3D imaging and transcriptome signatures of a rat model of polycystic kidney disease

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Background & Aim

Polycystic kidney disease (PKD) is a congenital fibrocystic disorder where cysts are forming within the kidney, causing kidney enlargement and declining kidney function eventually leading to chronic kidney disease (CKD). Translational animal models can inform about potential clinical efficacy of novel drug candidates for PKD. The PCK rat is an established genetic model of PKD with natural history and renal histologic abnormalities that resemble the human disease.

The present study aimed to characterize disease progression in the PCK rat model.

Methods

10 weeks-old male PCK rats (PCK/CrljCrl-Pkhd1pck/Crl) were from Charles River Laboratories. Male Sprague-Dawley rats served as healthy controls. Body weight was measured bi-weekly and plasma urea/creatinine, and urine albumin/creatinine was assessed. Upon termination at 17 and 25 weeks of age, kidney and liver weight was obtained, and left kidney was collected for RNA sequencing. Right whole-kidney cyst morphometrics was performed using 3D quantitative light sheet fluorescence microscopy (LSFM) imaging.

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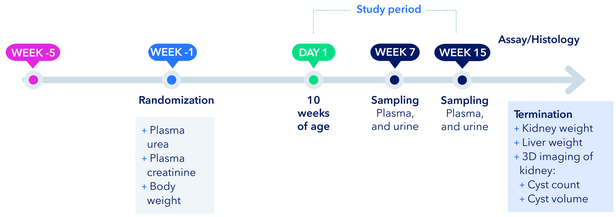
1 Study outline



Group	Animal	Gender	Number of animals	Age at termination
1	Sprague-Dawley rat	Male	7	**25 weeks**
2	PCK rat	Male	6	**17 weeks**
3	PCK rat	Male	6	**25 weeks**

2 Terminal body, kidney and liver weight

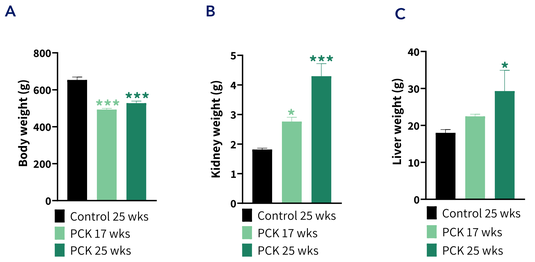


Figure 1. PCK rats demonstrate lowered body weight concomitant with progressively increased kidney and liver weight. **(A)** Terminal body weight. **(B)** Right kidney weight. **(C)** Liver weight. Mean + SEM. *p<0.05, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

3 Progressive kidney injury in PCK rats

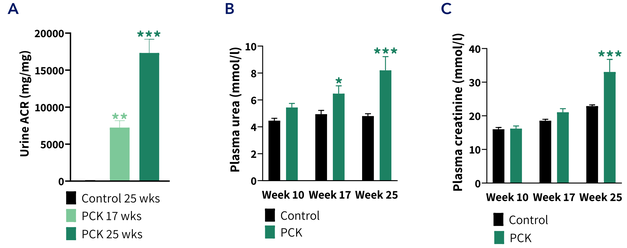


Figure 2. PCK rats show increased plasma and urine markers of kidney injury. **(A)** Urine albumin-to-creatinine ratio (ACR) at termination. **(B)** Plasma urea. **(C)** Plasma creatinine. Mean + SEM. *p<0.05, **p<0.01, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

4 Progressive cystic enlargement in PCK rats

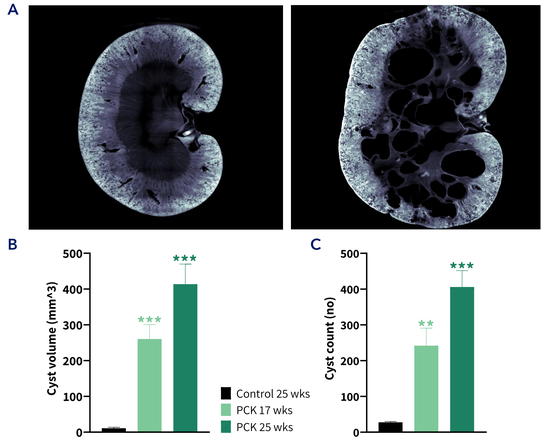


Figure 3. Quantitative whole-kidney LSFM imaging reveals progressive cyst formation in PCK rats. **(A)** Representative light sheet 3D image of right kidney from Control rat and PCK rat at 25 weeks of age (sagittal axis). **(B)** Cyst volume in right kidney, mean + SEM. **(C)** Cyst count in right kidney, mean + SEM. **p<0.01, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

5 Kidney transcriptomic profile in PCK rats

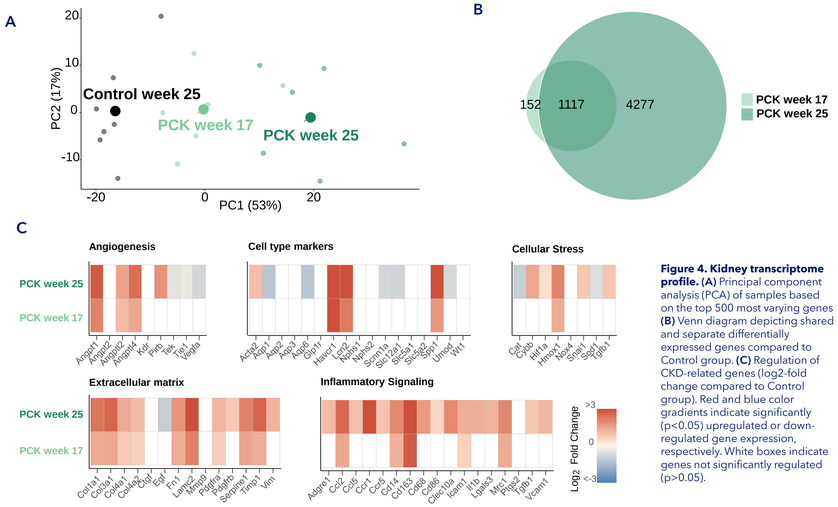


Figure 4. Kidney transcriptome profile. **(A)** Principal component analysis (PCA) of samples based on the top 500 most varying genes **(B)** Venn diagram depicting shared and separate differentially expressed genes compared to Control group. **(C)** Regulation of CKD-related genes (log2-fold change compared to Control group). Red and blue color gradients indicate significantly (p<0.05) upregulated or down-regulated gene expression, respectively. White boxes indicate genes not significantly regulated (p>0.05).

Conclusion

- The PCK rat demonstrates progressive kidney injury and enlarged kidneys
- The PCK rat shows marked and progressive renal cyst formation
- Light sheet fluorescence microscopy (LSFM) imaging is advantageous for 3D quantitative analysis of whole-kidney pathology in the PCK rat.

The PCK rat model is a translational preclinical model suitable for testing novel drug therapies for PCK

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