Chapter

1

Genetics of Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is a disease having renal and extrarenal manifestations. ADPKD is commonly associated with mutations in two primary genes; PKD1 on chromosome 16p13.3 and PKD2 on chromosome 4q21 (type II). There is an interaction of polycystin 1 and polycystin 2 (encoded on PKD1 and PKD2) located on the endoplasmic reticulum of cells lining the tubules. This is required for the mature polycystin complex to reach the cell surface. The two primary methods available for gene mutation are DNA linkage analysis and gene-based mutation screening. Linkage analysis involves highly informative microsatellite markers flanking PKD1 and PKD2. For the routine genetic screening of ADPKD direct DNA sequencing is employed.

INTRODUCTION

Polycystic kidney disease (PKD) refers to a variety of monogenic disorders characterized by the cyst formation in renal units with increase in size of these cysts. These changes lead to deterioration of renal function over the years.[1] Among the different forms, autosomal dominant polycystic kidney disease (ADPKD) is common.[2,3] As the disease is clinically silent in many individuals, the number of patients diagnosed during their lifetime is estimated to be less than half.[4] Major chunk of affected population develops the disease between the age group of 20 and 40 years although sporadic cases have been reported from *in utero* onset to late adulthood.[5] Renal cysts may have association with cysts in liver, spleen, pancreas, dysfunctional heart valves and aneurysms in brain.[6]

The genetics, types of protein anomalies and mutation detection strategies of ADPKD are discussed in this chapter.

Genes

PKD1, responsible for ADPKD type 1 is mapped on chromosome 16 (Fig. 1.1)[7] (16p13.3) and PKD2, responsible for ADPKD type 2 is mapped on chromosome 4q21. The PKD1 gene and gene for tuberous sclerosis (TSC2) are adjacently located. As per the available literature, approximately, PKD1 mutation affects 80–85% of ADPKD families, and 15–20% of the families are affected by PKD2 mutations.[8] If a given patient is negative for PKD1 and PKD2 it is prudent to look for the mutations in gene GANAB located on chromosome 11q12.3 (Fig. 1.1). GANAB gene presents with autosomal dominant polycystic liver disese. The ADPKD component is not severe. It accounts for ~0.3% of total ADPKD.[9] Similar to GANAB, four other genes, i.e.

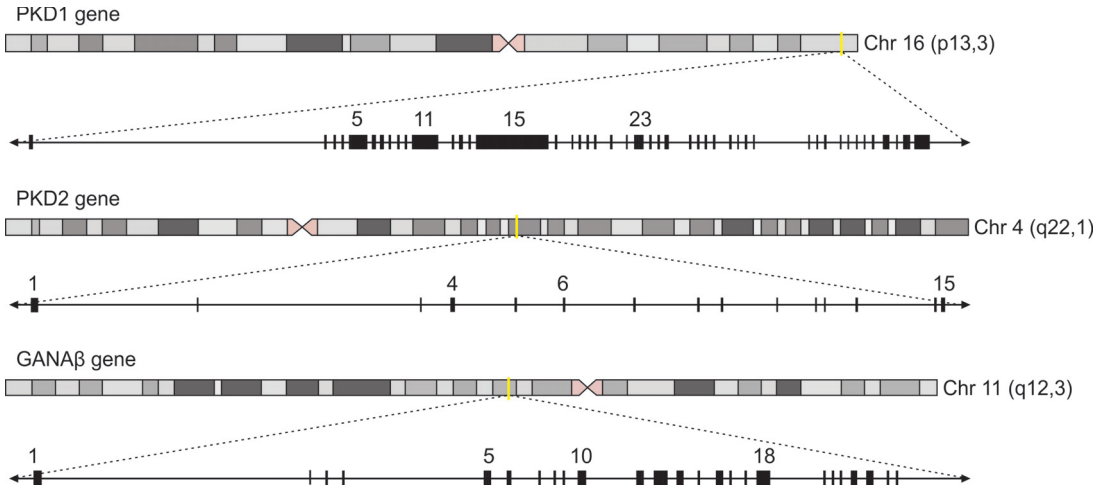

Fig. 1.1: Chromosome localization and genomic structure of *PKD1*, *PKD2*, and *GANA*β genes and structure of polycystin 1 (PC1) and polycystin 2 (PC2).Schematic representation of chromosomes and genomic structure for the genes[7]

ALG8, SEC61B, SEC63, and PRKCSH, have been identified.[10, 11] With the use of whole genome sequencing (WGS), an additional new gene, DNAJB11, has been identified recently, which presents with small renal cysts, non-enlarged kidneys, liver cysts and progressive renal failure.[12]

Types of Protein Anomalies

PKD1 and PKD2 encode proteins, polycystin 1 (PC1) and polycystin 2 (PC2) respectively (Fig. 1.2).[13, 15] Polycystin 1 (PC1) is characterized by a 11-transmembrane domain. Majority of the protein is in the extracellular region. The

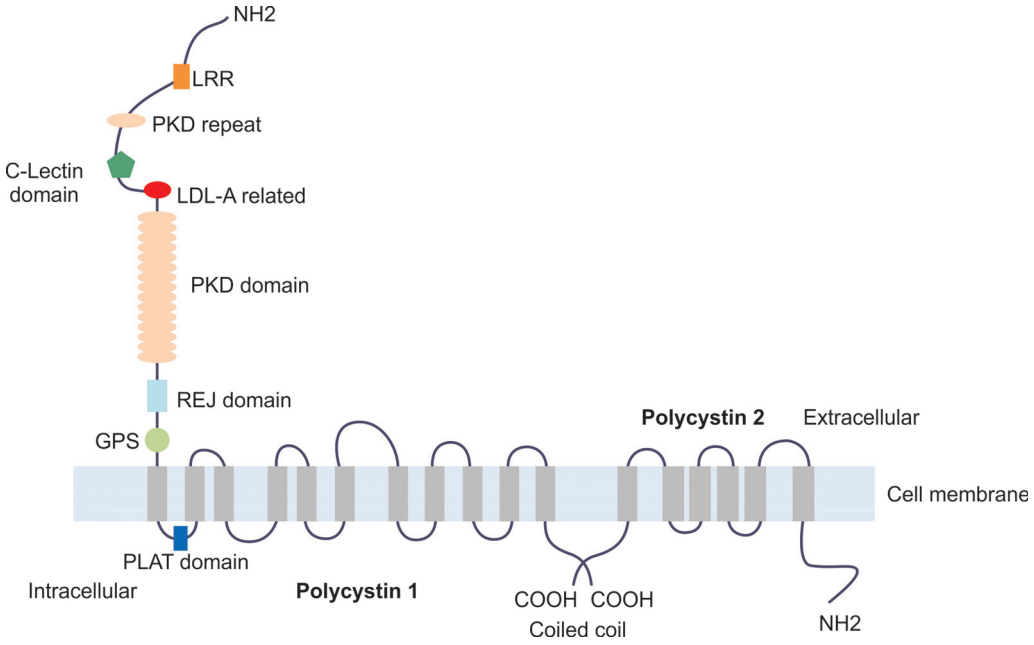

Fig. 1.2: Representation of *PKD1* and *PKD2* protein products: PC1 and PC2[7]

NH2 terminal of the extracellular domain is important in protein-protein interactions. NH2 terminal has a GPCR proteolytic site (GPS domain) and 12 PKD domains.[16,18] Among the several cleavage events, polycystin 1 undergoes, cleavage event at a juxtamembrane G protein-coupled receptor (GPCR) is significant. This is "*Cis*-autoproteolysis", as it occurs in the absence of any exogenous protease. Two non-covalently associated fragments by cleavage at the GPS domain (Fig. 1.3).[19] The importance of this cleavage event is that, it is fundamentally essential to maintain renal tubular morphology and mutation at the GPS site results in ADPKD with cysts primarily affecting the collecting duct as evidenced by knock-in mouse model with a mutation.[16,20]

Polycystin 2 (PC2) is a member of family of nonselective cation channels.[21] Morphologically, PC2 is characterized by a short N-terminal cytoplasmatic region, six transmembrane domains that are homologous with a portion of the transmembrane domain of PCI, and a short C-terminal fragment. A tetrameric structure is formed by four polycystin 2 channels with a voltage-sensing domain and a novel "TOP" domain comprised of the large extracellular loop between TM1 and TM2. The TOP domain is a hotspot for missense disease-causing variants and is important for channel assembly and/or function.[22, 23]

Polycystins are membrane proteins situated in plasma membranes and primary cilium. They are localized in renal tubular epithelia, pancreatic ducts and hepatic bile ductules.[24] The interaction of PC1 and PC2 in the endoplasmic reticulum is required for the mature polycystin complex to reach the cell surface, including the cilium. PC1 is involved in multiple cellular and matrix interactions.[25] Polycystin 2, located in endoplasmic reticulum, is involved in calcium signaling. PC1 and PC2 interact in a common signaling pathway which results in identical clinical manifestation of ADPKD1 and ADPKD2.[21]

Genotype–Phenotype Relationship

The molecular diagnosis of the mutations associated with ADPKD is important in prognostication of the disease. Patients with PKD1 mutations have larger kidneys and early onset of the disease than in patients with PKD2 mutations.[26, 27] GANAB mutation is associated

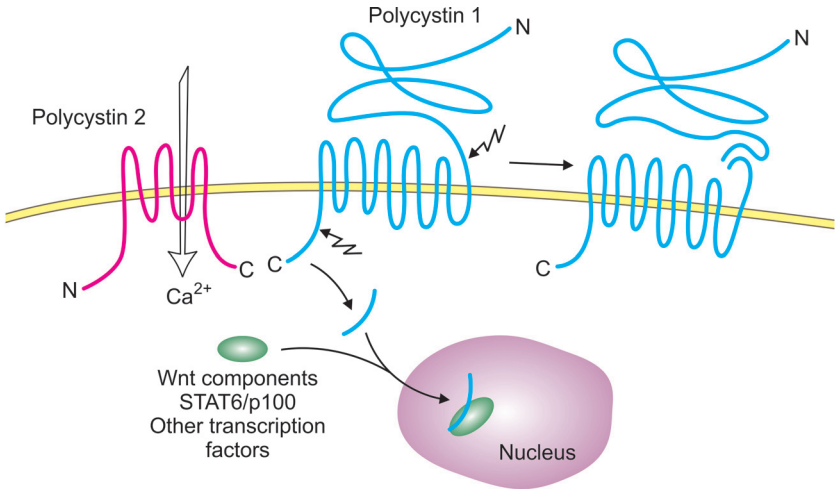

Fig. 1.3: Cleavage in extracellular and intracellular regions of polycystin 1 protein[19]

with a mild renal phenotype.[9] Truncated PKD1 mutations have a more serious disease. Milder form of disease is associated with non-truncated PKD1 mutations or mutations in PKD2. Truncating PKD1 mutations are associated with larger kidneys and that too in men, in women they manifest with liver disease.[27, 28] Genetic interaction and epistasis is a variation in the modifier gene, this leads to difference in the presentation as regards to progression of the disease in members of same family with same mutation.[29]

The PRO-PKD score, a prognostic index, developed by Cornec-Le Gall et al, is based on both, genetic and clinical data.[30]

Detection Strategies

DNA linkage analysis along with gene-based mutation screening are the two primary methods available for the detection of the mutations.[31] Haplotype reconstruction can be used to predict the status of other members of the family by performance of linkage analysis. This method may be considered in situations such as prenatal testing in which the mutation is unknown and for pre-implantation genetic diagnosis (PGD).[32]

Mutation screening for PKD genes using DNA or mRNA is the other method of detection currently used. Complete gene sequencing remains the gold standard for mutation analysis, but has the disadvantage of being highly expensive and time-consuming. For the routine genetic screening of ADPKD direct DNA sequencing is employed. In order to lower testing costs and minimize turn-around time, several mutation screening tools are available such as denaturing gradient gel electrophoresis (DGGE), single-strand conformation polymorphism (SSCP), DNA high-pressure liquid chromatography (DHPLC) screening method and multiplex ligation dependent probe assay (MLPA).[33–39] But, these methods have lower definite mutation detection rates. Presently, long-range polymerase chain reaction (PCR) strategy with specific primers are considered as a key strategy of gene mutation detection, as it has faster turnaround time, cost saving and reliable in the genetic diagnosis of ADPKD.[40, 41]

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