Magnetic Resonance Imaging of the Heart, Liver, and Kidneys of a Porcine Model of ARPKD

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INTRODUCTION There is a great need for large animal models of PKD that better recapitulates human physiology to facilitate the testing of therapies. In many respects, the anatomy, biochemistry, physiology, size, and genetics of pigs resemble those of humans making porcine models of PKD ideal for therapeutic testing. Moreover, their body size affords the use of clinical imaging modalities for accurate monitoring of disease. We report the first study utilizing magnetic resonance (MR) imaging of porcine models of PKD to characterize disease severity and follow progression.

METHODS Four genetically engineered ARPKD pigs with various *PKHD1* mutations were imaged at 3, 4, 5, and 6 months of age. The animals included two homozygous p.T36M/p.T36M mutants, a heterozygous p.T36M/+ mutant, and a mosaic animal with two inactivating frameshift mutations. All MR acquisitions were acquired on a GE 3T scanner (GE Medical Systems, Discovery MR750w) in the supine position utilizing a multichannel surface coil. Anesthesia of the animals was maintained with inhalation of 1–2% isoflurane. No intravenous contrast was used. The sequences included anatomic imaging of the heart, liver, and kidneys. CINE imaging was acquired of the heart, renal artery (for assessment of renal blood flow), and portal vein. Diffusion weighted imaging, blood oxygen-level dependent, and magnetization transfer (MT) pulse sequences were acquired for the kidneys. Texture analysis was also performed on the T2-weighted images.

RESULTS Shown in Figure 1 are T1 and T2-weighted MR images of the mosaic animal at 5 months of age. Numerous renal cysts and drastic cystic disease of the liver were observed in the mosaic female. A significant increase of 30% in total kidney volume (TKV) during 2-month follow-up (3–5 months) was measured for the two animals showing evidence of renal cysts. At baseline, median kidney R2* ranged from 13.7 to 15.6ms^{-1}, median MT_{600} from 38.1 to 46.7%, and median MT_{1200} from 25.9 to 31.4%. The liver in the mosaic animal was over 3000mL at 5 months of age.

CONCLUSIONS A *PKHD1* gene-edited porcine model of ARPKD was developed and characterized by longitudinal imaging to follow progression of the disease and evaluate both morphological and functional changes in heart, liver, and kidneys. Cyst development was observed in the kidneys of two of the pigs, and severe PLD was also found in a mosaic female with two inactivating frame shift mutations.

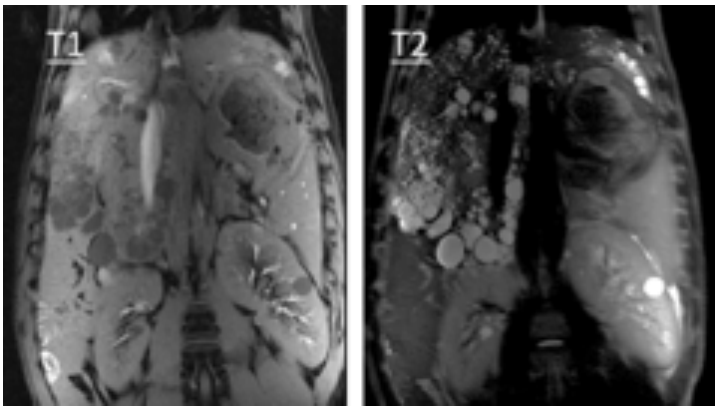

Figure 1. Example T1 and T2-weighted MR images of the mosaic female at 5 months of age. Numerous renal cysts are present, as well as very severe PLD.