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DISRUPTION OF NFATc1 NUCLEAR TRANSLOCATION CAUSED BY M527L MUTATION

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Abstract

Atrial fibrillation is the most common sustained heart arrhythmia in clinical practice and causes patients increased risk of stroke and early cardiovascular death. A Utahn family has been identified where the phenotype of early-onset atrial fibrillation segregates with a missense M527L mutation in the NFATc1 protein, an important transcription factor to normal cardiac function. This project aims to identify whether the M527L mutation disrupts the ability of the NFATc1 protein to translocate to the nucleus upon Ca^{2+} activation. Adenoviral overexpression in HL-1 cells was used to produce an abundance of wildtype and mutant NFATc1 protein fused to a GFP. These cells were then incubated for one hour with varying concentrations of isoproterenol to activate the signaling pathway before being fixed. Confocal microscopy was utilized to image these cells and quantify translocation differences between wildtype and mutant NFATc1. This study found significant differences in the trends between nuclear translocation between the wildtype and mutant NFATc1, with the mutant NFATc1 consistently experiencing less translocation upon Ca^{2+} activation. Reduced translocation could implicate reduced transcriptional activity of downstream gene programs that prevent atrial cells from functioning normally. These results continue to question the cell's ability to regulate NFATc1 nuclear importation and exportation in lieu of the M527L mutation. This abnormal functionality within an atrial model of cardiac cells could provide a starting explanation for the early-onset atrial fibrillation phenotypically identified in the aforementioned family as well as adding to the growing knowledge of gene control over cardiovascular disease.