Characterization of a new arrhythmogenic cardiomyopathy mouse model due to filamin c haploinsufficiency

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Background: Filamin C (FLNC) is widely expressed in heart and skeletal muscle. It participates in cell junction and sarcomere assembly and function. We have previously shown that heterozygous FLNC truncating variants (FLNCtv) cause arrhythmogenic/dilated cardiomyopathy (ACM/DCM) in patients. Diverse studies have suggested haploinsufficiency as the potential mechanism of this disease. However, animal models of FLNCtv have only been reported to develop ACM/DCM in homozygosity.

Purpose: To develop a new model of ACM/DCM caused by a FLNCtv and study the progression of the disease in heterozygosity.

Methods: Two gRNAs flanking exon 15 of the Flnc gene and SpCas9 protein were microinjected into mouse zygotes to generate a mouse line with a constitutive deletion of Flnc exon 15 (FlncWt/Ex15del). mRNA and protein stability were determined by qRT-PCR and western blot, respectively. Cardiac function was analysed by ECG and echocardiography every 2 months, starting at 8 weeks of age (Fig. 1B). The mean ECG values were calculated using 3 time intervals and standard ECG waves.

Results: FlncWt/Ex15del mice showed a reduction in Flnc mRNA and protein similar to that observed in a human ACM/DCM patient bearing a similar mutation, suggesting that this FLNCtv causes haploinsufficiency. Both male and female FlncWt/Ex15del mice developed cardiac electrophysiological defects, including reduced amplitude of the QRS complex and the P-wave, notched R and/or S waves, and increased QT interval times, and these defects worsened with time. At 40 weeks of age, FlncWt/Ex15del mice showed some initial signs of left ventricular dilatation.

Conclusions: Mice carrying FLNCtv in heterozygosity develop electrophysiological changes resembling pathological features of ACM/DCM patients due to haploinsufficiency. The development of this pathological phenotype in heterozygosity, as opposed to previous models, paves the way for the development of new gene therapies using this model.