Increased Disease Burden in Pediatric-onset *MYBPC3*-Associated HCM

Insights from the SHaRe Registry

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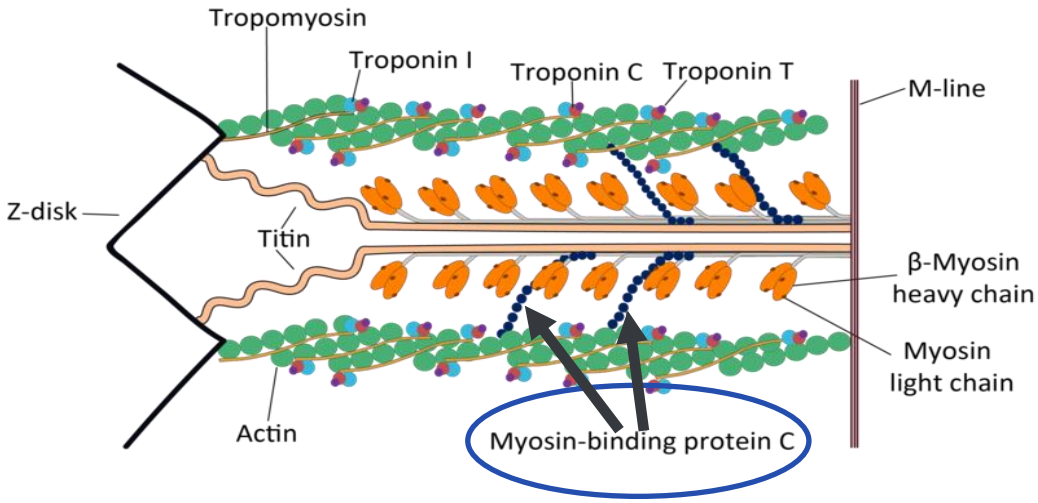
Disclosures

Dr. Tingley is an employee and stockholder of Tenaya Therapeutics

MYBPC3-associated Hypertrophic Cardiomyopathy (HCM)

- HCM is mainly due to mutations in the sarcomere genes.
- Cardiac MyBP-C acts as a modulator of sarcomere activity through interaction with components from both the thin (actin) and thick (myosin) filaments.
- Mutations in the *MYBPC3* gene are the most common cause of familial HCM. Most pathogenic mutations result in reduced functional MyBP-C protein levels (haploinsufficiency).
- *MYBPC3*-associated HCM patients have variable presentation in disease onset and severity, with different effects on infants, children and adults.
- Here, we present a comparison of pediatric- and adult-onset MYBPC3-HCM patients enrolled in the SHaRe registry (2024 Q1 datacut).



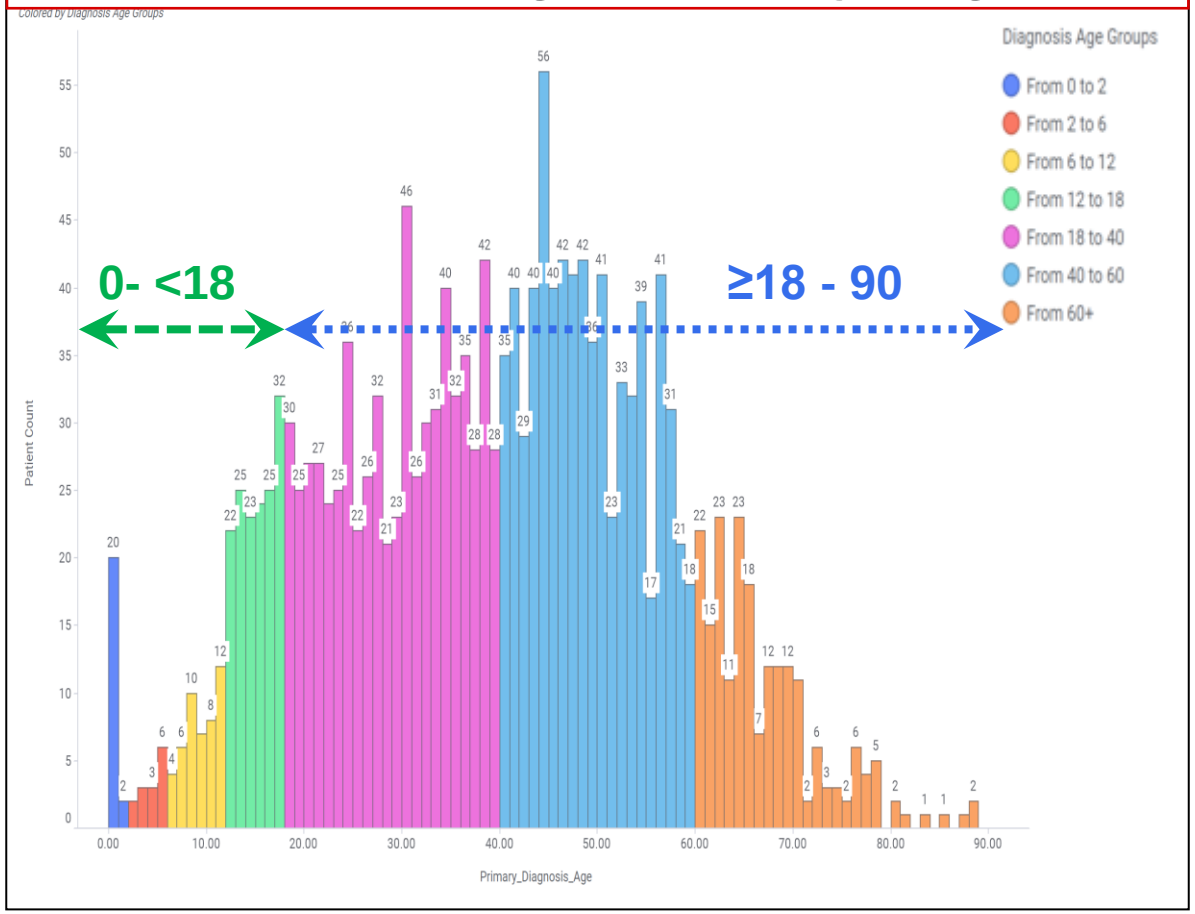
MYBPC3 = myosin-binding protein C; P/LP = pathogenic/likely pathogenic.

SHaRe: *MYBPC3*-associated HCM Patient Population

SHaRe Database: 12 cardiac centers in US, EU & Australia

- ***MYBPC3* mutation is one of the most frequent mutations responsible for HCM**
- **1,792 MYBPC3+ HCM Patients** (2024 Q1)
  - **Infantile (<1 yo) = 20 (1%)**
    - **95% proband**
  - **Childhood (1 – 17 yo) = 214 (12%)**
    - **75% proband**
  - **Adult-onset (≥18 yo) = 1558 (87%)**
    - **78% proband**

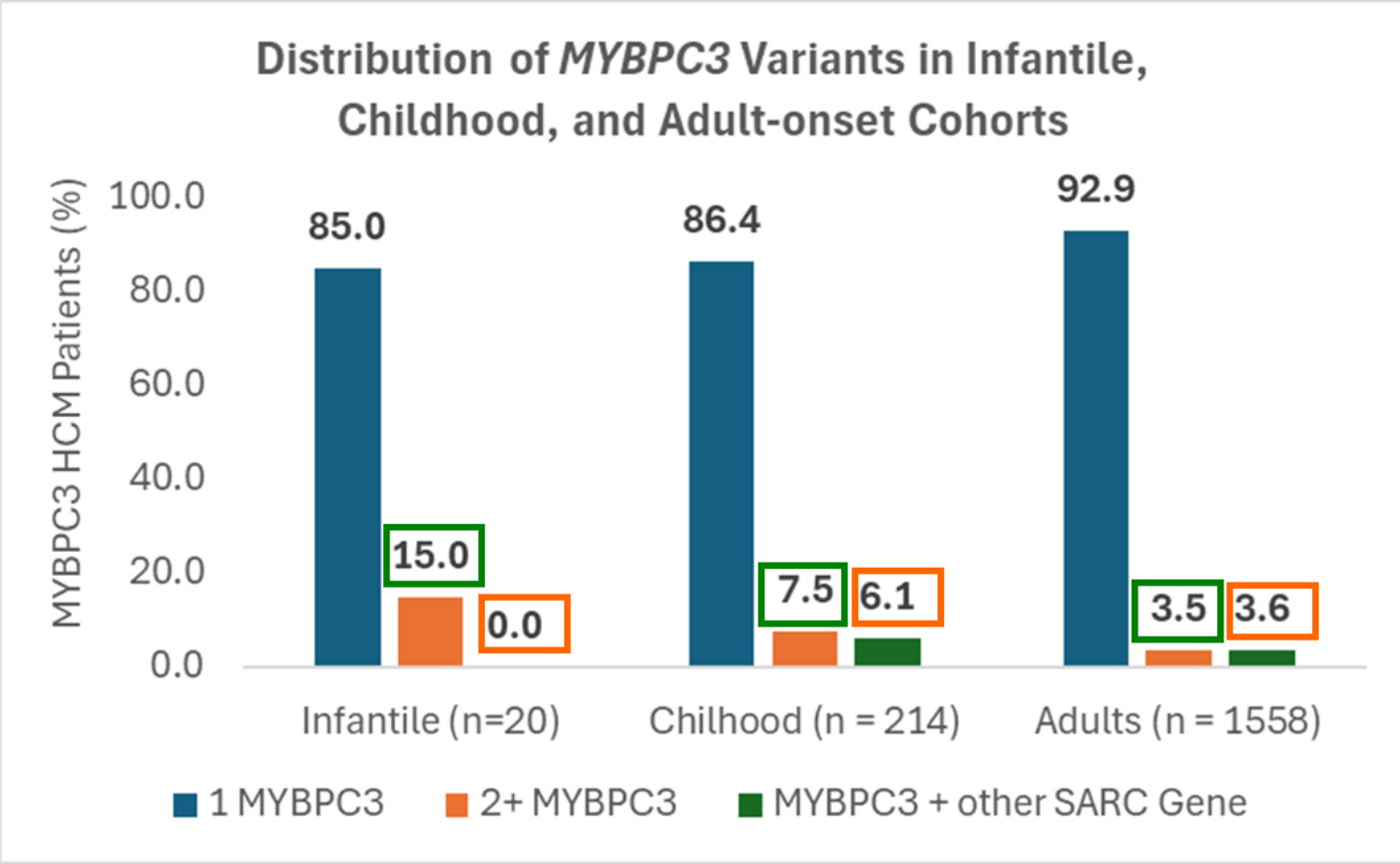
MYBPC3+ HCM: Age at Primary Diagnosis



MYBPC3 = myosin-binding protein C; P/PL = pathogenic/likely pathogenic.

Pediatric-onset Patients Have Higher Frequency of *MYBPC3* Compound Variants Compared to Adult-onset Cohort

Pediatric-onset patients are more likely to have two *MYBPC3* variants, or one *MYBPC3* variant plus another sarcomere gene variant, compared with Adult-onset group (p-value = **0.00325**)



Note: No MYBPC3 homozygous patients are reported in the database

Comparison of Outcomes in Pediatric- vs Adult-onset *MYBPC3*+ HCM Cohorts

SHaRE: Composite Events Definition

- **Overall Composite:**
  - NYHA III/IV
  - Transplant
  - VAD
  - Ventricular Arrhythmia Composite
  - Atrial fibrillation
  - Stroke
  - Death
- **HF Symptom Composite:**
  - LVEF < 35
  - NYHA III/IV
  - Listed for Transplant or Transplant
  - LVAD
  - Hospitalized for HF
  - Inotropes, or myosin inhibitors, or loop diuretics;

Ventricular Arrhythmia Composite:

SCD
Cardiac Arrest
ICD Appropriate Firing

HF, heart failure
ICD, implantable cardioverter defibrillator
LVAD, left ventricular assist device

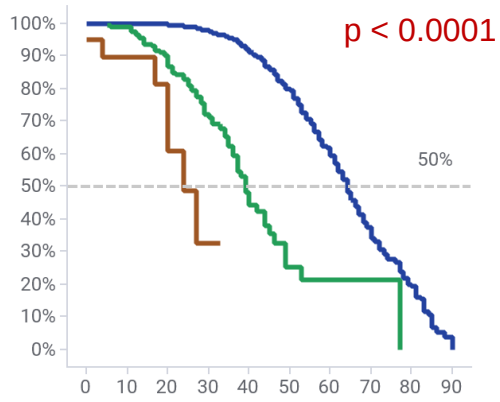
LVEF, left ventricular ejection fraction
NYHA, New York Heart Association (NYHA) Classification
SCD, sudden cardiac death

Markedly Greater Cumulative Disease Burden in Infantile- and Childhood-Onset *MYBPC3*+ HCM, Compared to Adult-Onset

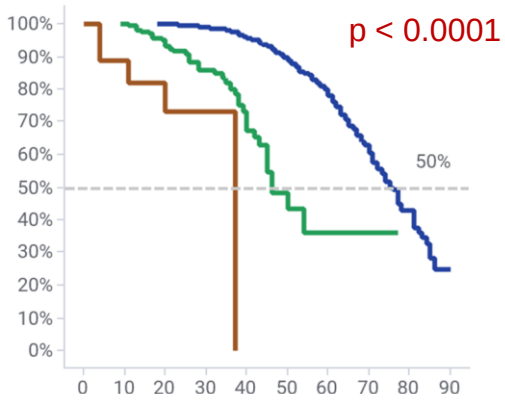
Age at Time of Event Since Birth

- Pediatric-onset (Infantile) < 1
- Pediatric-onset (Childhood) 1–17
- Adult-onset

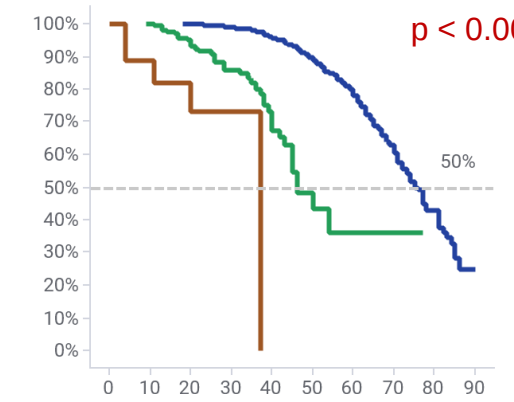
Overall Composite



HF Symptom Composite



Ventricular Arrythmia Composite

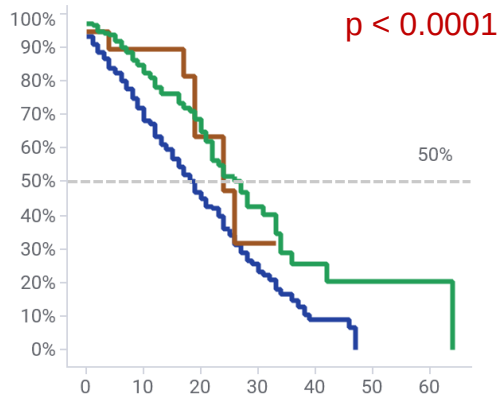


Age

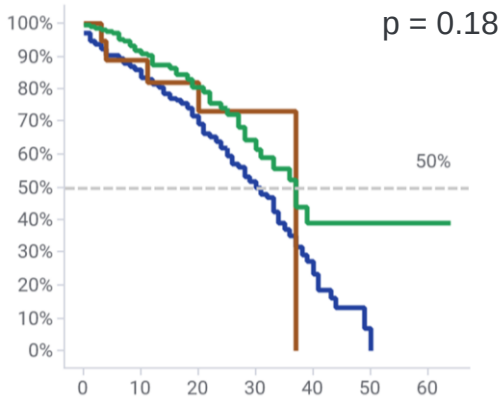
Time to Event Post Diagnosis

- Pediatric-onset (Infantile) < 1
- Pediatric-onset (Childhood) 1–1
- Adult-onset

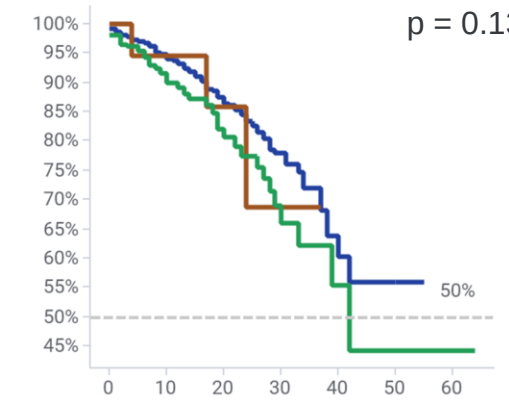
Overall Composite



HF Symptom Composite



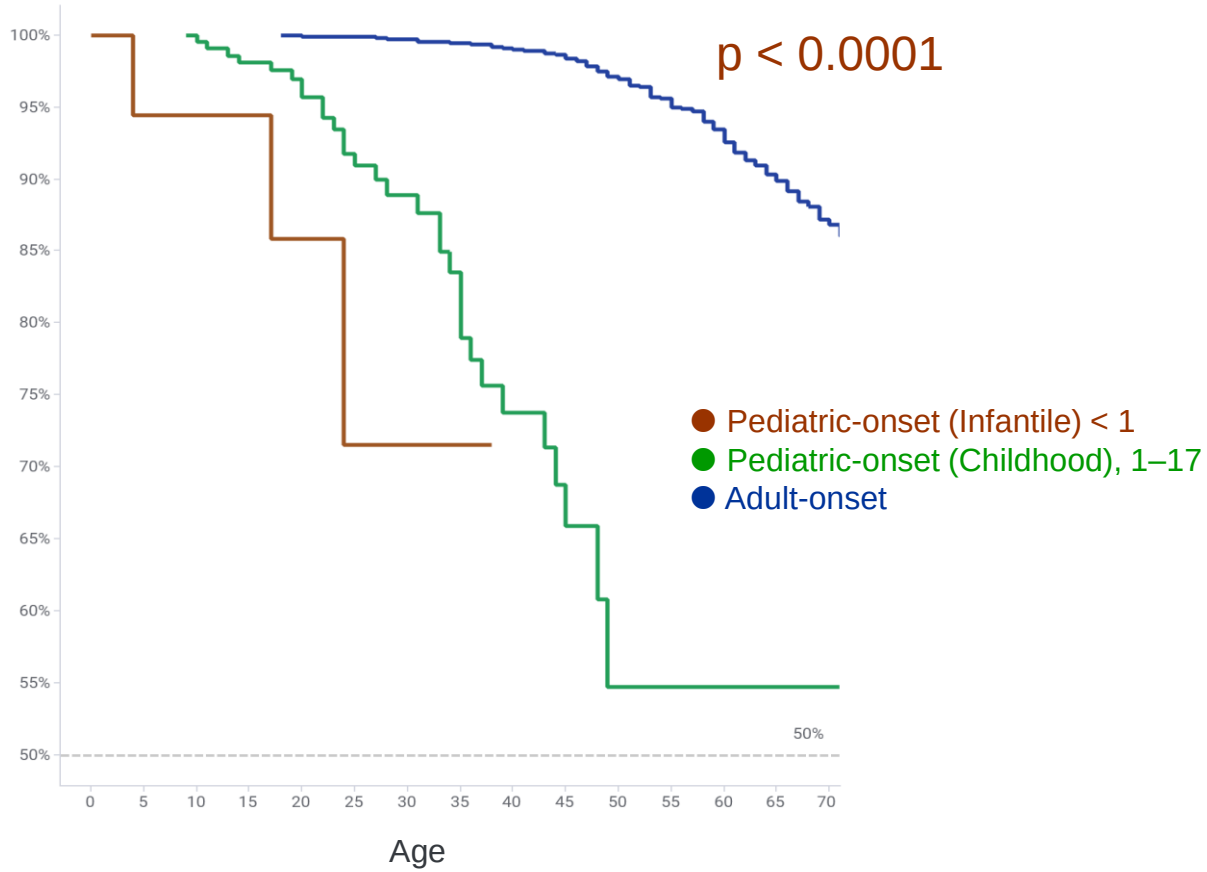
Ventricular Arrythmia Composite



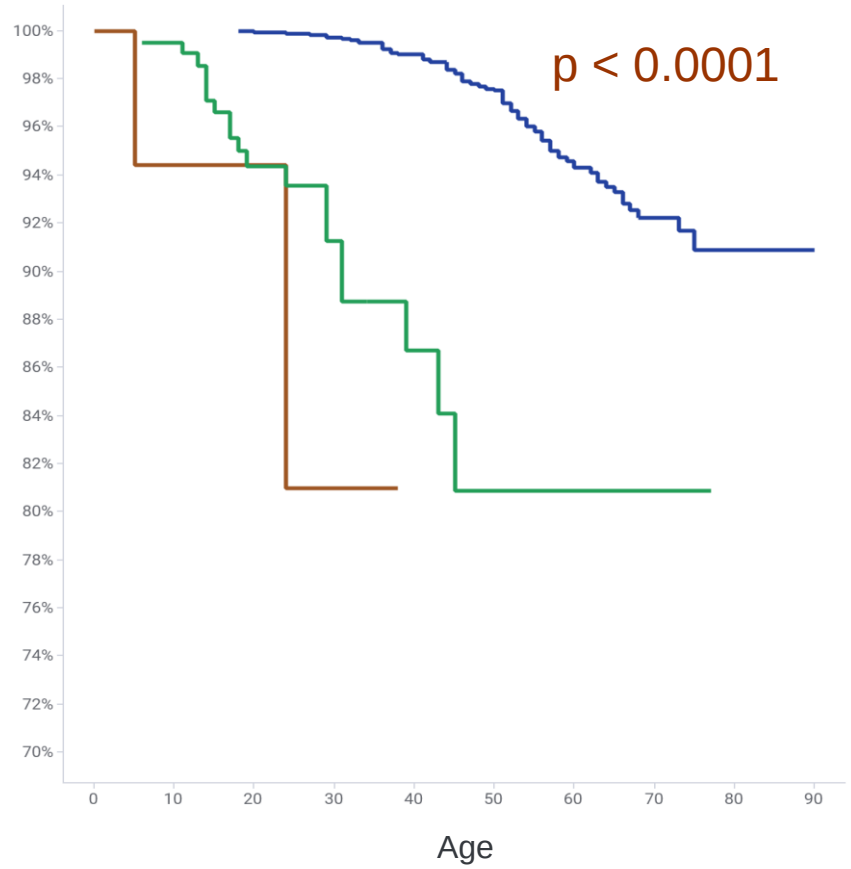
Years Post Diagnosis

Pediatric-onset *MYBPC3* HCM Shows Significantly Greater Event Rate of ICD Therapy and Cardiac Arrest Compared to Adult-onset

ICD Therapy
Age at time of event since Birth



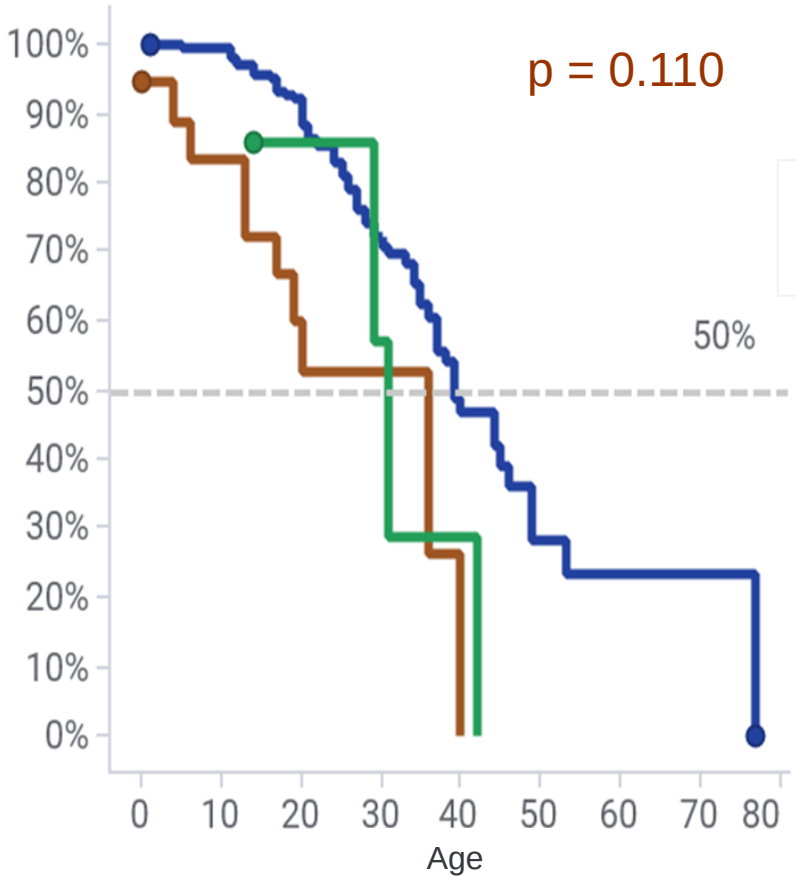
Cardiac Arrest
Age at time of event since Birth



Patients with Multiple *MYBPC3* Variants Show Comparable Composite Event Rates to Single Variant Cases in Both Pediatric- and Adult-Onset

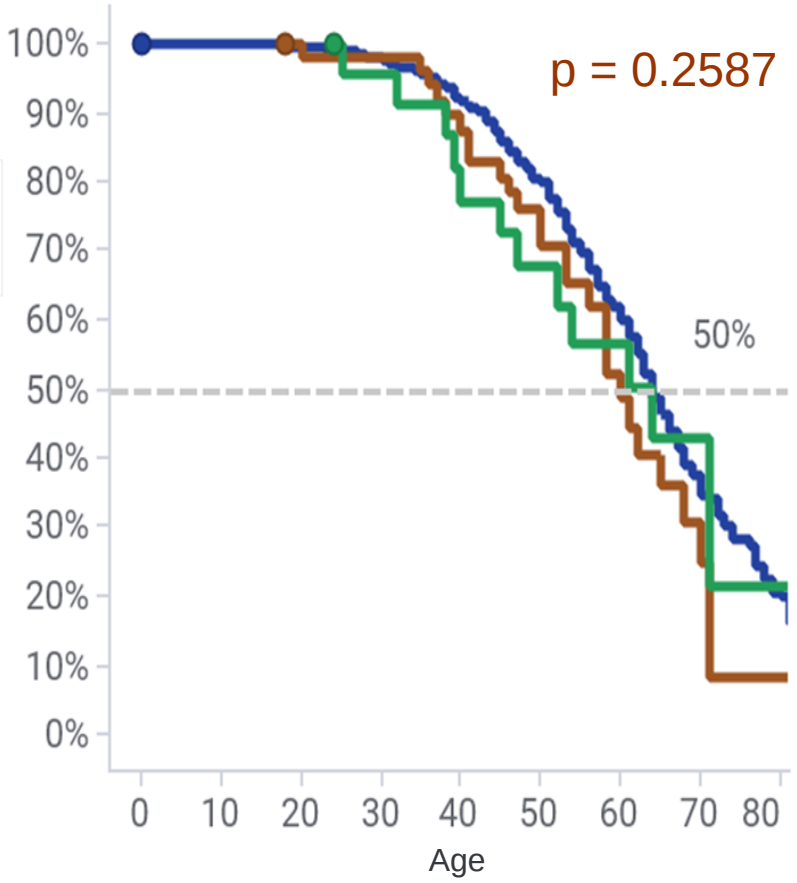
Age at Overall Composite Event Since Birth

Pediatric-onset (<18 yo)



1 MYBPC3 P/LP
2+ MYBPC3 P/LP/VUS
MYBPC3 P/LP + Other SARC P/LP

Adult-onset (≥ 18 yo)



P/PL = pathogenic/likely pathogenic *MYBPC3* = myosin-binding protein C
SARC = sarcomeric genes (MYH7, MYL2/3, MYBPC3, ACTC1, TNNI3, TNNT2, TPM1, TTN)

Conclusions

- ***MYBPC3* variants are the most common genetic cause of familial HCM,**
  - Among all the HCM patients, the prevalence was 25% MYBPC3 P/LP variants (vs 16% other sarcomere gene (ie. MYH7, MYL2/3) P/LP variants vs 19% genetic test positive VUS vs 40% genetic test negative)
- **SHaRe data suggest that *MYBPC3*+ HCM patients, both pediatric- and adult-onset, have high rates of serious outcomes, highlighting the need for timely diagnosis, active monitoring, and the use of precision therapies**
- **Pediatric-onset *MYBPC3*+ HCM patients face a greater cumulative lifetime risk than those diagnosed in adulthood, with 50% experiencing significant morbidity by age 40**
  - Younger onset correlates with increased burden of ventricular arrhythmia composite, including cardiac arrest
- **Early genetic testing and intervention could delay disease progression, reduce complications, and improve quality-adjusted life years by preventing or delaying disease progression**
- **Pediatric-onset patients with multiple *MYBPC3* variants show a trend toward worse outcomes compared to single variant cases in pediatric-onset**
  - This trend did not reach statistical significance, likely due to small sample size

Acknowledgement

Collaborating authors

Meisner J, Varfaj F, Wang W, Haroldson J, Harrison W, Tingley W, Lakdawala N, Owens A, Saberi S, Lin K, Stendahl J, Parikh V, Ingles J, Ashley E, Ware J, Michels M, Lampert R, Abrams D, Rossano J, Russell M, Ryan T, Olivotto I, Day S, Ho C, Helms A, Robertson L

Research Contributors

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Thank you for your attention

Any questions?