MR CHARACTERIZATION OF MURINE MODEL OF DYSTROPHY ON A DBA BACKGROUND

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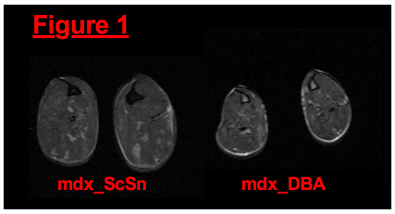
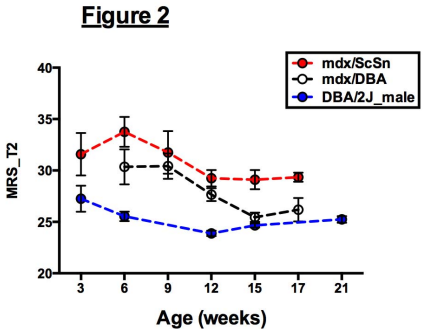
INTRODUCTION: Mutations in the gene encoding dystrophin and sarcoglycan leads to Duchenne muscular dystrophy (DMD) limb and girdle muscular dystrophy (LGMD) respectively. DMD and LGMD are characterized by progressive muscle weakness and replacement by fibrotic tissue. Muscle fibrosis is a hallmark of several muscular dystrophies and accumulation of fibrosis has been correlated with poor motor outcomes[1]. Different genetic modifiers have been shown to influence phenotypic variability both in humans and animal models [2, 3]. In animal models this can be achieved by knocking out the same gene on different background of mouse strains. Murine models of muscular dystrophy, *mdx* and Sgcg$^{-/-}$ on typical C57 background show relatively less severity over their lifespan compared to mouse models on DBA/2 background. *Mdx* and Sgcg-/- mice on DBA2/J background have increased fibrous tissue [4]. In this study, we used a multiparameter magnetic resonance (MR) to characterize murine models of dystrophy on DBA background.

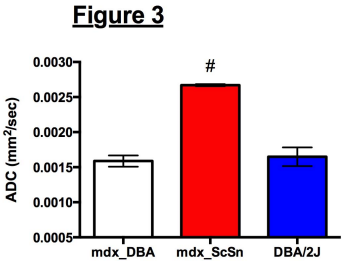
METHODS: **Experimental design:** Longitudinal MR measurements were performed every 2-3 weeks over 5 months on C57BL/ScSn-*Dmd*^{mdx} (*mdx*, n=6, 1 month old), D2.B10-*Dmd*^{mdx} (*mdx*_dba, n=5, 1 month old), D2.B10-Sgcg$^{-/-}$ (gDBA, n= 5, 4 months old), DBA/2J (n=5, 1 month old) mice within the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility at UF. All mice were imaged on a 4.7T Oxford Magnet with a Varian/Agilent operating system. **Lower limbs imaging:** (1) T_2-weighted single spin–echo images of the hind-limb muscles were acquired (TR 2,000 ms; TE 14 and 40 ms; field of view, 20x20 mm^2; slice thickness, 1.0 mm; acquisition matrix size, 256x128; averages, 2) using a custom built solenoid coil (2 cm diameter). (2) Stimulated echo acquisition mode (STEAM) spectra was acquired using a solenoid coil (2 cm diameter) in 1.5x3.0x1.5 mm^3 voxel placed in the posterior compartment of hind-limbs with 4 signal averages at TR = 9000 ms; TE: array of 29 TE's spaced between 5-130 ms. (3) 3D-GRE images were acquired using the following parameters: TR/TE = 50/7ms. (4) Apparent diffusion co-efficient (ADC) maps were generated by diffusion weighted images acquired with two gradient intensities (b value of 0 and 900 s/mm^2) with a spin echo sequence (TR/TE = 1,000ms/21 ms). **Data analysis**: T_2 values were derived using average signal intensity from anterior and posterior hind-limb muscles of each TE using OsiriX software. All values were described as mean ± SD.

RESULTS: *mdx*_DBA mice weighed significantly less than age matched *mdx*_ScSn mice (11.6 ± 2.1 gm vs 21.6 ± 2.1gm at 6 weeks; 21.5 ± 1.9 gm vs 32.1 ± 1.5 gm at 17 weeks of age). Furthermore, 3D MR images revealed severe atrophy of hind limb muscles of *mdx*_DBA mice (Figure 1). MRS T_2 revealed significant differences in both strains of *mdx* mice. T_2 was elevated in both strains of *mdx* mice and significantly different form DBA/2J between 6 and 12 weeks of age. After 3 months of age T_2 in *mdx*_dba dropped and significant differences were found in *mdx*_ScSn and *mdx*_dba strains (29.11 ± 2.10 ms vs 25.45 ± 1.01 ms) (Figure 2). The lowest T_2 were reported in gDBA mice (24.10 ± 1.30 ms). ADC data demonstrated significant differences between *mdx*_ScSn and *mdx*_DBA [(26.7± 0.01) x10^{-4} vs (15.9 ± 0.08) x10^{-4} mm^2/s] (Figure 3).

CONCLUSION: This study shows that MR can detect changes in skeletal muscles muscles of murine models of dystrophy on different genetic backgrounds with the same missing gene. Specifically. T_2 decreased faster in hind limb muscles of mice on DBA background, which may be attributed to increase in skeletal muscle fibrosis attributed to this strain. These results support that genetic modifiers play a strong role in determining dystrophic phenotype as detected by MRI.







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