



University of Utah

UNDERGRADUATE RESEARCH JOURNAL

ASSOCIATION OF NFATC1 WITH ATRIAL FIBRILLATION

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Atrial Fibrillation is the most common type of cardiac arrhythmia that usually presents as a progressive disease in the elderly (> 65 yrs.). It is characterized as a very fast atrial rate causing an increased risk of stroke, complications, and mortality. We have identified a family with young onset of atrial fibrillation where the phenotype segregates with a mutation on the cardiac transcription factor NFATc1, which is activated by Ca^{2+} and is essential for cardiac development. We hypothesize that an altered expression of NFATc1 in the heart could result in changes in transcriptional levels in several genes, including ion channels altering cardiac excitability.

To test this hypothesis, we used CRISPR/Cas9 genome editing to generate a NFATc1 zebrafish mutant with a 31 bp deletion in exon 2 predicted to cause a premature stop codon and loss of function (NFATc1^{-/-}). We used video microscopy to assess heart rate in 72 hours post fertilization (hpf) wild type and NFATc1^{-/-} whole embryos in control conditions and after adrenergic stimulation with isoproterenol. Di-4-ANBDQBS, a dye to record optical action potentials, was used in whole embryos and explanted hearts.

NFATc1^{-/-} embryos had a higher heart rate than the wild type (*p<0.05, WT n=8, NFATc1^{-/-} n=10). However, when we attempted to record optical action potentials from whole embryos, the dye (di-4-ANBDQBS) was retained in the skin and we were unable to record optical action potentials. We then explanted the heart from the embryos and were successfully able to record optical action potentials. We also recorded electrical action potentials to use as a standardized method to validate our results with optical recording methods.

NFATc1^{-/-} zebrafish embryos showed an increased basal heart rate and a blunted response to adrenergic stimulation when compared to WT. Our attempt to reproduce this result by recording optical action potentials from whole embryos was unsuccessful. However, we were able to load the dye and obtained electrical action potentials in WT explanted hearts. Future experiments include repeating these protocols in NFATc1^{-/-} explanted hearts and compare the result with WT.