Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an exercise induced ventricular arrhythmia disorder caused by mutation in the RYR2 gene. It has been classified as one of the most dangerous heart arrhythmias since 30% of individuals with CPVT die before the age of thirty (Leenhardt et al., 2012; Ylanen et al., 2010). CPVT's high lethality rate can be attributed to RYR2 mutations only producing the arrhythmia phenotype in the ventricles of the heart, the chambers responsible for pumping blood though the entire body. Since the first symptom of CPVT is often cardiac arrest, most deaths occur without knowledge of even having the disorder (Ylanen et al., 2010). Though genetic testing and modern medicine has helped our understanding of the disease, there is a lot still unknown and no cure has been found*. The dysfunction of RYR2 mutants has been identified, yet RYR2 expressional and functional differences within different regions of the heart have been overlooked. (Leenhardt et al, 2012).* In order to better understand disorder and advance its treatments, an investigation of how RYR2 is expressed and functions differently across regions of the heart is necessary and without this knowledge, further progress is nearly impossible.

Since the atria of the heart are unaffected by RYR2 mutations in CPVT individuals, there is reason to believe that RYR2 is functioning differently between chambers of the heart and this difference plays a key role the disorder. The primary ***goal*** of this project is to investigate how RYR2 functions differently between atria and ventricular muscle tissue. By determining the variance of function of RYR2 mutants, scientists will be able to better understand CPVT as a whole and use these results as a stepping-stone for further research and treatments.

We are proposing to use a mouse model to test both wild type and RYR2 mutants before and after exercise. This will allow us to compare RYR2's function and expression levels between the atria and the ventricles of the heart during normal and CPVT inducing conditions.

**Aim 1**: Identify how well RYR2 is conserved in mice in comparison to humans by using BLAST and Clustal Omega sequence alignments

Hypothesis: RYR2 will be highly conserved since it is an essential gene for normal heart contraction.

**Aim 2**: Determine RYR2 expression level differences between the atria and ventricles before and after exercise. This will be investigated in both wild type and RYR2 mutant mice by performing a microarray.

Hypothesis: There is be a noticeable expression level difference between samples from the two chambers. The expression level of RYR2 will change after exercise in RYR2 mutants but not in wild type mice.

**Aim 3**: Determine if RYR2's binding parters are affecting RYR2's function differently in the atria than in the ventricles. We will also determine differences in protein interactions in CPVT mutants as well. This will be achieved by attaching a TAP-tag to RYR2. RYR2 and its interacting proteins will be pulled down and quantified via mass spectrometry. Hypothesis: RYR2 will interact with a different set of proteins in atrial and ventricular tissue. These differences in interaction will be specifically be very noticeable in RYR2 mutants after exercise. This interaction difference would identify key proteins affecting RYR2's function.

By identifying novel functional differences of RYR2 within different regions of the heart, we will be able to  better understand RYR2 role in CPVT development. Results from these aims could help scientists understand one of CPVT's most dangerous features which is ventricular arrhythmia produced by RYR2 mutation. With this knowledge, doctors and scientists will be able to better assess and treat patients and use these findings to fill in the missing gaps needed to find a cure.

References:

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