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Title: Childhood Hypertrophic Cardiomyopathy caused by Beta-myosin Heavy Chain Variants Is Associated with a more Obstructive but Less Arrhythmogenic Phenotype than Myosin-binding Protein C Disease

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Childhood Hypertrophic Cardiomyopathy caused by Beta-myosin Heavy Chain Variants Is Associated with a more Obstructive but Less Arrhythmogenic Phenotype than Myosin-binding Protein C Disease

Running title: *Norrish et al.; Childhood MYH7 HCM: comparison with MYBPC3 disease*

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Nonstandard Abbreviations and Acronyms

ACMG	American College of Medical Genetics and Genomics
ASH	asymmetric septal hypertrophy
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
LVH	left ventricular hypertrophy
LVOTO	left ventricular outflow tract obstruction
MACE	major adverse cardiac event
MYH7	β-myosin heavy chain gene
MYBPC3	myosin-binding protein C gene
NSVT	non-sustained ventricular tachycardia

Hypertrophic cardiomyopathy (HCM) presenting in childhood is most commonly caused by sarcomeric variants, with the β-myosin heavy chain (*MYH7*) or myosin-binding protein C (*MYBPC3*) genes most frequently implicated[1-2]. We have recently described the clinical presentation and outcomes of children with HCM caused by *MYBPC3* variants and showed that these can cause early-onset disease with a high incidence of life-threatening arrhythmias[3], contrasting with previous suggestions that they cause late-onset disease[4].

Using the same methods[3], we established a retrospective, longitudinal cohort of children diagnosed with HCM aged <18 with a disease-causing variant in *MYH7* at our centre. Variant pathogenicity was reassessed according to ACMG criteria[5]. Anonymised retrospective clinical data were collected at baseline and during follow-up. Local ethical approval was obtained. Sixty-eight patients (male n=47, 69.1%) from 60 families were identified. Seven (10.3%) carried a variant of interest in another gene, but no patients had a second *MYH7* variant. Forty-five

(66.2%) were aged <12 years, and 6 (8.8%) < 1 year at presentation. Twenty-one (30.9%) were probands and 48 (70.6%) had a family history of HCM. Median age at baseline assessment following diagnosis was 9.5 (IQR 4.8-13.5) years. Thirty patients (44.1%) were symptomatic: dyspnoea (n=14, 20.6%), chest pain (n=12, 17.7%), syncope (n=8, 11.8%), pre-syncope (n=6, 8.8%), and palpitation (n=6, 8.8%). Distribution of LVH was asymmetric septal hypertrophy (ASH) in 64 patients (94.1%) and concentric in 4 (5.9%); 10 patients (14.7%) had resting LVOTO.

Patients were followed for a median of 3.4 (IQR 1.6-7.3) years. Nine (13.2%) underwent LV septal myectomy at a median age of 7.3 (IQR 5.0-12.1) years and twenty-seven (39.7%) had an ICD implanted for primary (n=24) or secondary (n=3) prevention at a median age 13.7 (IQR 7.1-9.1) years; of these, 4 (5.7%) had one or more appropriate ICD therapies for ventricular tachyarrhythmias at a median age 17.0 (IQR 10.9-22.9) years.

Nine patients (13.2%) experienced a MACE [arrhythmic death (n=1, 1.5%), heart failure-related death (n=1, 1.5%), cardiac transplantation (n=3, 4.4%), and appropriate ICD therapy (n=4, 5.9%)] with an overall incidence of 2.3 per 100 patient years (95% CI: 1.1-4.5). One- and 5-year survival free from MACE was 98.3% (95% CI: 88.2-99.8) and 95.8% (95% CI: 83.9-99.0), respectively. Patients experiencing MACE were more likely to be probands [n=6 (66.7%) vs non-probands n=3 (33.3%), p=0.01] and less likely to present through clinical family screening [n=2 (22.2%) vs n=42 (71.2%), p value 0.02] or have a variant in 'hot spot' exons 19 to 23 [n=2 (5.4%) vs n=7 (21.2%), p value 0.05].

The *MYH7* and *MYBPC3* cohorts are compared in Table 1. Twenty-one patients in the *MYBPC3* cohort (33.9%) had a 'complex' genotype, compared to seven (10.3%) in the *MYH7* cohort (p=0.001).

Patients with *MYH7* variants had higher LA diameter Z-scores [2.2 (± 2.7) vs 1.1 (±1.4), p=0.03], but were less likely to have NSVT on ambulatory ECG monitoring during follow-up [n=3 (4.4%) vs n=10 (16.1%), p=0.03]. There was no statistically significant difference in the incidence of MACE by genotype [*MYH7* 2.3 per 100 patient years (95% CI: 1.1 - 4.5) vs *MYBPC3* 3.0 per 100 patient years (95% CI: 1.5-5.7), p=0.3]. Patients with *MYH7* variants had a higher incidence of myectomy during follow up [2.4 per 100 patient years (95% CI 1.13–4.96) vs 0.67 per 100 patient years (95% CI 0.16 – 2.68), p value 0.03].

As a single centre study, the cohort was small, meaning there may not be sufficient statistical power to reach statistical significance and we were unable to account for related subjects. However, in agreement with previous studies, we saw no significant difference between phenotypes at baseline, with the exception of a higher mean BSA-corrected LA diameter in patients with *MYH7* variants. Although AF is uncommonly reported during childhood (and was not observed in the present cohort), the observation that LA dilatation is present in children with *MYH7* variants may suggest that remodelling starts at a young age, offering a possible therapeutic opportunity for disease-modifying therapies to change long-term outcomes. The finding that fewer patients in the *MYH7* cohort had complex genotypes suggests that a single *MHY7* variant is sufficient for childhood disease presentation.

Differences in long-term outcomes were observed between the cohorts. Patients with *MYH7* variants were more than 3 times more likely to undergo LV septal myectomy during follow-up, despite a similar proportion of patients with LVOTO at baseline. It is possible that patients with *MYH7* variants may be more likely to develop symptomatic LVOTO during childhood, or may be less likely to experience symptomatic relief with medical therapy, as surgical intervention in our institution is reserved for those with symptoms resistant to maximal

medical therapy. Future prospective studies will provide important data on the evolution of LVOTO in childhood sarcomeric HCM and its role in clinical outcomes.

Our data identify differences in childhood HCM caused by *MYH7* variants compared to *MYBPC3* variants.

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Table 1. Continuous, normally-distributed data are described as mean (± standard deviation). Continuous, non-normally-distributed data are presented as median (interquartile range (IQR)). The distribution of paired continuous variables was compared using 2 sample Student t test or Wilcoxon matched-pairs signed-rank test, as appropriate. The distribution of categorical and binary variables was compared using a chi-squared test. A significance level of 0.05 was used for all comparisons

		MYH7 **(n=68)**	***MYBPC3*** **(n=62)**	**P-value**
Median age at diagnosis (years)		9.5 years (IQR 4.8-13.5 years)	12.4 years (IQR 6.1-14.8 years)	0.01
Reason for diagnosis	Incidental	10 (14.7%)	18 (29.0%)	0.05
	Symptoms	12 (17.7%)	11 (17.7%)	0.99
	OOHA	2 (2.9%)	6 (9.7%)	0.11
	Family screening	44 (64.7%)	26 (41.9%)	0.01
Symptoms at baseline		30 (44.1%)	21 (33.9%)	0.23
Medications at baseline		26 (38.2%)	21 (33.9%)	0.61
Complex genotypes		7 (10.3%)	21 (33.9%)	0.001
Baseline echocardiogram				
Median MLVWT Z-score		8.5 (IQR 5.3-14.1)	10.3 (IQR 6.6-16.8)	0.25
Mean LA diameter (mean ± SD)		33.2 mm (± 8.9 mm)	31.4 mm (± 6.8 mm)	0.32
Mean LA diameter Z-score (mean ± SD)		2.2 (± 2.7)	1.1 (± 1.4)	0.03
Median LVOT gradient		8.5 mmHg (IQR 6.0-22.0 mmHg)	6.0 mmHg (IQR 5.0-12.0 mmHg)	0.88
LVOT gradient ≥30 mmHg		11 (16.2%)	7 (11.3%)	0.58
Outcomes				
Median age at last follow-up review		15.2 years (IQR 12.0-17.1 years)	15.8 (IQR 11.2-17.9 years)	0.50
NSVT on ambulatory ECG		3 (4.4%)	10 (16.1%)	0.03
Cardiac transplantation		3 (4.4%)	2 (3.2%)	0.73
Death		3 (4.4%)	5 (8.1%)	0.39
MACE		9 (13.2%)	9 (14.5%)	0.83