FHOD3 Frameshift Variant Associated with Hypertrophic Cardiomyopathy

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Introduction

- Hypertrophic Cardiomyopathy (HCM) is a genetic heart condition characterized by abnormal thickening of the heart walls

- Formin Homology Domain 3 (FHOD3) is a protein expressed strongly in the heart

- The isoform FHOD3 Long contains additional exons that allow FHOD3 to regulate sarcomere formation

-FHOD3 is associated with HCM and more than half of FHOD3 mutations are found in the "coiled coiled" region (Ochoa, 2018)

Objectives

- The purpose of this study was to determine the most common FHOD3 mutations and investigate their effects on HCM presentation

- We hypothesized that FHOD3 variants produce a form of HCM similar to sarcomeric HCM (S-HCM) and would thus have similar phenotypic and diagnostic characteristics

Materials and Methods

Analyses

- Each patient's whole exome was sequenced for FHOD3 variants.

- Sample frequency was compared to population frequency in gnomAD database. A chi-squared analysis was performed to determine significance.

- Groups were compared based on presence of FHOD3 variant, presence of S-HCM, demographic variables, echocardiogram data, and presence of health conditions

PCR

- Three patients with frameshift mutation rs14401785 and three patients without the mutation were identified

- Forward and reverse primers were generated to amplify the region of interest, and PCR was performed

Results

Location	Individuals Observed	AA/BP Mutation	Prevalence (%)	General Pop. Frequency(%)	p-value
637	39	R/Q	4.21	0.39	2.05E-77
638	10	R/W	1.08	0.10	3.01E-21
rs144071785	68	CAG→C	7.34	0.03	**00.00E+00**

Table 1. *Frequency of FHOD3 mutations within Tufts HCM Cohort versus Population Frequency of FHOD3 mutations.*

Category	Sarc (-)	Sarc (+)	p-value
total	763	163	-
men	492 (64.5%)	88 (54.0%)	0.012
Family History	186 (24.7%)	54 (33.1%)	0.027
HTN	303 (39.9%)	43 (26.4%)	0.001
HLD	330 (43.5%)	42 (31.3%)	0.008
Age at Diagnosis	47.6 (15.0)	40.7 (17.1)	<.001
Composite	52.2 (13.4)	48.0 (17.3)	0.003

Table 2. *Comparison of Demographic and Clinical Variables of Individuals with S-HCM versus Individuals with nonsarcomeric HCM (NS-HCM).*

Category	Sarc (-) FHOD3 (-) N=667	Sarc (+) N=163	FHOD3 (+) N=72	637+638 N=42	p-value
Maximum Thickness	18.4 (4.1)	20.1 (5.7)	18.8 (4.0)	19.3 (4.5)	***p*<0.001**
Ejection Fraction	64.2 (6.2)	63.4 (5.7)	64.4 (4.9)	64.0 (4.6)	NS
LA size(mm)	41.8 (7.0)	40.9 (6.7)	41.7 (6.7)	41.7 (6.7)	NS
LVEDD (mm)	42.2 (6.4)	42.2 (7.8)	44.1 (5.9)	44.1 (5.7)	NS
LVESD(mm)	26.6 (5.5)	26.1 (6.7)	27.8 (5.4)	28.2 (5.1)	NS

Table 3. *Comparison of Heart Characteristics of NS-HCM patients without a FHOD3 variant, S-HCM patients, NS-HCM patients with a FHOD3 Variant, and NS-HCM patients with a FHOD3 variant at position 637 or 638.*

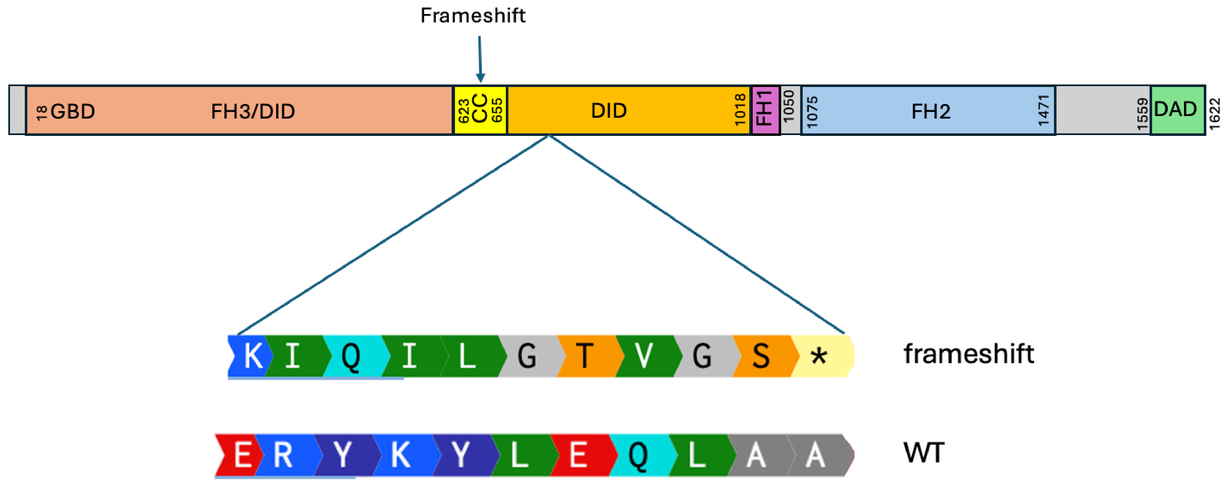

Figure 1. *Location of frameshift mutation is within the coiled-coil (CC) region of FHOD3 unique to the Long isoform around amino acids 634-636. Letters represent amino acid sequences for frameshift variant versus wildtype (WT). .* denotes stop codon. Two base-pair deletions cause formation of early stop codon at amino acid 683.*

- S-HCM group had a younger age at diagnosis (p<0.001) and lower composite score (p=0.003) than NS-HCM group most prevalent mutations were at positions 637 and 638

- S-HCM patients had a greater maximum wall thickness than NS-HCM patients without a FHOD3 mutation

- Frequency of rs 144071785, a frameshift characterized by two nucleotide deletions, was significantly higher in the Tufts HCM Cohort compared with control

Conclusions

- There is a significant difference in clinical presentation between S-HCM and NS-HCM

- FHOD3 variants are more prevalent in the HCM population but do not have any distinguishing clinical characteristics from NS-HCM

- rs144071785 is a frameshift variant that is strongly associated with HCM

- Future studies will sequence the variant to confirm its existence and analyze its effect on FHOD3 expression

References

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