Disease progression in a translational rat model of polycystic kidney disease (PCK)

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BACKGROUND & AIM

Polycystic kidney disease (PKD) is a congenital fibrocystic disorder where cysts are forming within the kidney causing kidney and liver enlargement, declined kidney function and eventually lead to chronic kidney disease (CKD). Animal models with improved clinical translatability can optimally 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.
Here, we characterised disease progression in the PCK rat with emphasis on clinical and histopathological hallmarks.

METHODS

Male PCK rats (PCK/CrljCrl-*Pkhd1pck*/Crl, Charles River Laboratories) arrived at 10 weeks of age. Male Sprague-Dawley rats served as healthy controls. Body weight was measured bi-weekly. Plasma urea/creatinine, urine albumin/creatine and right kidney size/volume (ultrasound imaging) was assessed. Upon termination at 17 and 25 weeks of age, kidney and liver weight was obtained, and right whole-kidney cyst morphometrics was performed using quantitative light sheet 3D imaging.

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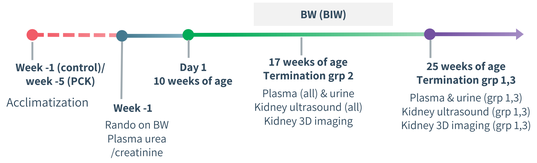
1 Study outline



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

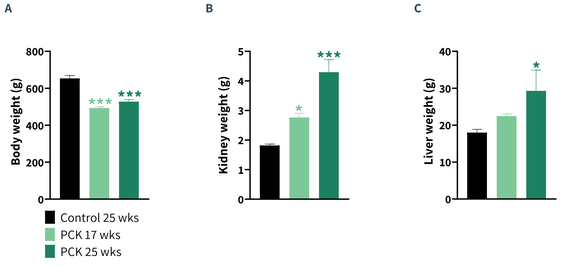


Figure 1. PCK rats demonstrate lowered body weight concomitant with progressively increased kidney and liver weight. (A) Terminal body weight. **(B)** Right kidney weight. **(C)** Liver weight. Mean + SEM. *p<0.05, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

3 Progressive kidney injury in PCK rats

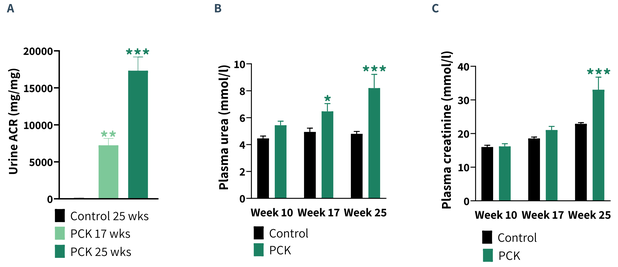


Figure 2. PCK rats show increased plasma and urine markers of kidney injury. (A) Urine albumin-to-creatinine ratio (ACR) at termination. **(B)** Plasma urea. **(C)** Plasma creatinine. Mean + SEM. *p<0.05, **p<0.01, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

4 Kidney enlargement in PCK rats – ultrasound imaging

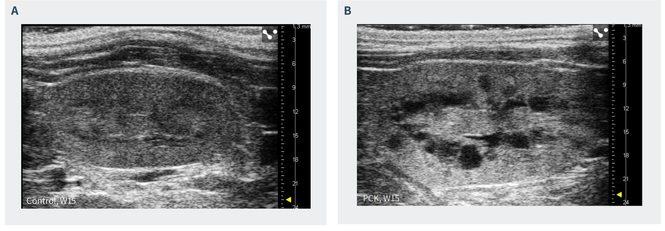


Figure 3. Ultrasound imaging reveals kidney enlargement in PCK rats. Representative ultrasound image of right kidney from Control rat **(A)** and PCK rat **(B)** at 25 weeks of age (sagittal axis). **(C)** Right kidney volume, mean + SEM. **(D)** Right kidney sagittal length, mean + SEM. ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

5 Progressive renal cystic enlargement in PCK rats – light sheet imaging

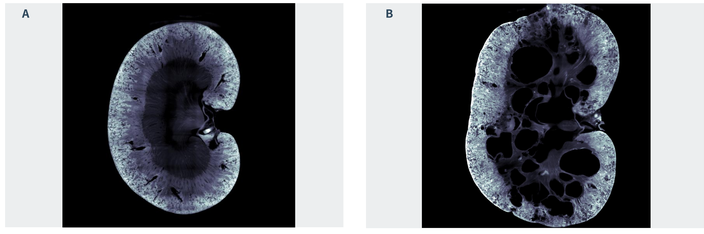


Figure 4. Quantitative whole-kidney light sheet imaging reveals progressive cyst formation in PCK rats. Representative light sheet 3D image of right kidney from Control rat **(A)** and PCK rat **(B)** at 25 weeks of age (sagittal axis). **(C)** Cyst counts in right kidney, mean + SEM. **(D)** Cyst volume in right kidney, mean + SEM. **p<0.01, ***p<0.001 compared to Control (Dunnett's test one-factor linear model).

CONCLUSION

- \+ PCK rats show progressive kidney injury and enlarged kidneys
- \+ PCK rats show marked and progressive renal cyst formation
- \+ Combined ultrasound and light sheet imaging is advantageous for 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.

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