177 DECIPHERING THE MECHANISMS OF DEVELOPMENTAL DISORDERS (DMDD): A POWERFUL NEW RESOURCE FOR STUDYING CONGENITAL HEART DISEASE

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Identifying the genetic components of heart disease remains challenging despite the transformation of clinical genetics by new DNA sequencing technologies. For congenital heart disease (CHD), animal models have provided a fruitful way to identify genes necessary for differentiation of cardiac tissue and subsequent morphogenesis of the embryo heart. These have identified candidate determinants of CHD, and their genetic manipulation in animal models such as the mouse offers the opportunity to identify the molecular mechanisms whose disruption results in foetal cardiac abnormalities. This is of potential clinical value not only for diagnostic screening of CHD; it also identifies critical molecular pathways whose disruption by environmental factors may account for the 80% of CHD for which there is no attributable genetic cause.

"Deciphering the Mechanisms of Developmental Disorders" (DMDD) is a five-year study dedicated to identifying genes essential for embryo development, many of which affect heart development when targeted by selective gene knockout. Here we present the first systematic study of the range, severity and penetrance of defects affecting the heart by the end of organogenesis (E14.5) in such embryonic lethal mouse mutants. Using comprehensive 3D imaging at near histological resolution, we have examined embryos from 42 different gene knockouts, identifying morphological abnormalities affecting the heart and great vessels. Abnormalities were scored using the Mouse Phenotype (MP) Ontology and all image and phenotype data from the study is freely available to the scientific community at dmdd.org.uk.

Cardiac defects were detected in 33 of the first 42 mutant lines studied (78%) and many comprise genes studied either for the first time or not previously associated with cardiac abnormalities. Many of the defects identified match congenital defects identified in newborn babies. Individual mutant lines varied widely in the number of unique cardiac phenotypes they exhibited, with as many as 20 distinct types in the most severely affected embryos. Over half of all lines examined showed defects affecting the atrial or ventricular septum; one third of the lines had abnormalities affecting development of the outflow tract (overriding aorta, double outlet right ventricle, persistent arterial trunk, transposition of the great arteries); a quarter showed defects affecting the structure of one or more heart chambers and a fifth of the lines had abnormalities in the atrio-ventricular junction.

These results demonstrate the remarkable power of an unbiased genetic screen in the mouse to reveal novel CHD genes when simply filtered by embryonic lethality. The DMDD data offers a rich and expanding resource for further study of both normal mammalian heart development and the aetiology of congenital heart disease.

178 APPLICATION OF CARDIAC MRI TO QUANTITATIVELY ASSESS MYOCARDIAL DAMAGE IN ISOPROTERENOL-INDUCED HEART FAILURE

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Introduction Cardiovascular disease is the Number-1 cause-of-death globally with an estimation of 17.5 million deaths annually. Being one of the most active organs of the body, the heart is vulnerable to damage. Isoproterenol (ISO) injection into mice can induce a stress cardiomyopathy model similar to Takotsubo cardiomyopathy. Cardiac MRI permits the detection, visualisation, quantification, and progression-monitoring of cardiac defects non-invasively, making it useful for monitoring stress cardiomyopathy. In this study, we used MRI to study the effects of ISO injection on cardiac structure and function in both immune-competent and immune-deficient mice.

Methods and Materials 12 week old C57B6 (n=14) and immunocompromised NOD-SCID mice (n=18) were assigned to Control and ISO Group with 0.9% saline or 1 mg/kg ISO administered daily for 7 days by i.p. injection. At 7 days imaging was performed using a 9.4T MRI system and 38 mm quadrature birdcage RF coil. Cardiac and respiratory gated cine-MRI was performed in the true short-axis orientation and covered the whole left ventricle. LGE-MRI was performed 20 min after i.p. injection of 0.5 mmol/kg Gd-DTPA-BMA using a multi-slice inversion recovery sequence. Data were analysed in a blinded fashion using ImageJ. LGE-MRI images were thresholded to the full width at half maximum of enhanced regions to identify areas of signal enhancement.

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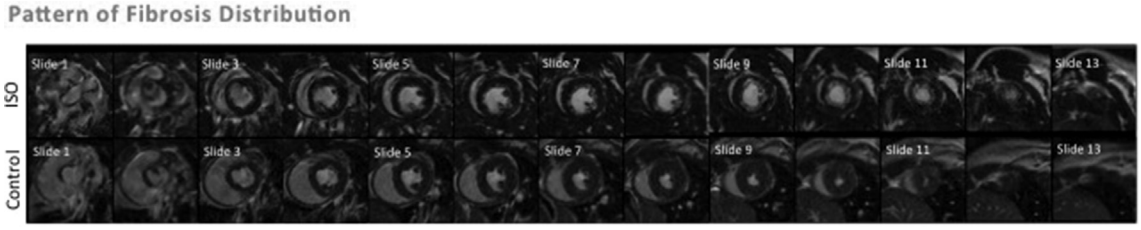
Cardiac Parameters	Control	ISO	Difference	P value
End Diastolic Volume (Î¼l)	52±2	63±4	10	0.02
End Systolic Volume (Î¼l)	12±2	23±4	10	0.01
Ejection Fraction (%)	77±2	65±4	−11	0.005
Left Ventricular Mass (mg)	79±1	92±7	−13	ns



Abstract 178 Figure 1 Late-gadolinium MRI image series (showing all slices from the base to the apex of the heart) in short axis view, with areas of enhancement (apical subendocardial enhancement) corresponding to regions of cardiac fibrosis, thereby demonstrating the endomyocardial nature of the cardiac fibrosis. Above – ISO. Below – Control.