Autosomal Dominant Polycystic Kidney Disease: At a Glance

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Abstract

Polycystic kidney disease (PKD) is a systemic disorder which adds majority of renal patients to end stage renal disease (ESRD). Among all type of PKD, autosomal dominant polycystic kidney disease (ADPKD) is most prevalent and fourth most leading cause of dialysis and kidney transplant. Polycystic kidneys in several genetic and non-genetic disorders suggest the role of multiple factors in cystogenesis. Linkage analysis revealed some closely linked loci two of which are identified as PKD1, PKD2 and an unidentified locus to ADPKD. Candidate gene products are central molecules of protein-protein complex located at primary cilia and adhesion junctions of cell. In present study, Adult age group 31-59 years patients were more in number and relatively enlarged kidney size was observed in 49 PKD cases. Almost equal incidence of PKD in females to males (48.8%:51.2%) was observed in Indian population. 30.95% of the total cases enrolled cases had positive family history. Two associated symptoms like hypertension and presence of liver cysts and hepatomegaly were found more in frequency 19% and 39% in polycystic patients. Expressivity and variability in symptoms of ADPKD at individual level imply the role of genetic heterogeneity, effect of modifier genes and environmental factors.

Keywords: Polycystic Kidney Disease; End Stage Renal Disease; Autosomal Dominant Polycystic Kidney Disease; PKD1; PKD2; Polycystin

Abbreviations: PKD: Polycystic Kidney Disease; ESRD: End Stage Renal Disease; ADPKD: Autosomal Dominant Polycystic Kidney Disease.

Introduction

Polycystic kidney is most frequently found renal abnormality associated with several genetic and non-genetic disorders. It is a condition in which unilateral or bilateral presence of multiple cysts; disrupt the precise architecture of kidneys [1,2]. Among all types of PKD, worldwide prevalence of ADPKD is 1:1000 and contributes 10% of ESRD in humans [2,3]. ADPKD primarily found in adults and are equally frequent in men and women in western world [4]. Linkage study showed the involvement of two known loci *PKD1* and *PKD2* to the

ADPKD [5-9]. Some affected families did not shown linkage to either PKD1 or PKD2 suggesting the involvement of unidentified gene/s [10-13].

Clinical description

Biochemical examinations of patients revealed increased level of blood urea and serum creatinine [14]. Cardinal symptoms of ADPKD are adult onset of bilateral, multiple renal cysts of variable sizes originated from 1-3% of all nephrons. Patients have complications of flank pain, hematuria, frequent urinary tract infection, cyst infection and cyst hemorrhage. Sometimes renal stone, extra renal cyst such as liver cyst, pancreatic cyst, cyst in testis and ovary are also present in ADPKD patients. Non-cystic manifestations like cardiovascular defects (25%), intracranial aneurysm (8%) and hypertension (70-80%) are also common in these patients [15]. There are some adult and pediatric cases found in Indian and other population [16] which state the concurrence of ADPKD with other pathophysiological conditions like diffuse proliferative glomerulonephritis [17,18], situs inversus [19], polycystic liver disease [20], cystic hemorrhage in kidney [21], recurrent pneumothorax [22]. Other gastrointestinal and musculoskeletal complications like diverticulosis and hernia are also observed in patients [23]. Genetic screening of affected individuals revealed the two genes and polycystic kidneys are result of genetic insult. Affected individuals with PKD1 defect manifest the disease condition at third to fourth decade of life and most of them reached to ESRD by the age of 55 years. However, age of disease onset for PKD2 defect is fourth to fifth decade of life and reaches to ESRD by the age of 70 years [24]. ADPKD has been reported in both familial and sporadic cases suggesting that both germinal and somatic mutations might be involved in cyst generation [25]. Based on clinical symptoms, radiology techniques help a lot to examine and collect the status of kidneys. Ultrasonography, CT scan and MRI are helpful in suspected individual's clinical diagnosis because small sizes cysts in kidneys. Ravine has defined the criteria to classify the ADPKD based on non-invasive techniques [26].

Genetics

The most common autosomal dominant form, ADPKD, is late onset, genetically heterogenous disorder caused by defective genes. Two genes PKD1 (16p), PKD2 (4q) are identified by linkage studies and the presence of an unidentified third locus is suggested [10-13]. PKD1 localized in terminal region of chromosome16 having highly repetitive GC rich sequence and extremely prone to

genetic rearrangement. It consists of 46 exons spanning 54Kb genomic region transcribes 14.1Kb mRNA of 12,909bp long coding sequence which translates 4,303 amino acids long 462kDa glycosylated, an integral membrane protein known as polycystin1 (PC1). Functional PKD1 gene transcribe two isoforms differ in one amino acid length is produced by alternative splicing of mRNA [27]. The first 33 exons of PKD1 have undergone intra-chromosomal duplication throughout human evolution and generate six pseudogenes 13-16 MB proximal to PKD1 gene on same chromosome. Three pseudogenes viz. HG-A (21Kb), HG-B (17Kb), HG-C (8.5Kb) transcribe and share >95% sequence homology to PKD1 [14,28,29]. Because of having cryptic stop codons, they are expected to give small proteins that may be functional or nonfunctional [28]. PKD1 gene encodes three major components of protein (i) extracellular N-terminal is coded by exons 1-25, (ii) the middle transmembrane region is encoded by exon 26 and exons 29-45 and (iii) intracellular C-terminal region by exon 45-46 [29]. The second gene PKD2 contains 15 exons acquires a 68Kb genomic region transcribes 5.3kb mRNA of 2904bp long coding sequence which encodes 968aa long 110kDa integral membrane protein polycystin2 (PC2). PKD2 gene encodes two major segments (i) transmembrane region and (ii) intracellular region having both N and C terminals. Five isoforms are produced by alternative splicing of mRNA [30,31]. Exon1 is 660bp long and is very GC- rich. Exons 1-2 encodes N- terminal region, exons 2-9 codes for transmembrane domains, exons 11-15 form C-terminal region and exons 3,4 and 5 codes for extracellular loop.PC2 is member of polycystin subfamily belongs to transient receptor potential superfamily has 6 membrane spanning domains and cytoplasmic N and C terminals. 450aa sequence of PC1 is highly similar to PC2 transmembrane region. This transmembrane region in PC2 form transient cation receptor potential channel and for PC1 it is suspected to have same function [32,33].

Mutational screenings of the candidate genes suggest about 85% cases are linked with PKD1 gene mutations and rest 15% are linked with PKD2 gene and an unidentified gene mutation [34]. To date ADPKD mutation database listed 436 and 115 DNA sequence variants in PKD1 and PKD2 respectively [35]. Several genetic mutations have been found universally spread through-out the candidate genes. It has been found that single nucleotide changes are more in frequency than large deletions, duplications and insertions [36]. PKD1 is highly polymorphic with about 10 neutral variants found in single patient from sequencing [37]. Some other

phenomenon like loss of heterozygosity, de novo mutations, mosaicism and hypomorphic allele are reported from familial cases which suggested alteration in the disease phenotype [38,39]. Mouse knockouts of both alleles pkd1 and pkd2 attribute embryonic lethality suggesting that mutation in both genes gives severity to the disease [40].

Polycystins

Immunohistology for PC1 explore that it is highly expressed in fetal kidneys and lower in adult kidneys. At organ level it is also found in brain, liver, pancreas, heart, intestine and cell lines such as HEK293T [41]. Cellular expression of PC1 is highly confined to epithelial cells and at subcellular level it is localized at plasma membrane. In >20 weeks old fetus and adult kidneys PC1 was mainly localized at loop of Henle and cortical tubules. In adult kidneys it is more localized to cell-cell junction, cilia, apical and basolateral portion of collection duct epithelial cells [41-43]. PC1 encoded by PKD1 is cardinal member of a novel class of proteins involved in developmental processes [44]. PC1 has evolutionary conserved domains of multiple functions [45]. PC1 regulates calcium ion influx via interaction of coiled coil domains of PC1 and PC2 [46]. Similarly, PC2 expressed in kidney, heart, ovary, testis, vascular smooth muscles and small intestine. This protein is expressed in all segments of nephron except glomeruli. Sub-cellular localization of PC2 is confined to Golgi compartment, endoplasmic reticulum, and plasma membrane. PC2 share structural feature with transient receptor potential (TRP) channel as well as voltage activated calcium and sodium channel. It can form homo and hetero multimer with the help of its C-terminal tail containing two different sites for PC2 and PC1 protein-protein interactions respectively [47]

Cystogenesis

Molecular studies performed in animal models and human kidneys reveals that several proteins are involved in cystogenesis and among all these two ciliary proteins PC1 and PC2 are found prominently. Genetic studies on polycystic kidney disclose that occurrence of renal cyst in many disorders expose multiple molecular signaling pathways regulating different cell processes and maintenance of extracellular environment which get dysregulated in cystogenesis [48]. Non-genetic and simple cystic disorders suggest the involvement of other modifier genes and environmental factors in cystogenesis independent of age and gender of individual [49]. Cyst formation starts from all parts of nephron at teen-age and with the age cyst number and size enlarges. Cysts spread throughout the cortex and medulla leading to disruption of renal parenchyma of kidney and become prominent fluid filled saccular entity at later stage of life. Bud like outgrowth formed due to uncontrolled cell proliferation of epithelium lining of nephron which shed off from parent nephron and form independent sac like structure [50]. Genetic defects containing epithelium cells have abnormal cell secretory nature which leads to expansion of sac. Presence of somatic mutations in epithelial cells of cultured cyst suggested "two hit mechanism" of cystogenesis in which inactivation of both copies of a candidate gene is required for cyst formation. The "first hit" is inherited through germ line mutation, whereas the "second hit" is somatic mutation acquired during life time elicit cyst formation [26,51]. Intrafamilial phenotypic variation suggests the involvement of some other modifying internal factors such as gene/s, metabolic products in this disease which can be targeted in disease management. Interfamilial pathophysiological variations suggest us searching of other external modifiers such as environment and unidentified gene/s aggravate the cyst formation [52].

Molecular studies performed in mouse model suggested contribution of Pkd1 gene dose like low expression [53], overexpression [54] in cystogenesis. Microsatellite marker-based studies performed on familial cases suggested the involvement of loss of heterozygosity cystogenesis [38]. Experiments on PKD null mice indicate that PC1 play important role in renal tubule maturation [55]. Overlapping of sub-cellular localization of PC1 and PC2 suggest their mutual function in different signaling pathways [48]. Disruption in polycystin resulted in the uncontrolled cellular programs such as cell proliferation, differentiation, apoptosis, cell polarity, adhesion, maturation and extracellular matrix maintenance which are all essential steps of kidney tubulogenesis and morphogenesis [4]. Gene expression studies on mouse model and ADPKD human kidney samples identified differentially expressed genes involved in wnt/beta catenin, receptor tyrosine kinase and G-protein coupled signaling which get dysregulate in cystogenesis [56-58]. PC1 and PC2 are ciliary proteins function as mechanosensor molecule to correctly sense luminal flow. Defect in the proteins unable to sense luminal flow induce the cystogenesis [59]. Renal tubular epithelium proliferation is controlled process but failure in cilium or basal body/centrosome complex assembly, play important role in mitotic tubules orientation during cell division could trigger uncontrolled cell proliferation [60]. Confirmation study of imbalance between the cell division and apoptosis was confirmed as the key factor of

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cyst growth in Han: SPRD rat model. It inhibits caspases and revealed reduction in tubular apoptosis and slow disease progression [55]. To be fully functional, PC1 must be able to undergo N terminal cleavage which generates the noncovalently attached N terminal region to remaining transmembrane domain. N terminal cleavage occurs at the G protein coupled receptor proteolytic site (GPS) [62]. Two other independent cleavages at C-terminal tail (CTT) of PC1 release ~35kDa and ~15kDa small soluble fragments which binds to intracellular transcription factors and signaling molecules to gene expression and signal transduction. Increased level of cleaved CTT is observed in ADPKD cystic cells [63]. Ribosome biogenesis, protein synthesis and cell size are regulated by mTOR complex. PC1 is involved in inhibition of mTOR cascade in association of TSC1and TSC2 proteins [64]. PC1 and PC2 form heterodimer through their C terminal cytoplasmic tails [65]. PC1 with copartner PC2 increase the p21, regulator protein of cell cycle and cell growth level through JAK and STAT proteins activation [66,67]. G-protein activation by PC1 and PC2 regulate apoptosis, cell proliferation, cell differentiation and cell adaptation through a complex network of binding proteins and signaling. PC1 activates G-protein alpha subunit and positively regulates activity of cJNK and AP1 transcription factor [68]. G-protein also activates calcineurin which in turn activate and localize NFAT (nuclear factor of activated T cells). PC1 suspected to have role in wnt canonical and wnt non-canonical mediated signaling which regulates gene expression, differentiation and planar cell polarity [69]. Functional analysis of PKD1 transgenic lines revealed that Ig-PKD domains in PC1 mediate cell-cell adhesion [70]. In nephron, PC1 located to cell-cell adhesion junction and focal adhesion junctions, whereas in cystic epithelial cells most of the protein is intracellular [71]. Polycystins regulates the cell polarity and localization of the membrane proteins like Na$^+$/K$^+$-ATPase pump, CFTR pump, EGF receptors, E-cadherins, matrix metalloproteinase and integrins etc. (4). Luminal

localization of channel protein by PC1 promotes sodium and water secretion into cyst resulting expansion of cyst and hence disruption of renal parenchyma and compression of normal nephron [72]. These cysts contain all feature of parent nephron but became a single entity which affects the function of nephron which leads to accumulation of waste products in blood. Affected individuals are eventually placed on dialysis and transplant. Role of Pkd1 gene in cyst growth was studied in Pkd1 deletion mouse model and found that Pkd1 gene deficiency does not initiate sufficient autonomous cell proliferation leading to cyst formation. It suggests that additional stimuli regulating cell homeostasis, differentiation, cell-cell interactions and cell-matrix interactions are also equally mandatory. This could be the result of differences in genetic heterogeneity, allelic heterogeneity and gene environment interactions.

PKD Research in India

The detailed research work is not available from India for understanding the pathophysiology of PKD. Very recently an India foundation for PKD has been established for the awareness of PKD in Indians and inspire the investigators for basic and applied studies on PKD. A detailed study conducted by us enrolled eighty-four north- Indian individuals and some of the family members were clinically diagnosed with Polycystic Kidney Disease. Based on clinical investigation like family history, symptoms and ultrasonography all recruited patients were confirmed for the disease. Patients with the positive family history were classified as familial case and patients without family history of PKD classified as sporadic cases. Almost equal incidence of PKD in females (48.8%) and males (51.2%) was observed. 30.95% of the total cases had positive family history (familial: FAM) while rest 69.05% had negative family history (sporadic: SPO) (Table 1).

Sample (blood)	Male	Female	Frequency (%)	Total cases (84)	With family member
Sporadic cases (negative family history)	28	30	69.04	**58**	-
Familial cases (positive family history)	15	11	30.95	**26**	22+4(43)

Table 1: Categorization of patients based on family history and gender.

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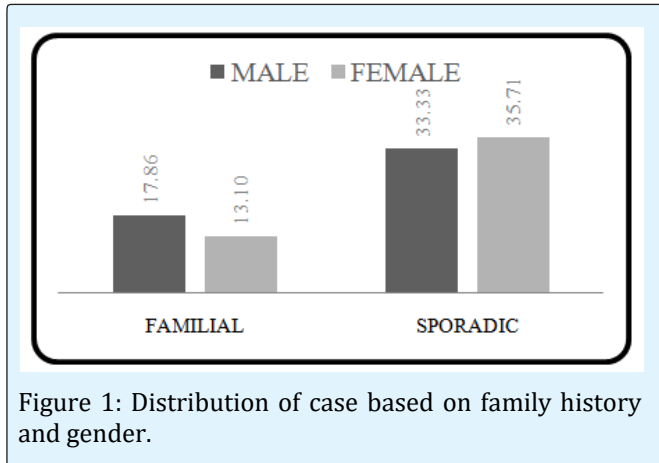
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Figure 1: Distribution of case based on family history and gender.

Further, four sub-categories were made based on gender and family history; (a) females with positive family history (FFAM: 13.1%), (b) female with negative family history (FSPO: 35.7%), (c) male with positive family history (MFAM: 17.86%) and (d) male with negative family history (MSPO: 33.33%) (Figure 1).

Cases were classified in different age groups based on gender and the age of disease manifestation. Age group 31-59 years patients were more in number compare to other two age groups (15-30 years and >60 years). (Figure 2) This suggests that the patients are adult onset group. Normally, the dimension of human kidney is 10-12 cm in length and 6 cm in width. In present study, relatively enlarged kidney size was observed in 49 PKD cases (Table 2).
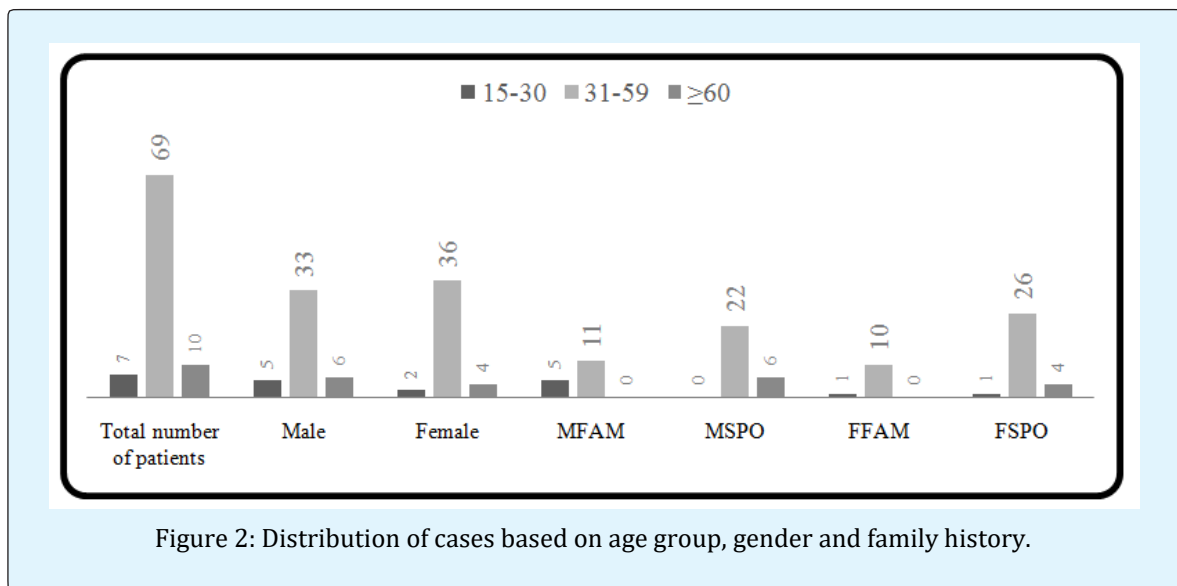

Figure 2: Distribution of cases based on age group, gender and family history.

49 PKD patients	Age (years)	Right Kidney-Length (11cm)	Right Kidney –Width (6cm)	Left Kidney-Length (12cm)	Left Kidney-Width (6cm)
Average ± deviation	46.6 ± 7.4	14.0 ± 2.5	6.7 ± 1.5	14.5 ± 2.4	7.0 ± 1.4

Table 2: Size of kidney in PKD cases.

Clinical symptoms of cases were evaluated to understand the nature of disease. Among renal and extra-renal associated clinical symptoms presented by PKD patients: extra renal cyst, hypertension and stone were the major contributors. Two associated symptoms like hypertension and presence of liver cysts and hepatomegaly were found in 19% and 39% of polycystic patients respectively (table 3).Clinical symptoms and the family history suggested that the patients might have favorable genetic background responsible for disease condition.

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Clinical Symptoms in PKD cases	Percentage
Liver cyst and hepatomegaly	39
Hypertension	19
Chronic kidney disease	17
Kidney stone	12
Type 2 diabetes mellitus	8
Gall bladder stone	6
Lymphadenopathy	5
Urinary tract infection	5
Hematuria	5
Prostatic cyst	5
Ascites	5
Benign prostate hyperplasia	4
Hypothyroidism	2
Liver stone	2
Cardiac valve defect	2
Asthma	2
Pancreatic cyst	1
Other symptoms	17

Table 3: Frequency of clinical symptoms in Indian PKD cases.

Conclusion

ADPKD is a slow progressive genetic disorder which could be treated by retarding the cyst expansion. Prevalence and susceptibility of disease depends of genotype of population and external environmental factors. There are several case reports published from all over the world to explain the exact scenario of ADPKD so that the genotype can be correlated with phenotype. A better understanding of the epidemiology and etiology of polycystic kidney disease will reveal the possible therapy and management of disease progression.

Acknowledgment

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