Polycystic Kidney Disease: A Paradigm in Major Kidney Disorders

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(Received on 14 March 2019; Revised on 23 August 2019; Accepted on 24 August 2019)

The normal architecture of the kidney is crucial for maintaining biological function and its homeostasis. Its proper development depends on highly dynamic processes which modulate the integrity of its associated cellular functions, interactive events and regulatory cascades altogether providing proper turnover in adult life. Any alteration in regulatory processes and normal utility holds crucial consequences for proper functioning of the kidney. These variations accompany renal injury, various etiologic events, deviation from genetic-wild type processes and metabolic disturbances leading to major lesion of end-stage renal disease (ESRD). Major renal disorders developing today and affecting millions of people globally include diabetes, hypertension, glomerulonephritis and Polycystic Kidney Disease (PKD). Among these diseases, PKD is becoming relatively common, and has emerged as one of the largest causes of renal transplantation and dialysis. Therefore, understanding the development, function and progression of normal kidneys vis a vis cystic renal kidneys serves an important way in understanding pathophysiology of PKD and cystogenesis.

Keywords: Kidney; Polycystic Kidney Disease; End-Stage Renal Disease; Polycystin-1; Polycystin-2

Introduction

The normal architecture of the kidney is crucial for maintaining biological function and its homeostasis. Its proper development depends on highly dynamic processes which modulate the integrity of its associated cellular functions, interactive events and regulatory cascades altogether providing proper turnover in adult life. Any alteration in regulatory processes and normal utility holds crucial consequences for proper functioning of the kidney. These variations accompany renal injury, various etiologic events, deviation from genetic-wild type processes and metabolic disturbances leading to major lesion of ESRD. Major renal disorders developing today affecting millions globally include diabetes, hypertension, glomerulonephritis and Polycystic Kidney Disease (PKD). Among these diseases, PKD is becoming relatively common, and has emerged as one of the largest causes of renal transplantation and dialysis. Therefore, understanding the development, function and progression of normal kidneys to cystic renal kidneys serves an important way in understanding pathophysiology of PKD and cystogenesis.

Kidney and Its Organogenesis

The kidney is a widely used model to study the systematic approaches toward intricacies of tissue development and vertebrate organogenesis. The mammalian kidney, or also known as the metanephros, arises at ~35th day of human gestation period. The events involved in kidney development were elucidated by manoeuvring the amphibian, avian and mammalian embryos through in vitro organ cultures. Permanent kidney establishment takes place by two fundamental processes (i) nephronogenesis and (ii) branching morphogenesis. Kidney starts developing from primordial mesodermal derivatives, and its induction begins when signals are sent by the ureter upon which the metanephric mesenchyme starts condensing around the ureteric bud (Lechner et al., 1997; Bjelakovic et al., 2018). The pronephros is composed of a single glomus, and projects into the nephrocoel filtering directly into the coelom. The mesonephros consists of multiple nephrons that develop in a cranial to caudal fashion. The metanephros at this stage comprises the ureteric bud, which enters the metanephric mesenchyme. The
condensed metanephric mesenchyme evolves into tubular epithelium of mature nephron. Once nephrogenesis begins, it leads to the formation of glomerulus and all tubules except the collecting ducts, and segments into glomerular and tubular domains by forming two clefts in renal vesicles (Kopan et al., 2007).

Collecting ducts, on the other hand, form by branching morphogenesis along with the calyces, renal pelvis and ureter bud (Saxén 1987; Yamashita and Nishinakamura, 2005). The ureter bud originates from the epithelial outgrowth of the caudal portion of the Wolffian duct hence, giving rise to the renal collecting system. By 20-22 weeks’ gestation period, completion of ureteric branches takes place followed by the collecting duct development. By 22-44 human fetal gestation, cortical and medullary domains of the developing kidneys are established. The renal cortex by birth represents 7% of the total kidney volume (Cebrían et al., 2004). Convergence of the collecting ducts in the inner medulla form papilla, which give rise to distinct morphological differences between medullary collecting ducts and those of the renal medulla. Once the inner mass and proper morphology of kidney develops, the full complement of glomerulus takes place by 32-34 weeks when nephrogenesis ceases. At birth the last glomeruli to be formed is the superficial glomeruli. Finally, by 3.5 years of age subsequent glomeruli development involves hypertrophy (Dressler 2006; Fetterman et al., 1965; Rosenblum 2008).

The attainment of proper morphological kidney for its correct functioning involves complex processes, which derive gene expression of renal cells to properly regulate homeostasis at molecular level. Early developmental stages of the kidney are rich in expression of various genes, and its proteins are highly expressed to regulate cellular proliferation and differentiation. Any mismatches in these genetically controlled programs, either hereditary or somatic, may lead to altered morphology or improper functioning of the kidneys.

Genetic Programs and Transcription Factors Controlling Kidney Development

Genetic programs during developmental stage of an organism play a decisive role in turning a particular cell type into a proper functioning tissue. Many of these genetically controlled programs also operate during early embryonic kidney development, and these potential signalling molecules affect its morphogenesis. The ‘master regulators’ set up a basic pattern formation of specific differentiation programs such as nephron development, mesenchyme differentiation or ureteric bud development.

In the initial stages of kidney development, nephrons, ureteric bud branches, metanephric and mesenchymal (stromal) cells themselves contribute towards normal kidney development (Cullen-McEwen et al., 2005). The expression pattern is controlled by forkhead box1 (Foxd1), retinaldehyde dehydrogenase 2 (Raldh2), retinoic acid receptor alpha (Rara) and –beta (Rarb2) along with fibroblast growth factor-7 (Fgf7), podocyte-1 (Pod1) and Bmp4. Another family of Pax genes encode evolutionary conserved transcription factors important in proceeding nephrogenesis in stepwise manner (Eccles et al., 1995; Gruss and Walther 1992; Torres et al., 1995). Along with other Wnt gene family, Wnt4 and BM7 are also known as important regulators of nephron maturation and many other morphogenetic events (Lyons et al., 1995) required for proliferation and differentiation. p53 and Hox genes expressed in the developing kidneys regulate cell cycle, apoptosis and specifying positional information and anterior posterior axis, respectively (Krumlauf 1994).

Any mutation or altered expression of the specific underlying genes may lead to severe form of renal disease. Renal mutation analyses in mice and human have yielded a great insight into the genes involved and their role in controlling kidney development. Expression of these genes has not only provided an insight into the transcriptional mechanisms, but molecular pathways have also been identified, which in turn have helped carry out further work on understanding kidney defects and diseases.

Polycystic Kidney Disease: Facts and Pathogenesis

Historical references to PKD can be found to be dated as early as 15th century when King of Transylvania died at the age of 53 years. His kidneys were found to have humongous size and “bumpy” surface. No reference on study of PKD existed till 1899 when its genetic basis was first suggested by Steiner, but understanding the genetic abnormalities underlying
PKD took almost another 100 years of research to unravel the mechanistic approaches by which the disease had become extremely prevalent. In the middle of the 20th century, comprehensive study describing the disease and its inheritance as an autosomal dominant trait was published by Dr. O. Z. Dalgaard in 1957, and throughout the years of extensive research PKD was established as a systemic heterogenetic life-threatening disorder among all racial groups. Today, approximately 12.5 million people are affected worldwide (Tan et al., 2011) including 2.3 million Indians alone (Modi and Jha 2006).

Heterogeneous group of cystic diseases are renal inherited conditions, which involve 33 genes covering X-linked autosomal dominant and autosomal recessive inheritance showing Mendelian inheritance (Deltas and Papagregoriou 2010), but cyst development and characterization of PKD is not properly understood. The cysts start as focal entities from dedifferentiated tubular epithelial cells forming single cell lining (Qian et al., 1996). As the disease progresses, formation of extra-cellular matrix is accompanied by slow and progressive cyst enlargement disturbing the normal parenchyma and renal architecture. Disease progression leads to enlargement of kidneys four to six times its normal size. PKD being highly heterogeneous, its symptoms may vary according to individuals and their lifestyles (Martinez and Grantham 1995). Frequent symptoms that affect majority of the individuals include kidney stones, urinary tract infections, hypertension, and severe abdominal pains. Although the name describes renal disorder, but the disease is systematic, and includes numerous cystic and non-cystic extrarenal manifestations. Cystic outgrowths are limited not only to kidneys, but liver, seminal vesicles, pancreas, spleen and thyroid also get affected. (Hossak et al., 1988; Pirson et al., 2002). Abnormalities in other organ functions gradually develop with time and patients suffer from cardiac valve defects, intracranial and aortic aneurysms, inguinal hernia and colonic diverticula especially in PKD patients (Demetriou et al., 2000; Gabow 1993; Gieteling et al., 1993; Scheff et al., 1980; Torra et al., 2008; Wiebers et al., 2003). Disrupted cell functions, aberrant renal epithelial organization and decline in nephron functioning takes place during renal transplantation and ESRD and hence, conferring patients with life expectancy of 53-60 years.

PKD Phenotypes
PKD inherited disorders are mainly characterized by the progression and severity of symptoms related to the type of variability. Three major forms of PKD are: (a) the common, late onset-autosomal dominant polycystic kidney disease (ADPKD); (b) the mainly infantile-autosomal recessive polycystic kidney disease (ARPKD); and (c) the lethal-syndromic, Meckel syndrome, characterized by renal cystic dysplasia.

Autosomal Recessive Polycystic Kidney Disease (ARPKD)
ARPKD is an inherited disorder effecting the newborns and younger patient population (Capisonda et al., 2003; Guay-Woodford and Desmond 2003) with an estimated incidence of approximately 1:20,000 live births (Zerres et al., 1998). Often the newborns are either stillborn or born with massively enlarged, cystic kidneys, and die in the perinatal period from respiratory failure. These cystic kidneys retain their reniform shape, but cysts are presented with increased cell proliferation, fluid secretion, cystic dilations mainly of the collecting ducts, dysgenesis of the biliary ductal plate and congenital hepatic fibrosis, altogether, resulting in death at the perinatal stage (Kaimori and Germino 2008). The kidneys are often bilaterally enlarged, multicystic depicting abnormal proliferation, differentiation and epithelial polarity defects (Woo 1995).

The linkage to ARPKD has been traced to 6p21.1-p12 caused by single gene mutation in the polycystic kidney and hepatic disease 1 (PKHD1) (Mücher et al., 1994). Being among the largest human genes with minimum 86 exons having alternatively spliced variants, it is highly expressed in kidney with lower levels seen in liver and pancreas. The longest and continuous open reading frame (ORF) yields 4,074 a.a (447 kDa) receptor-like integral membrane protein (fibrocystin/polyductin) containing multiple copies of an Ig-like domain (TIG) (Bergmann et al., 2004; Boletta et al., 2001; Onuchic et al., 2002; Ward et al., 2003). It is mainly localized to the branching ureteric bud; collecting and biliary ducts; and the ascending limb of Henle’s loop, but seen to be often absent from ARPKD. Screens of PKHD1 have revealed over 119 different mutations spread throughout the gene. Majority of the patients screened...
are compound heterozygotes having two truncating mutations with severe disease onset tissue (Harris and Rossetti 2004). Fibrocystin is found to be localized in the axoneme and primary cilia of renal epithelial cells supporting the link between ciliary dysfunction and cyst development hence, reinforcing a link with the PKD-related proteins (Harris and Rossetti, 2004; Landis et al., 2018).

**Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

Massive enlargement of kidneys with number of large cysts is hallmark of ADPKD afflicting approximately 1 in 1,000 individuals (Grantham 2008; Paterson et al., 2005; Wilson 2004). Roughly 50% of the patients with ADPKD require renal replacement therapy by the age of 60 years (Torra 2008). Cysts in ADPKD tremendously increase in size over a decade, displacing and destroying the three-dimension (3D) organ structure of the kidney by annihilating the normal renal parenchyma, and severely compromising its functional integrity. Cyst formation starts at an early stage and continues throughout the entire life of the affected individual ultimately resulting into ESRD. Although the magnitude of cellular de-differentiation and apoptosis is a consequence of small genetic dysregulation, but it gives rise to multiple renal cysts mainly derived from proximal and distal tubules and collecting ducts; and hence originate from less than 1% of the nephrons cysts remains connected to the nephron of origin (Baert 1978; Li 2011; Mochizuki 2013; Shibazaki et al., 2008). Dilations in the tubules from an early staged ADPKD patient show thickened and deformed basement membrane having single layer of lined epithelial cells with abnormal proliferation, protein sorting defects and altered planar cell polarity (Fick 1995; Happé et al., 2011; Milutinovic et al., 1980).

Many factors associated with the variability of the disease such as hypertension, early onset, male gender, increase in kidney size and growth rate of cysts in multiple organs, and microalbuminuria are said to contribute towards progression of the disease (Boucher and Sandford 2004; Fick et al., 2001; Grantham 2006; Schrier et al., 2003). Patients experience pangs of abdominal pain, hypertension, renal insufficiency, hematuria and/or proteinuria (Torres et al., 2007). Renal functioning begins to decline in the fourth decade of life especially males experiencing faster decline in GFR (glomerular filtration rate) than females (Grantham et al., 2008). GFR decreases by 4.4 to 5.9 L/min per year being inversely proportional to kidney size and cyst volume grossly varying from the normal (Grantham et al., 2006; King et al., 2003; Li, 2011; Torres and Harris 2009). Its progression and risk factors have been the prime targets, but in all cases evidence leads to large renal volume associated with decreased renal blood flow (Grantham 2008). Patient mortality is accredited to these extra renal manifestations, and each patient has his own signature of cyst growth that shows highly variable age of onset and clinical course (Churchill et al., 1984; Franz and Reubi 1983; Reeders et al., 1985). Although cyst growth is slow and progressive, it develops throughout the life of a patient hence, limiting the life of a patient to an average of 54.3 years (Hateboer et al., 1999).

**Genetics Defining ADPKD**

**ADPKD Genes: PKD1 and PKD2**

Linkage analysis has revealed at least three forms of ADPKD genes causing clinical presentations-PKD1 (Hughes et al., 1995; Reeders et al., 1985), PKD2 (Kimberling et al., 1993) and PKD3 (Daoust et al., 1995). PKD1 gene located on human chromosome 16p13.3 encodes a 14 kb mRNA that is spliced from 46 exons extending over ~50 kb of DNA translated into protein product polycystin-1 (PC-1). The PKD1 region is complex, with 5' region of the gene being composed up to exon 33, and repeated several times more proximal on chromosome 16 (Consortium 1996; Harris 1999). The other gene form PKD2 on human chromosome 4q21-23 spanning 15 exons encodes polycystin-2 (PC-2) (Hughes et al., 1995; Mochizuki et al., 1996; Lanktree and Chapman, 2017). Both genes involve loss of function mutations, deletion, frameshifts or nonsense mutations however, approximately 85% of the cases are attributable to PKD1 gene mutations, while PKD2 accounts for the remaining (~15%).

**PKD Proteins: Polycystin-1 and Polycystin-2**

**Polycystin-1(PC-1)**

PC-1 is a 4302 a.a (462 kDa) integral plasma membrane non-tyrosine-kinase receptor with a large
extracellular NH$_2$ terminal domain (3074 a.a with multiple binding domains), 11 transmembrane domains (1032 a.a.) and short COOH terminus (~222 a.a.). It is found in the basolateral plasma membrane domain of polarized epithelial cells participating in cell-cell or cell-matrix interactions (Wilson and Falkenstein 1995). The NH$_2$-terminal domain, involved in protein-protein and protein-carbohydrate interactions (Nims et al., 2003), contains distinct combination of recognized motifs including: two leucine-rich repeats, a C-type lectin, sixteen copies of PKD domain, a region of homology with a sea urchin protein-the receptor for egg jelly (SUREJ) (Moy et al., 1996) required for triggering transmembrane cation influxes of Ca$^{2+}$ ions for acrosome reaction (Trimmer et al., 1985) and a GPCR proteolytic site (GPS domain) (Ponting et al., 1999) suggesting that these unique regions of the protein may also play a role in regulating ion transport. One of the defining features of PC-1 is its homology with lipo-oxygenase (polycystin/lipo-oxygenase/á-toxin pr PLAT) domain embedded in the first cytoplasmic loop of PC-1. This suggests that PC-1 extends its interactions with other proteins. The regions REJ, GPS and PLAT domains, therefore, mark a defining feature of the protein. The COOH-terminus holds a G-protein binding and activation domain (Qian et al., 1997), phosphorylation sites and coiled coil domain required for interaction with COOH terminal of PC-2 (Parnell et al., 1998), including sequence that is rich in proline, glutamic acid, serine and threonine (PEST) are facilitating its ubiquitin-mediated degradation (Low et al., 2006; Rechsteiner and Rogers 1996).

A cleavage product of PC-1, the C-terminal tail, can translocate to the nucleus and regulate gene transcription regulating epithelial cell growth, migration, differentiation, cell cycle and apoptosis (Bhunia et al., 2002; Manzati et al., 2005; Nickel et al., 2002; Yu et al., 2011).

**Polycystin-2 (PC-2)**

PC-2 has been identified as a distant member sharing homology with the transient receptor potential family of ion channel (TRP) spanning six transmembrane domains with intracellular N and C termini (Chen 1999; Koulen et al., 2002; Mochizuki et al., 1996). PC-2 functions as a Ca$^{2+}$ permeable non-selective cation channel that transports and modulates intracellular Ca$^{2+}$, and releases calcium from intracellular stores in accordance with changes in local concentration (Vassilev et al., 2001). Several domains present in the PC-2s’ N- and C- terminals contribute to its protein-protein interaction and Ca$^{2+}$ sensitivity with EF hand domain having single Ca$^{2+}$ binding domain permitting protein to sense Ca$^{2+}$ and buffer changes. This domain ensures its localization to its subcellular maintenance to ER and Golgi. Having control over local Ca$^{2+}$ changes, cytoplasmic calcium levels are also indirectly regulated by PC-2 through interactions with two major intracellular Ca$^{2+}$ channels: the ryanodine receptor and the inositol 1,4,5-trisphosphate receptor (IP3R) (Anyatonwu et al., 2007; Di Mise et al., 2018; Kim et al., 2000).

Both PC-1 and PC-2 when localized to the primary cilium form a complex, which has a mechanosensory role in translating mechanical and chemical stimuli of Ca$^{2+}$ around inter- and intracellular responses. Cells showing PKD1 mutation fail to maintain calcium levels due to dysfunctional cilia.

**Expression Patterns and Interaction of PC-1 and PC-2**

Epithelial cells of the developing renal tissue show highest expression of PC-1 with mature renal tubules expressing lower, but detectable levels as well as other somatic tissues including heart, liver, bone, brain, bowel, placenta, thymus endocrine glands and endothelium arteries and veins (Ibraghimov-Beskrovnaya et al., 1997; Markowitz et al., 1999; Ong et al., 1999; Ward et al., 1996) with PC-2 localizing to the subcellular compartments of the ER along with PC-1 and early Golgi (Cai et al., 1999; Koulen et al., 2002). Maximum levels of PC-1 can be found in the fetal renal tissue with low levels present in adults (Chauvet et al., 2002). PC-1 and -2 are localized mainly in the cilia, but also found in the lateral domain of polarized renal epithelial cells (Huan and van Adelsberg 1999; Yoder et al., 2002), with PC-2 also seen residing in centrosome and mitotic spindles (Rundle et al., 2004). Collecting ducts are enriched in PC-1 and PC-2 dominating in the medullary thick ascending limb and distal cortical tubules (Foggensteiner et al., 2000) with their expressions higher during developmental stages as shown in animal studies. Mouse development as early as E9.5-E12.5 show highest levels of these proteins in mesoderm.
and ectoderm (Guillaume et al., 1999) with PC-1 detected significantly at E17.5 in the kidney in branching ureteric buds, tubules and Bowman’s capsules (van Adelsberg et al., 1997; Weston et al., 2003). Hence, this mutual subcellular localization of PC-1 and PC-2 explain their working in concert with each other in regulating kidney homeostasis.

The interactions of both PC-1 and -2 participate in fluid flow sensing through ciliary bending and kidney pressure (Patel and Honoré, 2010; Praetorious and Spring 2003), and are functionally co-dependent. Their strong co-localization in the primary cilium and ER suggests that their give-and-take interactions affect each other’s surface membrane and ciliary localizations impairing the function of one protein and affecting the nature of the other protein. Communication of both proteins is important in creating functional ion channel. A physical interaction of PC-1 and PC-2 occurs through their C-terminal cytoplasmic tail (Casuscelli et al., 2009; Tsiokas et al., 1997). The protein-protein mediated interaction is carried by specific tyrosine or serine targeted phosphorylation and proline rich SH3 sites (Li et al., 2004). This interaction not only carries functional stability for ion movement, but their inability to interact decreases PC-1’s ability to activate G-proteins and leading to cyst formation in ADPKD (Delmas et al., 2002). Depending on their interaction many pathways have been identified which activate and control normal functioning of PKD1 gene regulation by various transcriptional mechanism or activated through downstream signalling pathways.

**ADPKD and Pathogenesis**

The interaction of PC-1 and PC -2 leads to microenvironment changes in cell-cell, cell-matrix biology and intracellular mechanism. Any perturbation in their cross-talks effecting downstream signalling leads to ADPKD pathogenesis hence, culminating to renal cystogenesis and cystic lesions. Often these amended mechanisms cause cyst initiation and formation and are the key factors in targeting cyst growth and progression of the disease.

**Molecular Mechanism of Cyst Formation and Fluid Secretion in ADPKD**

Cyst formation mechanism shows variable pathways in cyst initiation and formation. ADPKD patients who have inherited one mutated copy of *PKD1* will develop and function normally into adulthood having only the “first hit”. However, if over the year’s cyst formation takes place in the patient’s kidneys, the cysts will have lost both the functional copies of this gene (Brasier and Henske 1997; Qian et al., 1996; Halvorson et al., 2010; Messchendorp et al., 2018). The “second hit” somatic mutation knocks out the normal *PKD1* or *PKD2* allele resulting into cells devoid of a functional allele causing cysts to form through uncontrolled proliferation of cells having two hits. This mechanism of cyst formation is a consequence of distinct somatic mutation event which contributes towards slow progression of the disease over the decades. Total inactivation of PC-1 and PC-2 in the kidneys of mice models has revealed severe cystic disease during the developing stages rather than complete loss of PC-1 and PC-2 in mature kidneys (Lantinga-van Leeuwen et al., 2007; Piontek et al., 2007). *PKD1* knockout in adult mice kidneys causes similar phenotype (Takakura et al., 2008) suggesting that injury may be sufficient in cyst formation in heterozygotes without requiring the “second hit”

| Table 1: Summary of ADPKD Genes and Protein Characteristics (Gallagher et al., 2010) |
|-----------------------------------|---------------------------------|----------------|----------------|----------------|
| Mutations in ADPKD families       | 85%                             | 15%            |                |                |
| Mean age of onset ESRD            | 53 years                        | 69 years       |                |                |
| Gene Characteristics              | Ch16q13.343 exons gene size, ~46 kb | Ch4q21-23, 15 exon gene size, ~3.5 kb |                |                |
| Protein Characteristics           | PC-1, 4302 a.a, 11 transmembrane domains receptor-like protein undergoes proteolytic cleavage | PC-2, 968 a.a, 6 transmembrane domains, Homology to TRP channels |                |                |
| Subcellular localization          | Cilia, cell junctions, apical and basolateral plasma membrane | Cilia, endoplasmic reticulum, plasma membrane |                |                |
| Function                          | Receptor                        | Cation channels |                |                |
mutagenesis. This mechanism suggests that somatic mutation is either allowing transcription of the mutated wild-type allele or blocking production of PC-1 and PC-2. Once the normal functional genes are inactivated, it gives way to abnormal focal proliferation of renal tubular cells, mitotic orientation defects and disruption of fluid flow sensitivity (Nauli et al., 2003; 2006).

Cells losing fluid flow-sensitivity leads to increased surface area of cyst wall and fluid secretion filling the cavity, and hence increasing the number of cells surrounding the cysts’ lumen (Grantham 1987). Renal cyst formation is mild in adult mice heterozygote for PKD1 and PKD2 mutations, but mice homozygous embryos possess severe cyst expansion from E15.5 day onwards.

Even though complete knockout of PKD1 and PKD2 causes massive cyst formation, another hypothesis proposed towards cystogenesis is the “gene dose effect”. This hypothesis explains complete absence, haploin sufficiency or transgenic over expression to be the basis of cyst formation (Koptides et al., 2000; Lantinga-van Leeuwenet al., 2004; Lu et al., 1999; Pritchard et al., 2000). Therefore, the development and growth of cyst requires a net influx of fluids converting the normal epithelium to cystic secretory epithelium. This transformation is predicted involving: cells organizing themselves into spherical rather than tubular structures, and filling of these lumens with fluid to expand into cysts. Increase in the cyst surface area is not due to stretching of the epithelial cells, but rather due to cells dividing unconditionally surrounding the cyst lumen (Chapin and Caplan 2010). Expansion of these cystic epithelium experience abnormal cell proliferation and apoptotic loss of nephrons and epithelial cells (Koupepidou et al., 2010; Woo 1995).

Microdissection and monolayer culture of the cystic ADPKD epithelia also exhibited fluid secretion, which can be induced by initial fluid formation or activation of the adenylate cyclase signal transduction pathway by cAMP (Grantham et al., 1995; Sullivan and Grantham 1996). Many studies have targeted various modulators implicated in fluid secretion mechanism. One study showed mislocalization of Na,K-ATPase to the basolateral cell surfaces (Carone et al., 1994) in murine cystic kidneys (mck), and its persistence in cystic collecting tubules (Avner et al., 1992). Other critical aspect of cyst formation is likely to be alteration in orientation of cystic tubules (Nishio et al., 2010) leading to defects in planar cell polarity. These ion-secretory epithelia derive the paracellular or trans-cellular osmotic water movement into the cyst lumen having Cl- as the prime component in the secretion stimulated by cAMP involving apical cystic fibrosis transmembrane regulator (CFTR) (Davidow et al., 1996). CFTR has been found to be expressed on the apical cell surface of cystic cells (Hanaoka et al., 1996). Cultured MDCK cells expressing full-length PC-1 with CFTR showed decreased surface localization of CFTR and cAMP stimulated activity (Ikeda et al., 2006) suggesting PC-1 misregulation may lead to increase in CFTR activity.

Cilia and ADPKD

Primary cilium is a hair-like structure rooted to the centriole projecting through the cell and involved in mechanical-sensation function. Experimental evidence has shown cilia bending to be triggered by fluid flow leading to increase in intracellular bending (Praetorius and Spring 2003), and playa central role in ADPKD pathogenesis. Mutational analysis of intraflagellar transport gene (IFT) required for maintenance of cilia structure has been associated with PKD development (Lehman et al., 2008; Mohieldin et al., 2015).

Localization of PC-1 and PC-2 in primary cilia of renal epithelium cells shows a strong co-relation of these factors in coordinating cellular response to changes in fluid flow mechanism in normal and renal cystic cells. Working as flow sensors and eliciting calcium transients due to response in bending involves role of PC-1 and PC-2 (Kotsis et al., 2013). Further
support came from inactivating Kinesin family member 3a (KIF3a), a component of the kinesin-2 motor complex required for cilia maintenance in the kidney which resulted in cyst formation (Lin et al., 2003).

**Animal Models of PKD**

Studies conducted using PKD experimental models have elucidated various mechanisms towards renal cyst formation, and its underlying pathophysiology. These models have immensely contributed towards studying the basis of pathophysiology of PKD hence, revealing an insight into possible molecular based disease outcomes, endogenous/exogenous athways related to disease progression and targeting possible therapeutic novelties in consideration to means operating in humans.

Spontaneous hereditary models of PKD possess symptoms of human PKD phenotype. One of the models developed was Han-SPRD-cy rat in which numerous renal cysts were caused by a missense mutation (C to T, R823W) in exon 13 of PKD1 gene on rat chromosome 5. Renal cysts were observed in both homo- and heterozygous rats (Kaspereit-Rittinghausen et al., 1989). PCK rats were initially derived from Sprague-Dawley (SD) outbreeding colony. In this rat, PKHD1 gene, an orthologous gene affected in human ARPKD patients, resulted in cystic kidneys and liver by frameshift mutation in exon 36 (Katsuyama et al., 2000). Many mice models such as cpk, pcy and jck also possessed single point mutations resembling ADPKD characteristics (Atala et al., 1993; Hou et al., 2002; Lu et al., 1997; Omori et al., 2006). Despite having spontaneous mutation in various strains leading to PKD phenotype, gene-modified models such as transgenic mouse models offered controlled expression of human orthologous PKD1 gene. Transgenic mice models with PKD1/−, PKD1Δdel2-6/+ and PKD2WS25− showed complete loss of renal function and severe cystic phenotype, haploinsufficiency, increased apoptosis, respectively. These models further helped target signaling pathways coherent with the human ADPKD (Takahashi et al., 1991). All models developed were specific in targeting various signaling pathways such as mTOR, MAPK, ERK and STAT3, which are important in implication of PKD cystogenesis (Nagao et al., 2012).

**Signaling Crosstalk and Transcription Factors in PKD**

Polycystin proteins modulate diverse signaling pathways and their downstream targets with hundreds of proteins interacting directly or indirectly with the polycystins (Yang et al., 2008). Many of these signal

### Table 2: Biomarkers and basic variables studied and their abbreviations

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Basic Variables</th>
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<tbody>
<tr>
<td>P-Selectin</td>
<td>E-selection</td>
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<tr>
<td>TNFRI</td>
<td>CRP, C-reactive protein</td>
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<td>SAA, serum amyloid A</td>
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<td></td>
<td>TIMP-1/2, tissue inhibitor of metalloproteinases-2</td>
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<td></td>
<td>ICAM, intercellular adhesion molecule</td>
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<td></td>
<td>VCAM, vascular cell adhesion</td>
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<td>MPO, myeloperoxidase</td>
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<td>IL-18, interleukin 18</td>
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<td></td>
<td>MCP-1, monocyte chemotactic protein-1</td>
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<td></td>
<td>RANGE, receptor for advanced glycationendproducts</td>
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<td></td>
<td>Hsp27, heat shock protein 27</td>
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<td></td>
<td>MMP-2/9, matrix metalloproteinase</td>
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<td></td>
<td>ApoA/B/E, apolipoprotein B</td>
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<td></td>
<td>LDL, low-density lipoprotein</td>
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<td>RANGE</td>
<td>BMI, kg/m²</td>
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<td>Hsp27</td>
<td>Total cholesterol, mg/dl</td>
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<td>TIMP-1/2</td>
<td>HDL cholesterol, md/dl</td>
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<td>ICAM</td>
<td>Systolic BP, mm Hg</td>
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<td>VCAM</td>
<td>Diastolic BP, mm Hg</td>
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<td>MPO</td>
<td>Age, years</td>
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<td>Smokers, %</td>
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<td>Previous history of MI or stroke (PH)</td>
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<td>Statin usage, %</td>
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<td>Aspirin usage %</td>
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<td>Physical activity, %</td>
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<td>Alcohol (oz)/month</td>
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</tbody>
</table>
transduction pathways are associated with either cilial function or carry out independent pathways. Perturbations in any of these strictly regulated pathways lead to alteration in transcriptional dysregulation, cellular proliferation and apoptosis which culminates into cyst formation.

One of the main pathways studied is the direct interaction of PC-1 and PC-2 and their downstream targets through regulation of intracellular levels of Ca^{2+} and cAMP accumulation during cystic growth. Alteration in this pathway further exasperates Ras/RAF/ERK activation (Arnould et al., 1998;
Table 4: Base variables considered based on sex and ethnicity (Kim et al., 2010)

<table>
<thead>
<tr>
<th></th>
<th>Women (n=1638)</th>
<th>Men (n=923)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (n=936)</td>
<td>NHW (n=702)</td>
</tr>
<tr>
<td>Age, Years</td>
<td>63.3±9.4</td>
<td>58.4±10.3</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>32.5±7.0</td>
<td>30.8±7.1</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>205.9±41.0</td>
<td>202.8±34.9</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>61.0±18.1</td>
<td>57.4±15.4</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>139.5±21.2</td>
<td>131.7±17.9</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.2±10.6</td>
<td>72.8±9.2</td>
</tr>
<tr>
<td>Ever Smoker, %</td>
<td>289(30.9)</td>
<td>284(40.5)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>282(30.1)</td>
<td>92(13.1)</td>
</tr>
<tr>
<td>Previous history of MI or stroke</td>
<td>78(8.3)</td>
<td>37(5.3)</td>
</tr>
<tr>
<td>Statin Use, %</td>
<td>170(18.2)</td>
<td>165(23.5)</td>
</tr>
<tr>
<td>Aspirin Use, %</td>
<td>287(30.7)</td>
<td>243(34.6)</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>9.6±3.1</td>
<td>12.8±4.9</td>
</tr>
<tr>
<td>Alcohol (oz)/Month</td>
<td>0.8±3.9</td>
<td>3.1±6.0</td>
</tr>
</tbody>
</table>

Table 5: Increased/decreased markers in women and men (irrespective of ethnicity)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Inflammation</td>
<td>CRP</td>
<td>TNFRI</td>
</tr>
<tr>
<td></td>
<td>SAA</td>
<td>IL-18</td>
</tr>
<tr>
<td></td>
<td>ICAM</td>
<td>TNFRI</td>
</tr>
<tr>
<td></td>
<td>VCAM</td>
<td>MCP-1</td>
</tr>
<tr>
<td></td>
<td>MPO</td>
<td>E-Selectin</td>
</tr>
<tr>
<td></td>
<td>RANGE</td>
<td>Hsp27</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>MMP-2</td>
<td>MMP-2</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>TIMP-1</td>
<td>TIMP-2</td>
</tr>
<tr>
<td>Lipoprotein metabolism</td>
<td>ApoA-I</td>
<td>Lp-PLA2 mass</td>
</tr>
<tr>
<td></td>
<td>ApoB</td>
<td>Lp-PLA2 activity</td>
</tr>
<tr>
<td></td>
<td>ApoC-III</td>
<td>LDL Size</td>
</tr>
<tr>
<td></td>
<td>LDL Size</td>
<td>Lp-PLA2 mass</td>
</tr>
<tr>
<td></td>
<td>Lp (A)</td>
<td>Ox-LDL</td>
</tr>
<tr>
<td></td>
<td>Ox-LDL</td>
<td></td>
</tr>
<tr>
<td>Adipocyte metabolism</td>
<td>Leptin</td>
<td>Leptin</td>
</tr>
<tr>
<td></td>
<td>Adiponectin</td>
<td>Adiponectin</td>
</tr>
</tbody>
</table>
Table 6: Increased/decreased markers in women and men (irrespective of sex)

<table>
<thead>
<tr>
<th></th>
<th>AA Increased</th>
<th>AA Decreased</th>
<th>WH Increased</th>
<th>WH Decreased</th>
<th>WH No difference</th>
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<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>IL-18</td>
<td>IL-18</td>
<td>CRP</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>ICAM</td>
<td>VCAM</td>
<td>ICAM</td>
<td>MCP-1</td>
<td>E-selectin</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td>TNFRI</td>
<td>TNFRI</td>
<td>HSP27</td>
<td>P-selectin</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>TNFRII</td>
<td>TNFRII</td>
<td>MPO</td>
<td>SAA</td>
<td></td>
</tr>
<tr>
<td>P-selectin</td>
<td>RANGE</td>
<td>RANGE</td>
<td>MMP-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP-27</td>
<td>MMP-9</td>
<td>MMP-9</td>
<td>TIMP-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO</td>
<td>TIMP-1</td>
<td>TIMP-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMP-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipoprotein metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoA-1</td>
<td>ApoC</td>
<td>ApoB</td>
<td>ApoA-1</td>
<td>ApoE</td>
<td></td>
</tr>
<tr>
<td>Lp(A)</td>
<td>Ox-LDL</td>
<td>ApoC</td>
<td>Lp(A)</td>
<td>LDL size</td>
<td></td>
</tr>
<tr>
<td>Lp-PLA₂ mass</td>
<td>Ox-LDL</td>
<td>Lp-PLA₂ mass</td>
<td>Lp-PLA₂ mass</td>
<td>Lp-PLA₂ mass</td>
<td></td>
</tr>
<tr>
<td>Lp-PLA₂ activity</td>
<td>Lp-PLA₂ mass</td>
<td>Lp-PLA₂ activity</td>
<td>Lp-PLA₂ mass</td>
<td>Lp-PLA₂ mass</td>
<td></td>
</tr>
<tr>
<td><strong>Adipocyte metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>Adiponectin</td>
<td>Adiponectin</td>
<td>Leptin</td>
<td>Resistin</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Clinical data evaluation using algorithm shows influencing biomarkers and variables to be considered based on gender and ethnicity

<table>
<thead>
<tr>
<th>Gender</th>
<th>AA+WH</th>
<th>AA+WH</th>
<th>AA</th>
<th>WH</th>
<th>AA</th>
<th>AA</th>
<th>WH</th>
<th>WH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>Women</td>
<td>Men</td>
<td>Men+ Women</td>
<td>Men+ Women</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td><strong>Type of Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>P-selectin</td>
<td>ICAM</td>
<td>VCAM</td>
<td>HSP27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMP-1/IL-18</td>
<td>CRP</td>
<td>CRP</td>
<td>TIMP-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAM</td>
<td>Adiponectin</td>
<td>Adiponectin</td>
<td>LDL</td>
<td>ApoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic Variables</td>
<td>Systolic</td>
<td>Systolic</td>
<td>Smokers</td>
<td>Aspirin</td>
<td>Alcohol</td>
<td>Alcohol</td>
<td>Alcohol</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td>Total cholesterol</td>
<td>PH</td>
<td>PH</td>
<td>PH</td>
<td>PH</td>
<td>PH</td>
</tr>
<tr>
<td>Age</td>
<td>Systolic</td>
<td>HDL</td>
<td>Alcohol</td>
<td>PAS</td>
<td>Diabetes</td>
<td>BMI</td>
<td>PAS</td>
<td>BMI</td>
</tr>
<tr>
<td>PH</td>
<td></td>
<td></td>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td>Statin</td>
<td></td>
</tr>
</tbody>
</table>

Yamaguchi et al., 2006), which in turn depends on Src and B-Raf. Other proposed mechanism also showed activation of ubiquitous pathways such as G-proteins by binding Goi/o proteins (Yuasa et al., 2004), mTOR, PI3-kinase, Jak2-STAT1/3, NFAT (nuclear factor of activated T cells), and NF-κB (nuclear factor kappa B) signaling (Bhunia et al., 2002; Boca et al., 2006; Shillingford et al., 2006). Many of these pathways involve Ca²⁺ as a second messenger at the primary stage of cyst initialization, and hence these
Table 8: Analysis of the associated kidney markers co-expressed with CVD markers by pathway analysis using STRING analysis

<table>
<thead>
<tr>
<th>CVD Markers</th>
<th>Kidney markers/signalling molecules co-expressed with CVD markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>P-selectin, ITGB2, VWF, ITGB2, STAT6, SELP</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>MMP-9, VEGFA, TGFβ1</td>
</tr>
<tr>
<td>IL-18</td>
<td>CASP1, NFκB1, IL1B</td>
</tr>
<tr>
<td>ICAM</td>
<td>ICAM-1, ICAM-2</td>
</tr>
<tr>
<td>CRP</td>
<td>C1S, SERPINE1, TNF, IL-6</td>
</tr>
<tr>
<td>VCAM</td>
<td>ICAM1, NFκB1, SEL, SELPLG</td>
</tr>
<tr>
<td>HSP27</td>
<td>HSPA1A, MAPKAPK3, HSPA8</td>
</tr>
<tr>
<td>LAM</td>
<td>ApoE, APOE, CETP, LPL, APOC3, MMP</td>
</tr>
</tbody>
</table>

Transcriptional elements regulating PKD1 promoter. Varying in their roles during gene regulation, different transcription factors have shown different response in regulating PKD1 gene promoter region. Diverse transcription binding sites have been identified which regulate DNA-protein interaction at gene level, and contributing imperatively to the basic target of gene regulation. PKD1 promoter region upstream of the transcription start site is a hub of transcription interactions involved in DNA-protein or protein-protein interaction. In the past decade, many of these gene controlling elements have played a crucial role in understanding proper transcription initiation of PKD genes.

Gene modifiers such as PPAR-γ, Ets, p53, Ap-1, retinoic acid, ZBP-89, E-box b-catenin element (Aguigari et al., 2012; Jeon et al., 2007; Lantinga-van Leeuwen et al., 2005; Rodova et al., 2002; van Bodegom et al., 2006, 2010; Yoshihara et al., 2012) have provided an important insight into PKD1 gene function and its relation to cystogenesis. Despite having their own cis-regulatory region with the promoter, these transcription factors also work in concert with various co-activators, which modify and/or enhance their DNA binding capacity through protein-protein interactions. Gene expression often experiences epigenetic modulation during developmental and regulatory processes (Strahl and Allis, 2000) influenced by histone acetylation and histone deacetylation. These post-transcriptional modifications increase or decrease the accessibility of transcription factors to gene promoter by changing secondary structures of histone proteins bound to DNA strands (Gregory 2001). Growing evidence in polycystin interaction with histone acetyl transferase (HATs) and histone deacetylase (HDACs) provide a fine tuned mechanism of transcription factors such as Sp1, p53 and β-catenin working in concert with HDAC with a better insight into PKD promoter activity, and its dependence on post transcription modifiers (Eberharder and Becker 2002; Enya et al., 2008; Lin et al., 2008; Verdone 2005).

**Sequence Conservation and Evolution of PKD1**

Sequence conservation and evolution of genes play an important role in studying primate evolution and their relation to other taxa. Mammalian gene evolution and their divergence from lower chordates indicate...
close proximity among their nucleotide sequences. This nucleotide divergence has been helpful in studying disease affliction among species and the challenge rose to find conservation among genes and their regulatory sites. Since human chromosome 16 carries the PKD1 gene at 16p3.3, but it is reiterated in several copies in 16p13.1, comprising six pseudogenes (Martin et al., 2004). Only the 3.5 kb region located at the 3' end of the PKD1 transcript is unique to humans (Consortium 1994), but in mouse there is only one PKD1 gene present at chromosome 17 and no further pseudogenes are found (Olsson et al., 1997). It is stated that human chromosome 16 is one of the most enriched chromosomes comprising segmental duplication clustered mainly along the p arm indicating creation of new primate gene leading to human genetic variation.

Conservation of the human PKD1 gene has been studied in various species. Evolutionary studies show that original duplication of PKD1 may have occurred before gorillas and humans diverged ~8MYA. Genetic evidence from orangutan subspecies from Sumatra and Borneo detected only single PKD1-signal using FISH-signal indicating single copy of PKD1. Many of the introns have also been studied for their sequence conservation involving intron 30, the largest intron in PKD1 and the highly conserved last intron 45. Studying intron conservation also reflect the mechanistic approaches involved in splicing mechanisms and gene silencing events in gene regulation and transcription efficiency (Kirsch 2008; Rodova et al., 2002).

Multispecies genome analysis of PKD1 promoter region shows various regulatory sites of transcription factor to be conserved among mammalian species. Nine elements were found to be conserved within the PKD1 promoter region including five elements conserved in the pufferfish Fugu Rubripes. Binding sites for E2F, E-box, Ets, MZF and ZBP-89 were found to be conserved in the 5'-flanking region of ~600bp of PKD1 promoter region (Lantinga-van Leeuwen et al., 2005). Hence, species comparison and evolution conservation among genomic studies helps to elucidate causes of evolution, effect on human phenotypes and changes in molecular events during evolution that are important in normal and diseased phenotypes. This not only presents comparative analysis of sequences, but can identify coding and conserved non-coding regions, including regulatory elements important in transcriptional activation of genes.

Clinical Manifestations Involving ADPKD

Signs and Symptoms

Patients with ADPKD are mainly asymptomatic. Some patients experience early clinical symptomatology having severe abdominal pain, enlarged and palpable abdominal mass, kidney stones, urinary tract infections and hematuria which brings them to medical attention (Schrier et al., 2014). Many patients come into attention by getting diagnosed due to positive family history or development of hypertension, which is one of the most complicated symptoms of ADPKD (Chruchill 1984; Edcr and Schrier 2009; Johnson and Gabow 1997) and is thought to be due to activation of renin-angiotensin system. Majority of the patients experience severe abdominal and flank pain which require pain management therapies, but acute abdominal pain and gross hematuria are also observed in patients having ruptured cysts (Granatham 2008). Urinary tract infections are commonly observed during the course of ADPKD. Patients having cysts and renal parenchyma involvement are given antibiotics for upper and lower urinary tracts infections. Once the afflicted patient experiences these symptoms, prolonged fever, weight loss and gastrointestinal symptoms start occurring making therapies even more complicated.

Diagnosis and Screening of ADPKD

An early diagnosis for ADPKD could have beneficial effects of various treatment therapies for the afflicted patients for slowing renal progression, and prevent other extrarenal complications. Total kidney volume and renal cyst volume is strongly correlated with decline of GFR and may be taken as biomarkers to assess kidney health in ADPKD (Fick-Brosnahan et al., 2002; Tangri et al., 2017), and is often observed in patients diagnosed with ADPKD. The foremost diagnosis for the patients showing abdominal pain is an abnormal outgrowth of the abdominal area. Once the patient has been tested for various other symptoms developed during ADPKD complications, the patient undergoes renal imaging and ultrasound, which till date has been the most common method of diagnosis, and remains to be the first and foremost approach.
Ultrasound diagnosis has been based on comparing ADPKD type I and type II which compares the frequency of the cysts in the normal unaffected population (Pei 2009). Presence of at least three renal cysts or two in each kidney are sufficient for diagnosis purpose of an individual at risk. The diagnosis criteria for ultrasound for at-risk individual (with positive family history, and between 30-60 years of age) is four cysts distributed bilaterally (Ravine et al., 1994). Identification of cysts by ultrasound in utero are rare (1:1100 pregnancies), however, increased echogenicity is the most common ultrasound finding, and has been observed as early as 17thcentury. Magnetic Resonance Imaging (MRI) and computed tomography are fast becoming reliable techniques in their sensitivity to detect cysts. Renal volume determined by MRI is an important prognostic marker of an individual patient to determine the progression of the disease (Nascimento et al., 2001; Torres and Harris 2009). Other than MRI, DNA sequence analysis, genetic testing, and DHPLC screening of PKD1 and PKD2 have also been carried out in the patients (Pei and Zhao 2008), but these methods including MRI are not cost effective. Various studies although have pointed out that total kidney volume (TKV) is a potential surrogate parameter for disease severity in ADPKD. Recent trials have, therefore, measured TKV by MR to monitor and predict disease progression, which is fast emerging as novel therapeutic strategies for ADPKD (Liebau and Serra 2013). However, reliable scientific markers to observe disease progression are underway in various clinical trials.

**Therapeutics Modalities**

Understanding the pathophysiology and availability of various animal models has given an edge over conducting clinical trials to test various interventions to identify candidate drugs for ADPKD. Many treatment therapies start out with primary symptoms for the patients such as treatments for hypertension, antibiotics for urinary tract infections, blood pressure control, analgesics for pain etc. (Chapman, 2008; Patel et al., 2009). Several potential drug therapies are now available which target signalling pathways leading to dysregulated fluid secretion and cellular proliferation in cystic kidneys. The main pathway operates via cAMP accumulation levels in the collecting duct, which is the main site of cyst development and has been targeted by vassopression through V2 receptor antagonists. Aiming at this pathway through OPC-31260 has led to reduced renal levels of cAMP, and significantly inhibited cyst development in ARPKD, ADPKD and nephrophthisis models (Gattone et al., 2003). Tolvaptan, another V2 receptor antagonist showing higher affinity, has also been trailed in mice models showing equal beneficial effects (Wang et al., 2005). Since cAMP has been the main target in reducing disease progression, somatostatin acting on SST2 receptors inhibits cAMP levels in kidney and liver. Octreotide, a metabolically stable analogue of somatostatine, has also seen considerable improvement in reducing cAMP levels in pck rat (Masyuk et al., 2003).

Altered intracellular calcium homeostasis is also one of the causes of accumulation of cAMP levels, and proliferative phenotype of the cystic epithelium is another line for treatment by administrating calcium channel blockers such as Triptolide. This strategy induced cellular calcium release through PC-2 by increasing p21 expression, and hence, arrested cystic growth in PKD1/–/– cells. Many CFTR inhibitors have also been shown to slow cyst expansion in MDCK cell culture models, metanephric kidney organ cultures and PKD1flox–/– Ksp-Cre mice (Magenheimer et al., 2006; Yang et al., 2008).

Activation of the mTOR pathways in PKD occurs through interaction with PC-1. This pathway has been inhibited by Rapamycin, a potential therapeutic agent serving as an immunosuppressive drug. Several rodent models of PKD have shown retardation in cyst expansion by using mTOR inhibitors (Tao et al., 2005; Shillingford et al., 2006). In many ADPKD transplants treatment with sirolimus has shown great improvement in renal volume as compared with calcineurin inhibitors (Qian et al., 2008). AMP-activated protein kinase has also been suggested to have a beneficial effect toward reduction in ADPKD development. This pathway directly inhibits CFTR by phosphorylation and also inhibits mTOR through tuberin phosphorylation. On similar strategies metformin also showed reduction in MDCK cysts growth and kidneys of PKD1 knockout mice (Takiar et al., 2011).

Cystic tissues usually overexpress Tumor Necrosis Factor-α (TNF-α), TNFR-I, and TNF-α-
Etiology of Autosomal Dominant Polycystic Kidney Disease

Bjelakovic MD, Vlajkovic S, Petrovic A, Bjelakovic M and Antic inhibitor and S-CR8 showed cell cycle inhibition, transcriptional regulation and inhibition of apoptosis which showed successful inhibition of cystogenesis in two PKD murine models (Bukanov et al., 2006, 2011), and increased levels of p21 which is down regulated in PKD.

In summary, current knowledge of PKD has immensely helped in supporting the importance of this disorder. However, further understating needs to be established in order to identify molecular markers, sequence analysis to establish therapeutic intervention, which will contribute towards the clinical manifestations that exist in treatment for PKD.

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