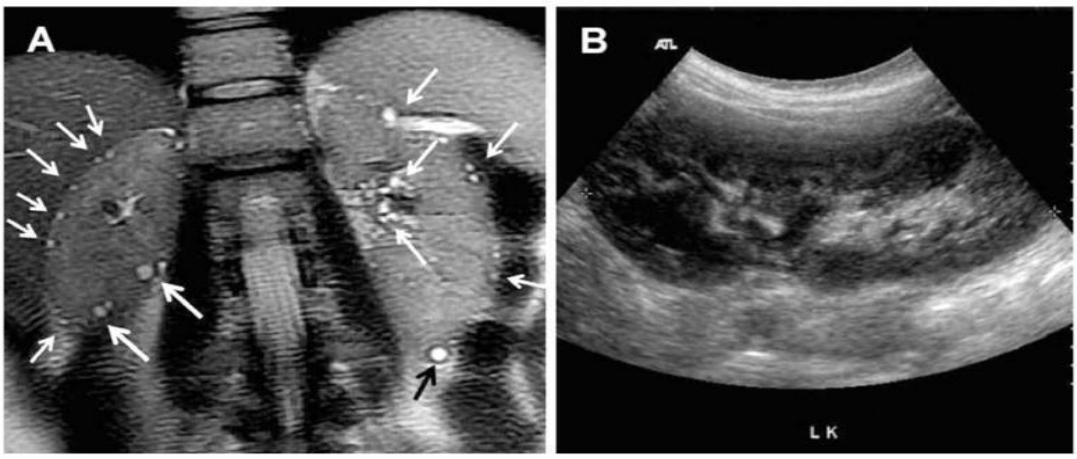

Figure 1: T2 weighted breath-held MRI showing multiple tiny cysts in a cortical and perihilar distribution (white arrows)

The exact same research study [21] examined the efficiency attributes of various ultrasound requirements in at-risk individuals of unidentified gene type using a statistical re-sampling method called "bootstrapping" to imitate the PKD1 and PKD2 case mix (ie, PKD1: PKD2 = 85:15). The suggested requirements are summarized in (**Table 2**) [21].

Table 2: Ultrasound criteria for diagnosis of ADPKD [21]

Age	PKD1	PKD2	Unknown ADPKD Gene Type
15-30	≥3 cysts		
	PPV=100%	PPV=100%	PPV=100%
	SEN=94.3%	SEN=69.5%	SEN=81.7%
30-39	≥3 cysts		
	PPV=100%	PPV=100%	PPV=100%
	SEN=96.6%	SEN=94.9%	SEN=95.5%
40-59	≥2 cysts in each kidney		
	PPV=100%	PPV=100%	PPV=100%
	SEN=92.6%	SEN=88.8%	SEN=90%

- **Treatment options for PKD:**

Some therapies approaches target fluid secretion, while others target cellular growth and expansion. cAMP was one of the very first molecules implicated in the hyper-secretory phenotype of cyst formation that has been targeted by particular therapeutic interventions. Increased cAMP levels are a typical function of a lot of models of PKD (22,23). cAMP is also involved in the stimulation of the MAPK/ERK signaling path through SRC and RAS[24]. Although the accurate mechanism underlying the increase in cAMP is not known, it has actually been noted that vasopressin levels are increased in human ADPKD [25]. Upregulation of the vasopressin V2 (V2) receptor is likewise discovered in the PKD2, cpk, and pcy(WS25/-) mouse designs, and PCK rat design of cystic disease [22,26]. The V2 receptor stimulates cAMP build-up. Blockers of the V2 receptor have actually produced impressive therapeutic effects in animal models of cystic disease. In addition, triggering the somatostatin receptor reduces cellular cAMP levels, and somatostatin analogues have likewise produced promising lead to human trials [27]. Ongoing clinical trials are currently assessing the effectiveness of the V2 receptor villain, tolvaptan, and long-acting somatostatins [28,29]. Other possible treatments that are directed at addressing fluid secretion include CFTR inhibitors and KCa3.1 inhibitors, which inhibit the basolateral potassium channel essential for cAMP-dependent chloride secretion [30].

Although the paths governing proliferation are complicated and rather intertwined, a variety of possible therapies have actually emerged that particularly target upregulated pathways. Provided the parallels between the hyper-proliferative phenotype of PKD and the uncontrolled cellular division in neoplasia, numerous chemotherapeutic agents have been checked out in efforts to reduce cyst development. These therapies include paclitaxel, epidermal growth factor receptor (EGFR) tyrosine kinase inhibition, TNF-a converting enzyme inhibition, and c-SRC inhibition [31,32]. While some of these agents have actually produced impressive lead to animal designs, it is important to keep in mind that these anti-mitotic representatives should be tolerated over a patient's whole lifetime in order to be useful as a treatment for ADPKD, as it is likely that cyst development will resume as quickly as inhibition of proliferation is eliminated.

Numerous interesting prospective target particles for drug therapies have been discovered to be upregulated specifically in PKD. Efforts to make use of some of these possible targets have explored representatives directed at CyclinD, B-raf, and mitogen-activated protein kinase/extracellular signal-- regulated kinase (MAPK/ERK) kinase [33,34,35]. Intriguingly, it has likewise been shown that mammalian Target of Rapamycin (mTOR) activity is elevated in models of PKD [36]. mTOR is a serine/threonine kinase that manages cell development and expansion, in addition to transcription and protein synthesis. Shillingford et al. have reported that mTOR is regulated by polycystin-1. Rapamycin, also referred to as sirolimus, binds to FK506-binding protein (FKBP) and this complex then binds to and inhibits mTOR's kinase activity [37,38]. Treatment with rapamycin has actually been shown to improve kidney cystic indices in the orpk and Tg737 rescue models for cystic kidney disease as well as the Han: SPRD rat model of ADPKD [39].

4. CONCLUSION

Autosomal dominant polycystic kidney disease (ADPKD) is a common, acquired condition for which there is presently no effective specific medical therapy, pathologic accumulation of fluid in epithelium lined cavities causing the damage of adjacent regular parenchyma. Acquired cystic diseases, consisting of the most prevalent form, ADPKD, kidney ultrasonography is commonly utilized for the medical diagnosis of ADPKD and age-dependent criteria have been specified for subjects at-risk of PKD1. The utility of the PKD1 ultrasound criteria in the center setting is uncertain considering that their efficiency qualities have not been specified for the milder PKD2 and the gene type for a lot of test topics is unknown.

REFERENCES

[1] Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369:1287–301.

[2] Rossetti S, Harris PC. Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. J. Am. Soc. Nephrol. 2007;18:1374–80.

[3] Harris PC, Torres VE. GeneReviews; Genetic Diseases Online Reviews at Gene-Test-GeneClinics. Seattle; Univ. Washington: 2006. Autosomal dominant polycystic kidney disease.http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pkd-ad.

[4] Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. N. Engl. J. Med. 2006;354:2122–30.

[5] European Polycystic Kidney Disease Consortium The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. Cell. 1994;77:881–94.

[6] Hughes J, Ward CJ, Peral B, et al. The polycystic kidney disease 1 (*PKD1*) gene encodes a novel protein with multiple cell recognition domains. Nat. Genet. 1995;10:151–60.

[7] International Polycystic Kidney Disease Consortium Polycystic kidney disease: the complete structure of the *PKD1* gene and its protein. Cell. 1995;81:289–98.

[8] Mochizuki T, Wu G, Hayashi T, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science. 1996;272:1339–42.

[9] Rossetti S, Consugar MB, Chapman AB, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol. 2007;18:2143–60.

[10] Hateboer N, van Dijk MA, Bogdanova N, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. Lancet. 1999;353:103–7.

[11] Harris PC, Bae K, Rossetti S, et al. Cyst number but not the rate of cystic growth is associated with the mutated gene in ADPKD. J. Am. Soc. Nephrol. 2006;17:3013–19.

[12] Davila S, Furu L, Gharavi AG, et al. Mutations in *SEC63* cause autosomal dominant polycystic liver disease. Nat. Genet. 2004;36:575–77.

[13] Drenth JP, Te Morsche RH, Smink R, et al. Germline mutations in *PRKCSH* are associated with autosomal dominant polycystic liver disease. Nat. Genet. 2003;33:345–47.

[14] Rossetti S, Burton S, Strmecki L, et al. The position of the polycystic kidney disease 1 (PKD1) gene mutation correlates with the severity of renal disease. J. Am. Soc. Nephrol. 2002;13:1230–37.

[15] Magistroni R, He N, Wang K, et al. Genotype-renal function correlation in type 2 autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol. 2003;14:1164–74.

[16] Rossetti S, Chauveau D, Kubly V, et al. Association of mutation position in polycystic kidney disease 1 (PKD1) gene and development of a vascular phenotype. Lancet. 2003;361:2196–201.

[17] Connor A, Lunt PW, Dolling C, et al. Mosaicism in autosomal dominant polycystic kidney disease revealed by genetic testing to enable living related renal transplantation. Am. J. Transplant. 2008;8:232–37.

[18] Consugar MB, Wong WC, Lundquist PA, et al. Characterization of large rearrangements in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. Kidney Int. 2008 online doi:10-1078/Ki.2008.485.

[19] Nascimento AB, Mitchell DG, Zhang XM, Kamishima T, Parker L, Holland GA. Rapid MR imaging detection of renal cysts: age-based standards. Radiology. 2001;221:628–632.

[20] Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet. 1994;343:824–827

[21] Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20:205–212.

[22] Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH., 2nd Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nat Med. 2004;10:363–4.

[23] [Yamaguchi T, Nagao S, Kasahara M, Takahashi H, Grantham JJ. Renal accumulation and excretion of cyclic adenosine monophosphate in a murine model of slowly progressive polycystic kidney disease. Am J Kidney Dis. 1997;30:703–9.

[24] Kolch W. Meaningful relationships: the regulation of the Ras/Raf/MEK/ERK pathway by protein interactions. Biochem J. 2000;351(Pt 2):289–305.

[25] Danielsen H, Pedersen EB, Nielsen AH, Herlevsen P, Kornerup HJ, Posborg V. Expansion of extracellular volume in early polycystic kidney disease. Acta Med Scand. 1986;219:399–405.

[26] Gattone VH, 2nd, Maser RL, Tian C, Rosenberg JM, Branden MG. Developmental expression of urine concentration-associated genes and their altered expression in murine infantile-type polycystic kidney disease. Dev Genet. 1999;24:309–18.

[27] Hogan MC, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, Kim B, King BF, Glockner J, Holmes DR, 3rd, Rossetti S, Harris PC, LaRusso NF, Torres VE. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. J Am Soc Nephrol. 2010;21:1052–61.

[28] Miyazaki T, Fujiki H, Yamamura Y, Nakamura S, Mori T. Tolvaptan, an orally active vasopressin V(2)-receptor antagonist - pharmacology and clinical trials. Cardiovasc Drug Rev. 2007;25:1–13.

[29] Patel V, Chowdhury R, Igarashi P. Advances in the pathogenesis and treatment of polycystic kidney disease. Curr Opin Nephrol Hypertens. 2009;18:99–106.

[30] Yang B, Sonawane ND, Zhao D, Somlo S, Verkman AS. Small-molecule CFTR inhibitors slow cyst growth in polycystic kidney disease. J Am Soc Nephrol. 2008;19:1300–10.

[31] Cowley BD., Jr. Recent advances in understanding the pathogenesis of polycystic kidney disease: therapeutic implications. Drugs. 2004;64:1285–94.

[32] Gattone VH., 2nd Emerging therapies for polycystic kidney disease. Curr Opin Pharmacol. 2005;5:535–42.

[33] Bukanov NO, Smith LA, Klinger KW, Ledbetter SR, Ibraghimov-Beskrovnaya O. Long-lasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. Nature. 2006;444:949–52.

[34] Park EY, Sung YH, Yang MH, Noh JY, Park SY, Lee TY, Yook YJ, Yoo KH, Roh KJ, Kim I, Hwang YH, Oh GT, Seong JK, Ahn C, Lee HW, Park JH. Cyst formation in kidney via B-Raf signaling in the PKD2 transgenic mice. J Biol Chem. 2009;284:7214–22.

[35] Omori S, Hida M, Fujita H, Takahashi H, Tanimura S, Kohno M, Awazu M. Extracellular signal-regulated kinase inhibition slows disease progression in mice with polycystic kidney disease. J Am Soc Nephrol. 2006;17:1604–14.

[36] Wahl PR, Serra AL, Le Hir M, Molle KD, Hall MN, Wuthrich RP. Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD) Nephrol Dial Transplant. 2006;21:598–604.

[37] Sabers CJ, Martin MM, Brunn GJ, Williams JM, Dumont FJ, Wiederrecht G, Abraham RT. Isolation of a protein target of the FKBP12-rapamycin complex in mammalian cells. J Biol Chem. 1995;270:815–22.

[38] Cardenas ME, Cutler NS, Lorenz MC, Di Como CJ, Heitman J. The TOR signaling cascade regulates gene expression in response to nutrients. Genes Dev. 1999;13:3271–9.

[39] [145] Shillingford JM, Piontek KB, Germino GG, Weimbs T. Rapamycin ameliorates PKD resulting from conditional inactivation of Pkd1. J Am Soc Nephrol. 2009;21:489–97.