

Supplemental Phenotype Information:

Phenotype characteristics of family TSRVD001 carrying the Thr2896Ile *TTN* mutation

The proband (III-1) of family #1 (Thr2896Ile) presented at the age of 49 years with a history of syncope and biventricular heart failure. He had atrial fibrillation, ventricular tachycardia and required a pacemaker for bradyarrhythmias. An endomyocardial biopsy showed fibrous-fatty infiltration of right ventricular wall. He progressed to pump failure and died at the age of 66 years. His sister (III-3) presented with similar symptoms and severe right heart failure in addition to atrial fibrillation, ventricular tachycardia and third degree atrio-ventricular block requiring a pacemaker. Her ECG showed an epsilon wave. She died of progressive heart failure at the age of 58 years and had transmural fibro-fatty infiltration of the right ventricular myocardium at autopsy (Fig. 3C). A first cousin once-removed (IV-6) also presented with syncope and symptoms of right and left heart failure. The ECG showed atrial fibrillation, and atrio-ventricular block requiring a pacemaker. She was found to have ventricular tachycardia with left bundle branch morphology and on echocardiography diffuse hypokinesis dilatation and budging of the right ventricle and left ventricular dysfunction. An endomyocardial biopsy was significant for fatty-substitution of the right ventricular myocardium. She was transplanted for progressive heart failure at the age of 57 years. Following her diagnosis, other relatives (IV-4, IV-7, V-3) developed syncope and heart failure and fulfilled the criteria of ARVC. Relative IV-5 died suddenly at the age of 35. Relative IV-3, who carried of the Thr2896Ile mutation,

had atrial fibrillation and a history of coronary artery disease. He did not fulfill the criteria for ARVC and was considered as “unknown status”. Among the family ancestors there were three other unexplained sudden deaths (II-5, III-5, III-6) at ages 40, 63 and 26 years, and two other relatives had sudden deaths at unknown ages (II-1 and II-3).