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Murine Models of Hereditary Renal Diseases

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Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common life-threatening inherited diseases, and the PKD1 gene is responsible for most cases of this disease. Previous efforts to establish a mouse model that recapitulates the phenotypic characteristics of ADPKD, which have used conventional or conditional knockout of the mouse orthologue Pkd1, have been unsuccessful or unreliable. In our previous study, we described the generation of a novel Pkd1 hypomorphic allele, in which Pkd1 expression was significantly reduced but not totally blocked. These Pkd1 homozygous mutant mice rapidly developed renal cystic disease, supporting the hypothesis that 'haploinsufficiency' explains development of the ADPKD phenotype. In the present study, we further investigated the Pkd1 haploinsufficiency effect by generating Pkd1 knockdown transgenic mice with co-cistronic expression of two miRNA hairpins specific to Pkd1 transcript and an Emerald GFP reporter driven by a human ubiquitin B promoter. Two transgenic lines which had ~60–70% reduction of Pkd1 expression developed severe renal cystic disease at a rate similar to that of human ADPKD. These results further support the haploinsufficiency hypothesis, and suggest that the onset and progression of the renal cystic diseases are correlated with the level of Pkd1 expression. The two novel mutant lines of mice appear to be ideal models for the study of ADPKD.