# *JPH2* p.(Thr161Lys) is a Finnish founder mutation associating to hypertrophic cardiomyopathy with or without systolic heart failure and conduction abnormalities

Blueprint Genetics

**Sari U.M. Vanninen**[1], Krista Leivo[2], Eija H. Seppälä[3], Julie Hathaway[1], Tiia Maria Luukkonen[1], Katriina Aalto-Setälä[1,4], Olli Pitkänen[5], Piia Suursalmi[6], Antti-Pekka Annala[7], Ismo Anttila[7], Tero-Pekka Alastalo[3,5], Samuel Myllykangas[3,8], Tiina Heliö[1,‡], Juha W. Koskenvuo[3,9,*,‡]

[1]Heart Center, Tampere University Hospital, Tampere, Finland; [2]Heart and Lung Center, Helsinki University Hospital, University of Helsinki, Finland; [3]Blueprint Genetics, Helsinki, Finland; [4]Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland; [5]Divisions of Pediatric Cardiology, Children's Hospital/Helsinki University Hospital, Helsinki, Finland; [6]Department of Pediatrics, Tampere University Hospital, Tampere, Finland; [7]Department of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland; [8]Institute of Biomedicine, University of Helsinki, Finland; [9]Department of Clinical Physiology and Nuclear Medicine, HUS Medical Imaging Center, Helsinki University Hospital and University of Helsinki, Finland; ‡Equal last authorship

## 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 Junctophilin-2 gene (*JPH2*) is the major structural protein in cardiomyocytes for coupling of transverse (T) tubule-associated L-type $Ca^{2+}$ 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.482 C>A, p.(Thr161Lys)

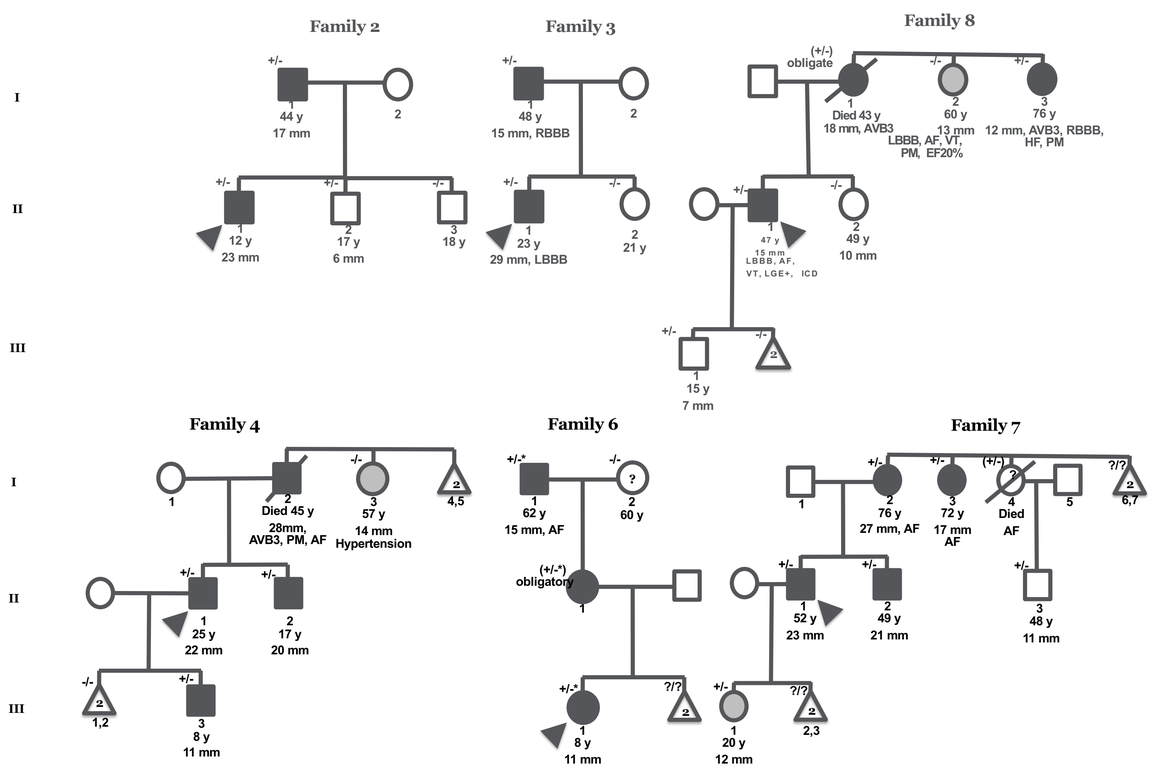


***Figure 1.*** *The heterozygous JPH2 c.482C>A, p.(Thr161Lys) (NM_020433.4) missense variant was observed in nine unrelated Finnish probands with cardiomyopathy. The variant is rare (not present in the Exome Aggregation Consortium (ExAC) or in Genome Aggregation Database (gnomAD)). Threonine is a conserved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

*The variant was detected in 20 affected individuals and 26 individuals in total. The variant co-segregated with HCM in six families (Families 2-4, 6-8, 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.I.2) who was not evaluated clinically and two individuals with LVH likely explained by severe hypertension (Family 4:I.3 and Family 8:I.2). Penetrance 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

| Family | Age (M/F) | Genotype | Conduction defect | Arrhythmias | PM, ICD | LV-WT | LVEDD (mm)/ EF (%) | proBNP (ng/l) | Age at dg | Phenotype | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Family 1** | | | | | | | | | | | |
| **I.1** | **52M** | **+/-** | **no** | **AF** | **ICD** | **20** | **46/56%** | **400** | **47** | **HCM** | |
| **Family 2** | | | | | | | | | | | |
| **I.1** | 44M | +/- | no | no | no | 16 | 46/72% | 76 | 44 | HCM | |
| **II.1** | **12M** | **+/-** | **no** | **VT** | **no** | **23** | **48/77%** | **315** | **12** | **HCM** | |
| **II.2** | 16M | +/- | pRBBB | no | no | 6 | 51/63% | NA | - | normal | |
| **Family 3** | | | | | | | | | | | |
| **I.1** | 48M | +/- | RBBB | no | no | 15 | 49/72% | 44 | 41 | HCM | |
| **II.1** | **23M** | **+/-** | **LBBB** | **no** | **no** | **29** | **44/75%** | **145** | **13** | **HOCM** | **Pk-grad 81mmHg** |
| **Family 4** | | | | | | | | | | | |
| **I.2** | 45M | n.a. | AVB3, LAHB, RBBB | AF, VT | PM | 28 | 55/20% | 8425 | 17 | HOCM, SHF | Pk-grad 50 mmHg Died 45y |
| **I.3** | 57F | -/- | no | no | no | 14 | 43/60% | 33 | - | LVH/Hypertens | BP 160/110 mmHg |
| **II.1** | **25M** | **+/-** | **no** | **SVT** | **no** | **22** | **45/67%** | **104** | **9** | **HCM** | |
| **II.2** | 17M | +/- | LAHB | no | no | 20 | 49/55% | NA | 1 | HCM | |
| **III.3** | 8M | +/- | no | no | no | 11 | 35/>50% | NA | 1 | HCM | |
| **Family 5** | | | | | | | | | | | |
| **I.1** | 54M | +/- | no | SVT | no | 10 | 50/70% | NA | - | normal | SVT ablation |
| **I.2** | 53F | -/- | no | no | no | 11 | 44/83% | 164 | - | normal | |
| **II.1** | **25F** | **+/-** | **RBBB, LAHB** | **VES, VT, SVT** | **no** | **22** | **43/60%** | **5700** | **12** | **HCM, SHF** | **Multiple VSDs, PDA operated aged 2 years. During pregnancy LVEF 45%** |
| **Family 6** | | | | | | | | | | | |
| **I.1** | 62M | +/-,* | LAHB | AF | no | 15 | 40/52% | 998 | 61 | HCM | |
| **I.2** | 60F | -/- | NA | NA | NA | NA | NA | NA | - | NA | |
| **II.1** | F | (+/-,*) | NA | NA | NA | NA | NA | NA | - | HCM | |
| **III.1** | **8F** | **+/-,*** | **NA** | **no** | **no** | **11** | **33/>60%** | **3928** | **7** | **HCM** | |
| **Family 7** | | | | | | | | | | | |
| **I.2** | 76F | +/- | LAHB | AF | no | 27 | 49/56% | NA | ? | HCM | |
| **I.3** | 72F | +/- | no | AF | no | 17 | 45/60% | NA | ? | HCM | |
| **I.4** | 80F | (+/-) | no | AF | no | NA | NA | NA | ? | ? | Died age 80 |
| **II.1** | **52M** | **+/-** | **AVB1** | **VES, SVT** | **no** | **23** | **49/63%** | **NA** | **43** | **HCM** | |
| **II.2** | 49M | +/- | AVB1 | no | no | 21 | 60/50% | NA | ? | HCM | |
| **II.3** | 48M | +/- | no | no | no | 11 | NA | NA | - | normal | |
| **III.1** | 20F | +/- | no | SVT | no | 12 | 44/66% | NA | 19 | normal | |
| **Family 8** | | | | | | | | | | | |
| **I.1** | 43F | (+/-) | AVB3, LBBB | AF, VT | PM | 18 | 70/30% | 6637 | 25 | HCM, SHF | Died aged 43. HF. WT at autopsy 15 mm. |
| **I.2** | 60F | -/- | no | no | no | 13 | 40/71% | 160 | - | LVH/Hypertens | |
| **I.3** | 76F | +/- | AVB3, LAHB, RBBB | no | PM | 12 | 46/40% | 5267 | 67 | HCM | Mixed cardiomyopathy |
| **II.1** | **47M** | **+/-** | **AVB1, LBBB** | **AF, VT** | **ICD** | **15** | **51/37%** | **4426** | **36** | **HCM, SHF** | |
| **II.2** | 49F | -/- | no | no | no | 10 | 49/66% | 31 | - | normal | |
| **III.1** | 15M | +/- | no | no | no | 7 | 46/66% | NA | - | normal | |
| **Family 9** | | | | | | | | | | | |
| **I.1** | **63F** | **+/-** | **no** | **AF** | **PM** | **19** | **45/60%** | **4082** | **63** | **HCM** | |

***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

| | *JPH2* p.(Thr161Lys) | *MYPBC3* p.(Gln1061*) | *TPM1* p.(Asp175Asn) |
|---|---|---|---|
| **Age of disease onset** | **27 yrs** | **52yrs** | **49 yrs** |
| **Heart Failure** | **25% with SHF; 50% LV dysfunction*** | **0% with HF 31% with dyspnea** | **0% with systolic dysfunction, 5% with hx of SHF** |
| **Conduction disease/arrhythmias** | **45% with 3rd degree AV-block or R/LBBB 45% with AF** | **23% chronic or paroxysmal AF 9% sustained VT or VF** | **33% life threatening arrhythmias induced with PVS** |
| **Family hx of sudden death** | **0%** | **26%** | **9%** |
| **Other** | | **26% with presyncope/syncope** | |

***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. 2004) are described.*

*Nineteen JPH2 variants (17 which are missense) 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.(Glu85Lys) 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.(Glu169Lys) exhibited HCM at the age of 5 months (Jääskeläinen P et al., Annals of Medicine 2013), similarly as two patients in this study. (Beavers DL 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**

Conflict of interest statement: All authors are employed by Blueprint Genetics.