Cardiac AAV:PKP2 Gene Transfer Prevents Development of Arrhythmogenic Cardiomyopathy in a *PKP2*-deficient Mouse Model

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiac disease associated with ventricular arrhythmias and sudden cardiac death. Mutations in the desmosome gene *PKP2*, *Plakophillin-2*, are the most common genetic cause of ARVC. Currently there is no known effective treatment available for ARVC patients. Here we report an AAV-based gene transfer approach preventing ARVC development in a cardiac specific knock-out mouse model of *PKP2*. Early proof-of-concept studies using PKP2-deficient human iPSC-derived cardiomyocytes show cellular recovery of desmosome components and rescue of contractility upon expression of exogenous PKP2. Cardiac AAV:PKP2 gene delivery significantly improves life span of *PKP2*-cKO ARVC mice by 1) preventing adverse cardiac remodeling; 2) maintaining ventricular functions; 3) reducing arrhythmia event frequency and severity. Our results indicate that AAV:PKP2 is a viable gene transfer approach to address the major genetic cause of ARVC.