**Background**

During the last two decades, variants in the sarcomere genes have been found to comprise the most common cause for hypertrophic cardiomyopathy (HCM); however, a significant number of patients with dominant HCM are left without a molecular genetic diagnosis. Next generation sequencing (NGS) enables not only the evaluation of established HCM genes but also candidate genes for cardiomyopathy. Identifying a variant in said candidate genes may lead to a situation where a conclusive interpretation of the result extensive family studies.

The Juncophilin-2 gene (JPH2) is the major structural protein in cardiomyocytes for coupling of transverse (T) tubule-associated L-type Ca²⁺ channels and type-2 ryanodine receptors on the sarcoplasmic reticulum within junctional membrane complexes (JMC). Downregulation of the JPH2 gene has been associated with heart failure and variants in this gene have been suggested to associate with HCM. The role of the JPH2 gene in cardiomyopathies has been obscure as only one rare variant segregating with any type of cardiomyopathy has been published (Sabater-Molina M et al., Clin Genet. 2016). This study characterizes the cardiac phenotype related to JPH2 c.482C>A, p.(Thr161Lys) variant in nine Finnish index patients and their family members.

**Methods**

Index patients with the JPH2 variant c.482C>A, p.(Thr161Lys) and their relatives were included. HCM was clinically diagnosed according to ESC Guidelines. Family history was obtained and all participants were of Finnish ethnicity. Adult assessments involved a physical examination, 12-lead ECG, appropriate laboratory tests, and transthoracic echocardiography (TTE). Cardiac MRI was performed in some cases. Genetic testing was carried out using the OS-Seq™ (oligonucleotide-selective sequencing) NGS method using the Blueprint Genetics Core Cardiomyopathy (69 genes) or Pan Cardiomyopathy Panels (103 genes). The presence of the variant in relatives was studied by bi-directional Sanger sequencing.

**Results**

Pedigrees of Six Families Demonstrating Segregation of JPH2 c.482C>A, p.(Thr161Lys)

**Figure 1.** The heterozygous JPH2 c.482C>A, p.(Thr161Lys) (NM_020433.4) nonsense variant was observed in nine unrelated Finnish probands with cardiomyopathy. The variant is rare (not present in the Exome Aggregation Consortium (ExAC) or in Genome Aggregation Database (gnomAD)). Threonine is a conserved amino acid at this position across mammals, Polysphen, SIFT, and Mutation Taster predict it to be deleterious.

The variant was detected in 20 affected individuals and 26 relatives in total. The variant co-segregates with HCM in six families (Families 2, 4, 6, 7, Figure 1) and was absent in three family members without LV hypertrophy who were over 20 years of age. It was also absent in an asymptomatic 60-year-old female (Family 6.1.2) who was not evaluated clinically and two individuals with LVH likely explained by severe hypertension (Family 4.1.3 and Family 4.1.2). Penetration of HCM was 48%, 71% and 100% by age of 40, 60, and 80, respectively.

Black-filled symbols represent individuals who fulfill ESC 2008 diagnostic criteria for HCM. The age of the family members at last follow-up, maximum LV wall thickness, and some other key signs of clinical disease are listed below the symbols. Arrows indicate index patients.

**Clinical Characteristics of Probands and Their Family Members**

The heterozygous JPH2 p.(Thr161Lys) variant is a Finnish founder mutation associated to hypertrophic cardiomyopathy with or without systolic heart failure and conduction abnormalities.

**Table 1.** Main clinical features were left ventricular hypertrophy, arrhythmia vulnerability, and conduction abnormalities including third degree AV-block. End-stage severe left ventricular heart failure with normal or mildly enlarged diastolic dimensions was also detected. Systolic heart failure or conduction abnormalities were observed in every family and in 12/20 (60%) of the affected patients including ten heterozygous affected individuals and two obligate carriers.

**Clinical Features Distinguishing JPH2 p.(Thr161Lys) from Two Other Published Finnish HCM Founder Variants**

**Table 2.** The JPH2 p.(Thr161Lys) variant identified in nine Finnish index patients with HCM co-segregated with cardiomyopathy in six of these families. The cardiac phenotype differs somewhat from typical HCM. Differences in the clinical features of this variant and two other published Finnish founder mutations (MYBPC3 p.(Gln1061*) and TPM1 p. (Asp175Asn) (Hedman A et al., J Mol Cell Cardiol. 2006) are described.

Nineteen JPH2 variants (17 which are nonsense) associating with dilated or hypertrophic cardiomyopathy are listed in the HGMD (Qiagen) and ClinVar databases (July 8, 2017). Before this study, no convincing evidence of segregation within large pedigrees except for the p.(Glu115Leu) and no de novo JPH2 mutations had been reported in patients with HCM. Most of the previously published variants in JPH2 are absent or rare in ExAC or gnomAD reference populations. The clinical data on HCM related to the previously published JPH2 missense variants is limited. Clinical HCM associated with JPH2 appears to be diagnosed after teenage years, except for the patient with p.(Glu115Leu) exhibited HCM at the age of 5 months (Häkkinenläinen P et al., Annals of Medicine 2013), similarly as two patients in this study. (Beavers IX et al., J Am Coll Cardiol. 2013)

**Conclusions**

- The heterozygous JPH2 p.(Thr161Lys) variant is a new Finnish founder mutation causing atypical HCM
- The JPH2 p.(Thr161Lys) is now classified as pathogenic based on ACMG variant classification scheme [37]
- This is the first JPH2 variant shown to be causative for HCM