John Taylor Babbitt Foundation
2021 Research Update

The JTB Foundation is currently funding research by Dr. Victoria Parikh, a cardiologist at Stanford University who specializes in the care of patients with inherited cardiovascular diseases. Dr. Parikh's research investigates the multiple causes of

cardiomyopathy in the laboratory with a particular clinical and scientific interest in inherited arrhythmogenic cardiomyopathies.

Dr. Parikh's current research program is focused on the genetic underpinnings of sudden cardiac death in various types of cardiomyopathy including hypertrophic cardiomyopathy (HCM), using patient cohort genetics, high throughput molecular biology and human induced pluripotent stem cell derived cardiomyocytes. To build a platform for assessment of variant pathogenicity across genes of interest, she has first chosen to focus on the gene RBM20, which has previously only been associated with dilated cardiomyopathy (DCM). Her recent publication on the genetic architecture and clinical characteristics of RBM20 cardiomyopathy will be out in Circulation: Heart Failure by the end of Spring. In this report, Dr. Parikh and colleagues assembled an international registry of patients with familial cardiomyopathy harboring RBM20 variants and found that the phenotypes associated with these variants span not just DCM but also left ventricular noncompaction and HCM. The most salient feature across these patients was high rates of dangerous arrhythmias and sudden cardiac arrest. Dr. Parikh went on to use population-level genetic data to predict regions of the gene in which genetic variants were most likely to cause this disease, and showed that patients in this international registry harboring variants in such regions were more likely to have had the arrhythmogenic outcomes described above. Further, in comparison to other causes of DCM, she showed that RBM20 cardiomyopathy is really distinct in its clinical arrhythmogenicity, indicating that, while it may cause many different types of cardiomyopathy (including HCM), it is truly arrhythmogenic and should be treated as such.

The next step in this project, funded in part by the JTB foundation, is to perform a position-specific analysis of the disease causality of each possible genetic change in RBM20 to aid in clinical identification of patients at highest risk of cardiac

arrest, and in which patients cascade genetic testing will be most helpful in preventing sudden death in their families. This study will be performed in induced pluripotent stem cells in a high-throughput fashion. Dr. Parikh has created cell lines harboring deletions of RBM20, and is in the process of using state of the art genetic engineering techniques to create all possible genetic variants in likely disease causing regions of RBM20. She will then test the effect of these genetic variants on heart cells derived from these induced stem cell lines.