

## Chapter 02

# Role of Animal Models in the Study of Human Genetic Polycystic Kidney Disease

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## Abstract

Study on animal models plays important role in understanding the molecular basis underlying the human genetic diseases. Dozens of animal models for human polycystic kidney disease (PKD) have been established and provided insightful information in better understanding of PKD in either pre-genomic or post-genomic time. Here we highlight studies of genetic animal models for PKD that brought novel insights on understanding the pathogenesis of PKD

**Polycystic kidney disease (PKD)** is a common genetic disease characterized by the accumulation of multiple fluid-filled cysts in each kidney and other organs. The renal cysts originate from the renal tubular epithelial cells lined by a single layer of cells that have higher rates of cellular proliferation and apoptosis, and are less differentiated than the normal tubular cells. Progression of cysts in the kidneys ultimately causes end-stage renal disease (ESRD) which makes PKD one of the leading causes of ESRD in children and adults [1]. PKD consists of two forms: ADPKD (Autosomal Dominant Polycystic Kidney Disease) and ARPKD (Autosomal Recessive Polycystic Kidney Disease). ADPKD is the most common genetic disease affecting 1 in 500 to 1 in 1000 in adults of all ethnic groups worldwide. ARPKD is far less common, affecting 1 in 6,000 to 1 in 40,000 at an extremely young age, including newborns, infants and children. While kidney cysts arise from all the segments of the nephron and collecting ducts in ADPKD, they arise from collecting ducts in ARPKD. Extrarenal systems are affected in PKD [1].

Genes that are responsible for ADPKD were identified in the mid 1990s. PKD1 gene was isolated by two research groups independently in 1994 [2], and 1995 [3], while PKD2 was identified in 1996 [4]. ADPKD is caused by mutations on a single gene of either PKD1 or PKD2. The gene responsible for ARPKD was identified in 2000 and named as PKHD1 (Polycystic Kidney and Hepatic Disease 1) reflecting its clini-

cal presentations [5,6]. Mutations have been identified throughout the gene of any among those three genes in affected PKD individuals without evidence for clustering. ARPKD is a recessive form with two germline mutations. ADPKD was hypothesized to be a disease as recessive trait at molecular level that “second-hit” is required during development, [7], as Loss of Heterozygosity (LOH) was found in the study of human renal cystic epithelia cells [7]. The genetic animal model which provided direct evidence for the first time in support of the “second-hit” hypothesis was reported in a conventional knockout mouse model of *Pkd2* in 1998 [8]. In this knockout mouse model, a mutant allele that carries a mutant exon 1 in tandem with wild type exon 1 at the *Pkd2* mouse locus was established. This is an unstable allele that would undergo somatic inactivation by intragenic homologous recombination to produce a true null allele recapitulating the recessive mechanism proposed occurred in patients. Establishment of this unique transgenic animal provides a faithful experimental tool in vivo for extensive studies on the pathogenesis of PKD and offers an in vivo platform for the study of therapeutic targets for the human genetic PKD disease [9].

Animal models established in lower species have also brought significant novel insights into the PKD research. In 1999, Barr et al reported the discovery in the little worm, *Caenorhabditis elegans* (*C. elegans*), that the ADPKD gene homologues, *lov-1* and *PKD-2*, homologue to human *PKD1* and *PKD2* respectively, are localized to the same cell/subcellular locations and are required for male mating behavior [10]. *C. elegans* is a free-living, transparent nematode, which is about 1 mm in length and comprises hundreds of cells and lives in temperate soil environments, has been used extensively as a model organism since 1974. The striking discovery in this report that has been further proved to be significant on PKD research is the observation that the PKD gene proteins are localized in cilia, an unique subcellular organelle, little of which function had been studied [10,11]. The expression of PKD proteins in cilia would be difficult to be visualized in the context of in vivo level such as in a rodent animal model or in human tissue since little attention was paid on this longtime

ignored organelle at that time. Later study on a genetic mouse model for PKD, TgN737RpW [12,13], further revealed at first time that defects in the non-motile primary cilia structure caused PKD [14]. To this date, dozens of human genes such as the genes for Bardet-Biedl syndrome, nephronophthisis, Meckel-Gruber syndrome, and Senior-Loken syndrome, in addition to PKD, have been found linked to the cystic diseases which have been grouped as “ciliopathies”, reflecting the significant impact resulting from discoveries made in experimental animal models.

While the conventional genetic animal models for PKD recapitulates its clinical pathogenesis and thus provide faithful tool for extensive studies of the disease in the lab, creations of novel experimental conditions by manipulation of inactivation time point on targeted gene or by introduction of multiple targeted genes in a single animal line of PKD model have provided striking clues and insights into the understanding of molecular genetics in PKD. Among these models, early or late inactivation of *Pkd1* gene introduced by conditional knockout technique resulted in significantly different rate of progression in cysts formation in the mouse models reported by Piontek et al. [15]. This was the first published animal model that the relationship of onset time point to the progression of PKD was systematically studied by manipulating the experimental conditions genetically. Study on this model uncovered a previously unrecognized brake point during renal growth that corresponds to significant changes in genes expression. More importantly, information raised from those models suggests that selection of appropriate animal model is critical for studies of therapeutic targets for PKD. In another genetic model reported recently [16], Combination of inactivation and overexpression of multiple genes responsible for cystic disease (PKD or PLD: polycystic liver disease) that introduced into a single mouse line allows to define the functional interrelationships among the targeted genes. By these experimental approaches, the authors revealed that polycystin-1, gene product of *PKD1*, is the rate-limiting component in cyst formation in human cystic diseases including ADPLD, ADPKD, and ARPKD [16].

There are near a dozen of murine models for PKD generated from mutation in genes that are either not identified or not orthologous to human PKD genes [17]. Although these models served as important experimental tools, such as the Tg737 model discussed above, for the better understanding of PKD pathology and pathogenesis, it is worthy to be noticed that the molecular pathway(s) underlying the cystic phenotypes in those models may not necessarily be completely faithful to that in human PKD. It would be important to have further verifications in the animal models orthologous to human PKD for establishing a complete understanding for the human disease.

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## *Top 10 Contributions on Genetics*

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