Title: Early Childhood-onset HCM in a Family with an In-frame *MYH7* Deletion

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Early Childhood-onset HCM in a Family with an In-frame *MYH7* Deletion

Running title: *Field et al.; An in-frame MYH7 deletion causing early-onset HCM*

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Nonstandard Abbreviations and Acronyms:

ACMG	American College of Medical Genetics
AMP	Association for Molecular Pathology
ASH	asymmetrical septal hypertrophy
ECG	electrocardiogram
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LV	left ventricular
LVOTO	left ventricular outflow tract obstruction
MLVWT	maximal left ventricular wall thickness
MRI	magnetic resonance imaging
MYH7	β myosin heavy chain
SVT	supraventricular tachycardia

Sarcomeric protein gene mutations are the commonest cause of hypertrophic cardiomyopathy (HCM) in all age groups. Pathogenic variants in the β myosin heavy chain (*MYH7*) gene are identified in around 20% of HCM cases. Here, we describe a family (Figure 1A) with early onset, severe HCM, segregating with a rare in-frame deletion in *MYH7*. Informed consent was sought from the family prior to publication.

The female proband (**II-1**) was diagnosed aged 14 years, after presenting with syncope and documented supraventricular tachycardia (SVT). Her echocardiogram showed asymmetrical septal hypertrophy (ASH) with left ventricular (LV) hypertrabeculation. She was treated for atrial arrhythmia during adulthood and underwent insertion of a primary prevention implantable cardioverter defibrillator (ICD) due to non-sustained ventricular tachycardia on ambulatory monitoring and extensive late gadolinium enhancement (LGE) on cardiac MRI. Her phenotype became restrictive, and she developed biventricular systolic

dysfunction before unexpectedly dying aged 48 years, with no evidence of arrhythmia on ICD download.

Her sister **(II-2)** was diagnosed with apical HCM during family screening aged 10 years and later required treatment for SVT. She also underwent primary prevention ICD implantation during adulthood. Echocardiogram of the proband's son **(III-2)** revealed ASH at 7 weeks of age, with maximal LV wall thickness (MLVWT) of 8mm (Z-score +5.9). At 6 years, MLVWT was 9mm, with mildly impaired LV diastolic function and no resting left ventricular outflow tract obstruction (LVOTO). Electrocardiogram (ECG) consistently demonstrated tall voltages and inferolateral Q waves. By 11 years, MLVWT had increased to 18mm (Figure 1B). At this time, the patient reported exertional breathlessness, palpitations and pre-syncope. Cardiac MRI showed left ventricular mass of 148g/m^2 (an increase from 88g/m^2 two years prior) and patchy LGE in the intraventricular septum. He was considered at intermediate-to-high risk of ventricular arrhythmia (HCM-Risk Kids[1] 5-year estimated risk of 6.46%) and therefore underwent implantation of a primary prevention ICD. Antenatal echocardiography in the proband's nephew **(III-6)** detected hyperechogenic foci without evidence of hypertrophy. He was diagnosed with HCM aged 4 months, with MLVWT of 10mm (Z-score +6.4) (Figure 1C). This increased to 12mm by his most recent review (aged 6 years), with hypertrabeculation of the apex and LVOTO. There has been no evidence of ventricular arrhythmia on ambulatory monitoring and he remains asymptomatic.

Following appropriate counselling, genetic testing was performed on a 21 gene HCM panel in **III-6** aged 18 months and a likely pathogenic in-frame deletion in *MYH7* (c.2791_2793delGAG; p.Glu931del) was detected. The variant is located in exon 23, corresponding to the 'neck' region of the *MYH7* protein, where disease-causing variants are frequently identified[2].

Cascade genetic testing identified the variant in all other diagnosed family members **(II-1, II-2 and III-2)**. In addition, **III-1** was found to carry the familial variant; although this 14 year old individual does not meet diagnostic criteria for HCM, his ECG has shown voltage criteria for biventricular hypertrophy and pathological Q waves inferolaterally since early childhood (Figure 1D), with apical trabeculation on echocardiogram. Four family members **(I-2, III-3, III-4 and III-5)** with normal cardiac test results, including the proband's mother, were found not to be carriers of the variant and were discharged from follow-up. The proband's father **(I-1)** died of non-cardiac causes before genetic testing was possible but had normal clinical investigations; the possibility of germline mosaicism can therefore not be excluded.

The identified *MYH7* variant was not previously described in control population databases but had been reported in individual HCM probands. Both **III-2** and **III-6** were reported elsewhere in the literature as members of a cohort previously described by Norrish *et al*[3]. The variant was reported segregating with disease in one other family with severe HCM[4].

As observed across the genome, the majority of mutations identified in *MYH7* HCM are missense[2], with other mutation mechanisms detected less frequently. Although in-frame deletions are rarely identified in *MYH7* HCM, the phenotypes observed in this family suggest that such variants have potential to cause severe and early onset disease, with diagnosis made at initial cardiac screening in three individuals, in two of these during infancy. As the nucleotide deletion is not predicted to cause a frameshift/truncated protein, the functional consequences are likely similar to missense variants (i.e.: not through haploinsufficiency), but further mechanistic work is needed to confirm this.

The in-frame *MYH7* variant segregates with features of disease in five members of this family and is associated with ECG abnormalities and development of LV hypertrophy from early childhood. Such early disease penetrance as described here was not reported in

previous descriptions of this variant. Application of *MYH7*-modified ACMG/AMP criteria supports the continued classification of this variant as likely pathogenic[5]. While functional data relating to the variant are not currently available, this mechanistic insight might contribute towards its future reclassification. Our findings highlight the importance of clinical and genetic cascade screening for HCM in all age groups and provide further evidence for severe phenotypic expression of atypical mutation mechanisms.

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Disclosures: None

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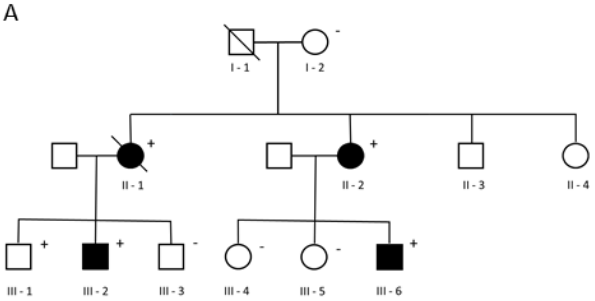
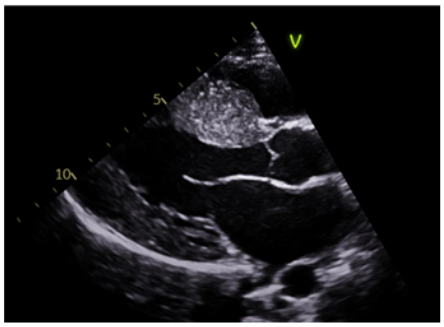
Figure Legend:

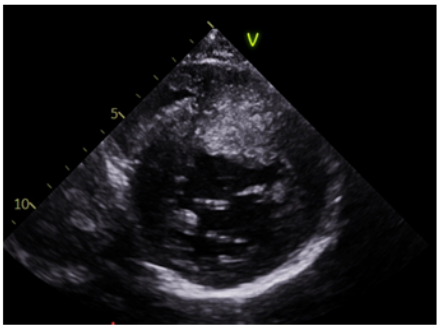
Figure 1: A: Family pedigree, indicating individuals meeting diagnostic criteria for HCM; **B:** Current PLAx and PSAx of III-2, aged 12 years; **C:** PLAx and PSAx of III-6, at 6 months of age; **D:** Current ECG of III-1, aged 14 years.

A



B





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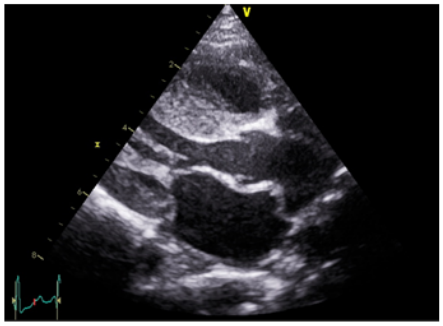

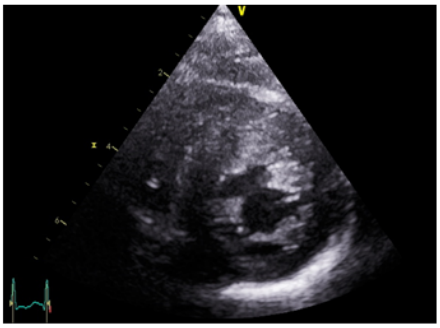

D