Pkhd1-Pkd1 interact in a dose-dependent manner to exacerbate a dysregulated ciliary compartment

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Autosomal dominant- and autosomal recessive- polycystic kidney disease (ADPKD and ARPKD, respectively) are the two most common monogenic causes of kidney failure. Though genetically these diseases are distinct from one another, ADPKD caused by mutations in *PKD1* or *PKD2* while mutations in *PKHD1* are causative for ARPKD, both have similar renal disease presentations; development of cystic structures due to proliferation of tubular epithelial cells. Previously, it has been shown that *Pkd1* and *Pkhd1* genetically interact to exacerbate the PKD phenotype in mice, however the mechanism of this interaction is unknown.

Breeding *Pkhd1* null ($Pkhd1^{LSL/LSL}$) animals to the *Pkd1* hypomorphic model (p.R3277C; RC) ($Pkd1^{RC/RC}$), we generated $Pkhd1^{-/-}$;$Pkd1^{RC/RC}$ (digenic) mice, and homozygous/heterozygous combinations. We assayed the kidney phenotype by macroscopic and microscopic techniques and performed bioinformatics analysis of differential expressed genes (DEGs) in postnatal day 0 whole kidney tissue.

The digenic mice were viable (median survival time=P17, p=0.0001) with enlarged and severely cystic kidneys, a phenotype similar to ARPKD, whereas $Pkhd1^{-/-}$ or $Pkd1^{RC/RC}$ animals presented no or mild disease (%KW/BW at P0: 2.73±0.52 vs 1.0±0.32 or 1.44±0.19, respectively, p<0.0001 [ANOVA]). Interestingly, at 6m the %KW/BW and cyst index of $Pkhd1^{-/-}$;$Pkd1^{+/RC}$ and $Pkhd1^{+/-}$;$Pkd1^{RC/RC}$ animals were not significantly different from single homozygote controls (%KW/BW: 1.57±0.12 and 2.01±0.15). Biochemical assays did not show an interaction between the *Pkhd1* protein (fibrocystin/polyductin) and PC1/PC2. By RNAseq and gene set enrichment analysis, we found a significant enrichment of upregulated genes annotated to cilium organization (GO:0044782) in each of the $Pkhd1^{-/-}$, $Pkd1^{RC/RC}$ and digenic data sets (enrichment score [p- value]: 2.24 [4.33×10^{-3}], 2.69 [1.03×10^{-6}], 2.84 [4.27×10^{-5}], respectively). Furthermore, we found that mean ciliary length in each mutant model paralleled the cilia-associated enrichment score (αm: WT, 2.86±1.24; $Pkhd1^{-/-}$, 3.06±1.17; $Pkd1^{RC/RC}$, 3.63±2.24; digenic, 5.0±1.99).

Taken together, our phenotypic, biochemical and transcriptome analysis reveals that ARPKD and ADPKD have separate disease-causing thresholds that each are sufficient to cause a dysregulated primary cilia compartment, indicating that the synergistic interaction observed in $Pkhd1^{-/-}$;$Pkd1^{RC/RC}$ deficient cells is mechanistically caused by an enhanced dysregulation of primary cilia. These data highlight that there may be potential therapeutic targets that could both benefit ARPKD and ADPKD patients.