## MR Characterization of Mouse Hypertension Model

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Recent studies suggest that hypertension is closely related to renal function. Glial cell derived neurotrophic factor (GDNF), its ligand binding co-receptor GFRα1, and the receptor tyrosine kinase c-RET, play a critical role in kidney organogenesis. Homozygous mutation in any of these loci results in bilateral renal agenesis. However, the majority of heterozygous mice are born with both kidneys. Histological analysis of kidneys of *Gdnf*$^{+/-}$ animals showed a reduction (~32%) in nephron number at birth. We found that these animals are hypertensive by one year of age while clinical diagnosis of renal function, such as serum creatinine or BUN levels, remains normal. The congenital reduction of nephron number mediated by *Gdnf* haploinsufficiency provides us with a genetic model system to explore early diagnosis of subtle kidney insufficiency by MRI approach. We evaluated the sensitivity of MR imaging to detect genotype- and age-dependent renal structural changes on both excised kidneys and in live organisms and compared these results with histological analysis.

Kidneys of wild type and *Gdnf*$^{+/-}$ mice (1, 6, 12 and 18-month of age) were excised and fixed in 4% paraformaldehyde prior to immersion in perfluorinated hydrocarbon oil in a sealed tube for imaging in a 7T Bruker Avance scanner. $T_2$ weighted 3-D gradient echo images were acquired (parameters: isotropic resolution 0.03 mm, TR/TE= 200/10 ms). For *in vivo* imaging, mice (6 and 18 months of age) anesthetized with isoflurane were placed in a 35 mm radio frequency coil. Core body temperature was maintained at $37^0$C with a heated circulating water pad. All scans were synchronized with the respiration cycle. MR imaging was performed on a horizontal 7T Bruker Avance scanner. A series of coronal slices covering dorsal side (to visualize both kidneys) of the mouse was acquired using a fast spin echo sequence (slice thickness= 0.75 mm and in-plane resolution = 0.25 mm, TR/TE=3000/10 ms, 4 echos). The *in vivo* and *ex vivo* images from age, sex matched groups were analyzed to calculate the kidney volume and the relative contrast in selected regions of interest in the cortico-medullary regions in the left kidney.

A significant decrease in density in the cortical regions of the kidneys was found in *Gdnf*$^{+/-}$ mice at all age groups and matched well with quantitative reduction of glomerular density in mutant kidneys. At six months of age, we found significant decrease in density in all regions of the kidney analyzed, such as cortex, medulla, whole cortex or whole kidney, etc. At 18 months of age, the cortex area is the only region with reduced density. Based on a large-scale population study, we have observed premature aging/mortality phenotypes in *Gdnf*$^{+/-}$ mutant mice, hence, the renal imaging data seem to track the dynamic compositional changes in *Gdnf*$^{+/-}$ cohort based solely on quantitative renal structural analysis.

*Gdnf*$^{+/-}$ mice are predetermined to manifest renal induced hypertension with age. Hypertension is the major risk factor for cardiovascular disease, stroke, myocardial infarction and end-stage renal failure. MRI provided a sensitive approach to detect subtle reduction in nephron number in *Gdnf*$^{+/-}$ mice, as early as one month after birth, hence make effective calibration of renal capacity, prediction of disease risk and progression of renal and renal-induced diseases in humans possible.

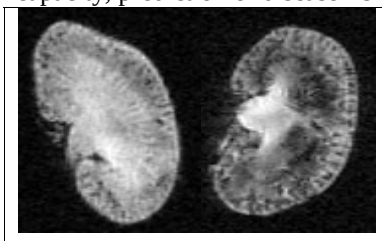

Figure 1. Center slice of 1-month old wild type (left) and *Gdnf*$^{+/-}$ (right) excised kidney.

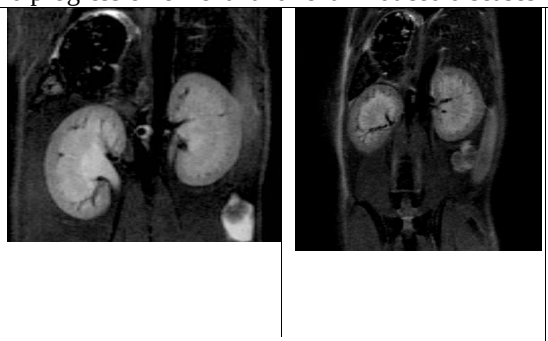

Figure 2. Center slice of 6-month old wild type (left) and *Gdnf*$^{+/-}$ (right) kidneys.

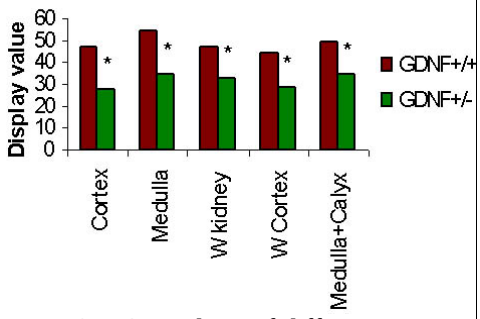


Figure 3. ROI analysis of different regions of 6-month old wild type and *Gdnf*$^{+/-}$ mice.