Cardiac magnetic resonance imaging of the Ts65Dn murine model of Down Syndrome

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Introduction:

In humans, Down syndrome (DS) is associated with a triplication, or trisomy, of the human chromosome 21, Hsa21 [1]. Congenital heart defects are reported to occur in 40-60% of patients with DS, with complete atrioventricular septal defect being the most common defect [1]. Other frequently occurring lesions include atrial and ventricular septal defects and tetralogy of Fallot. Unfortunately, congenital heart defects are the leading cause of death in children with DS under ten years of age [1]. Several murine models have been developed to simulate the genotype/phenotype correlation in DS. The Ts65Dn mouse is the most-studied of murine models for DS phenotypes given that these mice demonstrate many of the features observed in DS individuals, including congenital heart defects. To date however, the Ts65Dn cardiac defects have only been characterized by histological and immunohistochemistry analyses [2,3]. To extend these studies for the first time, we have utilized cardiac magnetic resonance imaging (MRI) to assess the cardiac functional defects of the left and right ventricles of Ts65Dn mice.

Method:

Ts65Dn Mice. Ts65Dn dams (B6EiC3Sn a/A-Ts(17^{16})65Dn) were bred to B6Eic x C3Sn F_1 male mice [2,3]. Female offspring were inbred with the male F_1 mice to increase transmission of the Ts65Dn chromosome to future offspring [2,3].

MRI. Imaging was performed using a vertical-bore Bruker 11.7T MRI system equipped with Paravision 4.0 (Bruker, BioSpin, Germany). Age and sex matched mice were anesthetized using an Isoflurane-carbogen gas mixture (1-2% Isoflurane). Contiguous short-axis, T1-weighted gradient echo FLASH-cine images were completed in order to cover the entire left ventricle of the heart. Scans were cardiac-gated with the following parameters: TR/TE = 8/1.4; α= 15°; matrix = 256 x 192; FOV = 3.0 cm; slice thickness = 1.0 mm; frames per cardiac cycle adjusted based on heart rate. Images were manually analyzed to measure left and right ventricle end-diastolic volume (ml), end-systolic volume (ml), stroke volume (ml), ejection fraction (%), cardiac output (ml/min), and LV and RV masses at end diastole and end systole (ml). End-diastolic and end-systolic interventricular septal volumes (mm^3) were also measured using the acquired cine images. Results were expressed as averages ± SD. A one-way ANOVA was completed to determine statistical significance, with a $p < 0.05$ considered significant.

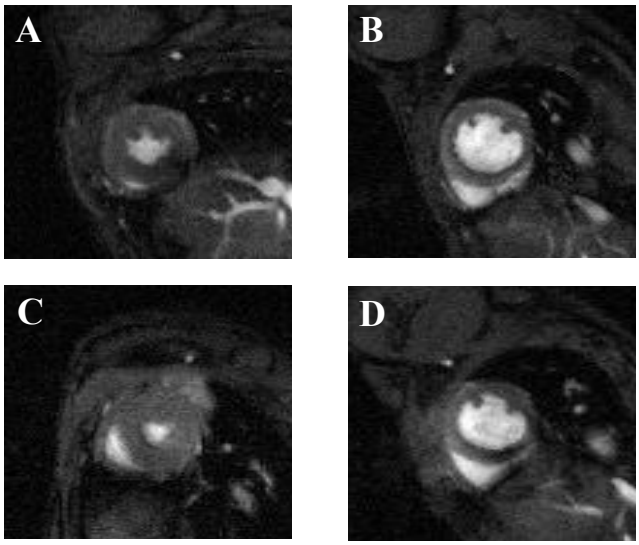

Fig 1: Mid-ventricular comparison of left ventricle end-diastolic and end-systolic volumes for wild-type and Ts65Dn mice. The LV end-systolic (A) and end-diastolic (B) volume of the wild-type mice (N=5,6) was significantly larger than the ESV (C) and EDV (D) of the Ts65Dn mice (N=6,7) (*p<0.05).

Results:

MRI. LV. The difference in ejection fraction between the wild-type (80.744 %) and transgenic (81.744 %) groups was not significant. The end-diastolic (ED) and end-systolic (ES) LV mass was significantly larger for the wild-type mice, when compared with the transgenic mice (67.487, 79.444 vs. 50.422, 56.088 mg, respectively). Additionally, LV end-systolic, end-diastolic, and stroke volumes were larger for the wild-type mice (0.011, 0.050, 0.040 ml, respectively) compared with the Ts65Dn mice (0.007, 0.039, and 0.033 ml, respectively). *RV.* Wild-type ejection fraction (62.973 %) decreased relative to transgenic values (69.016 %). However, a significant increase in ED RV mass was observed for the wild-type mice (28.878 mg) compared with transgenic mice (35.438 mg). *IVS volume.* A significant increase in ED IVS volume was observed for the wild-type mice (26.156 mm^3), when compared with the transgenic mice (21.164 mm^3).

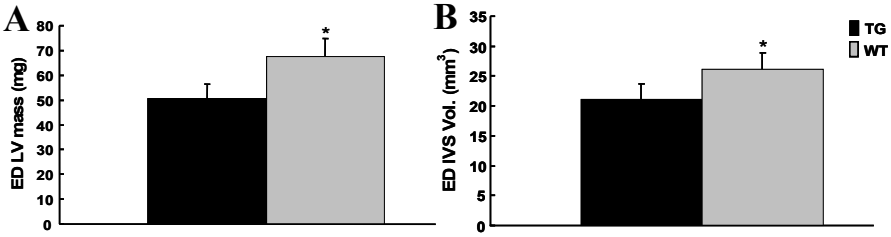

Fig 2: Left ventricle end-diastolic mass and interventricular septal volume for wild-type and Ts65Dn mice. Wild-type mice showed significant increases in both LV ED mass (A) (N=6) and IVS volume (B) (N=5) when compared with the Ts65Dn mice (N=7,6) (*p<0.05).

Conclusion:

In this study significant increases were observed in LV SV, EDV, ESV, ED mass, ES mass of the wild-type mice when compared with the Ts65Dn Down syndrome mice. Additionally, wild-type mice showed significant increases in ED LV mass and ED IVS volumes compared with the Ts65Dn mice. Taken together these results suggest that Ts65Dn mice present extensive cardiac functional abnormalities similar to those observed in Down syndrome patients. Furthermore, these cardiac defects can easily be detected using high-field cardiac magnetic resonance imaging.

References:

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