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Poster presentation

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Micro-MRI phenotyping of a novel double-knockout mouse model of congenital heart disease

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Introduction

CHARGE and DiGeorge syndromes are conditions with incidences of 1 in 10,000 and 1 in 4000 and are strongly associated with haploinsufficiency of specific genes (CHD7 and TBX1). Both conditions are characterised by cardiovascular defects. Knockout mouse models are an important tool for the identification and characterisation of genes implicated in congenital heart conditions. Micro-MRI is an emerging technique for high resolution cardiac phenotyping in a reduced time compared to conventional histology, enabling the acquisition of 3D images of multiple embryos in a single scan[1].

Purpose

Given the phenotypic overlap of these conditions we sought to examine the effect on cardiac morphology in double-knockout mouse embryos ($Chd7^{+/-}Tbx1^{+/-}$)[2], performing an initial assessment of these mice using MRI.

Methods

Study Design

18 embryos (1 wild-type, 7 $Chd7^{+/-}$, 2 $Tbx1^{+/-}$ and 8 $Chd7^{+/-}Tbx1^{+/-}$) were imaged and examined for cardiac abnormalities.

Embryo Preparation

16.5 dpc embryos were fixed for at least 2 weeks in a solution of 4% formaldehyde-PBS with 8 mM Gd-DTPA (Bayer-Schering AG) and then embedded in 1% agarose gel (doped with 8 mM Gd-DTPA) in 50 ml centrifuge tubes.

Imaging

Performed on a Varian 9.4 T VNMRS system with 33 mm quadrature birdcage coil (RAPID Biomedical GmbH), using a 3D gradient echo sequence (TE/TR/FA/NSA = 9/

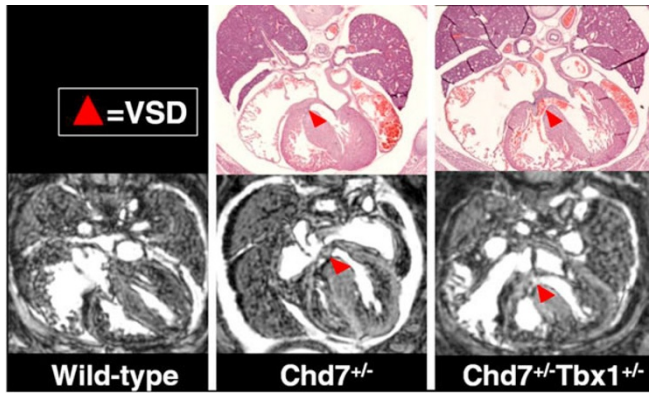

Figure 1
Axial sections through example embryo datasets showing the presesnce of ventricular septal defects (indicated by red triangles) in both Chd7+/- embryos and double Chd7+/-Tbx1+/- heterozygotes.

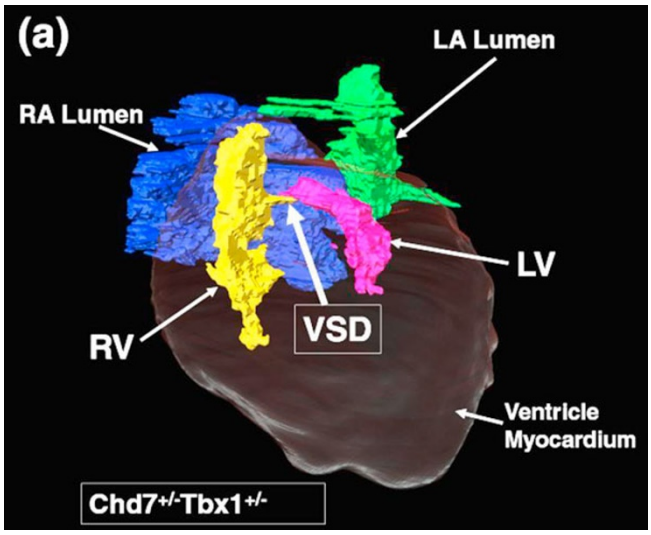

Figure 2
Volume rendering of a heart in a Chd7+/-Tbx1+/- double heterozygous embryo. (RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle). A clear ventricular septal defect can be seen between left and right ventricles.

20/60/7, FOV = 27 × 27 × 27 mm^3, voxel size = 52 × 52 × 52 μm^3).

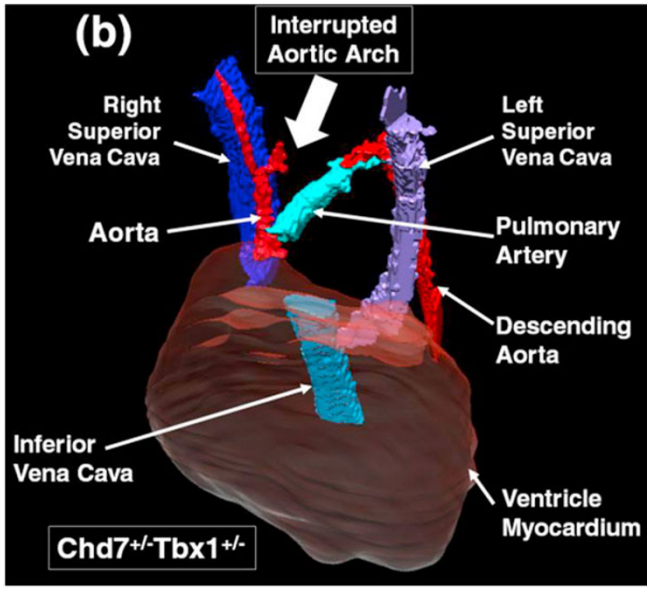

Figure 3
Volume rendering of the same embryo showing great vessel structures, An interrupted aortic arch was identified in this embryo (arrow).

Image analysis

Datasets were zero-filled to 26 × 26 × 26 μm^3 and reviewed in Amira (v5.2, Visage Imaging Inc.).

Histology

Embryos identified with abnormal hearts by MRI, were then histologically examined by H&E staining.

Results

Of the 18 embryos scanned for MR analysis, we identified abnormal (thin or patent) ventricular septa (VSDs) in 6 embryos. Of these, 1 was a Chd7$^{+/-}$heterozygote (an incidence of 1/7 in this study, see Fig. 1). VSDs were seen in 5/8 Chd7$^{+/-}$Tbx1 embryos (Fig. 2). In one double heterozygote we also observed an interrupted aortic arch, in addition to a VSD, which was readily seen by MRI (Fig. 3).

Conclusion

Using micro-MRI we have successfully identified cardiac abnormalities in genetically-modified embryos. A single Chd7$^{+/-}$ embryo was found to have an abnormal ventricular septum. A relatively high incidence of VSDs was observed in Chd7$^{+/-}$Tbx1$^{+/-}$ compared to Chd7$^{+/-}$mice, indicating possible interaction of these two genes. An interrupted aortic arch was identified in one Chd7$^{+/-}$Tbx1$^{+/-}$ embryo. All abnormal findings were later confirmed by histology which indicates that micro-MRI is an effective technique for cardiac phenotyping.

References

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2. McCue K, Randall V, *et al.*: **06-P038.** *Mech of Dev* 2009, **126:**S131.