

# Family screening of hypertrophic cardiomyopathy in children: a case report

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## Background

Paediatric hypertrophic cardiomyopathy (HCM) caused by sarcomere protein gene mutations is more common than previously thought. We present the case of a 9-year-old boy that was diagnosed with HCM during family screening.

## Case summary

We present a case of a 9-year-old boy with a family history of sarcomeric HCM who was diagnosed with hypertrophic obstructive cardiomyopathy (HOCM) during clinical screening. Echocardiography and cardiovascular magnetic resonance imaging revealed asymmetric left ventricular hypertrophy with a maximum wall thickness of 18–19 mm. Cardiovascular magnetic resonance late gadolinium enhancement imaging showed patchy fibrosis within the area of maximum wall thickness. Genetic testing confirmed the presence of the familial mutation in the *MYL2* gene. The patient was started on bisoprolol. Furthermore, risk stratification was performed and a recommendation for implantable cardioverter-defibrillator implantation was made.

## Discussion

This case demonstrates that significant HCM can already start in childhood and discusses the recommendations for family screening on the basis of recently published studies and the present European Society of Cardiology guideline.

## Keywords

Hypertrophic cardiomyopathy • Sarcomeric protein mutations • Childhood-onset inherited disease • Case report

## Learning points

- In the context of family screening, sarcomeric causes in patients with childhood-onset hypertrophic cardiomyopathy are more common than previously thought.
- A timely diagnosis can be of prognostic value, and this should be considered in the recommendations for family screening.

## Introduction

Hypertrophic cardiomyopathy (HCM) is a heart muscle disease that is commonly caused by disease-causing variants in sarcomere protein genes ('sarcomeric HCM') but can also be caused by other 'non-sarcomeric' causes (e.g. RASopathy syndromes, neuromuscular diseases, inherited errors of metabolism). Paediatric HCM comprises a heterogeneous group of disorders with a high prevalence of non-

sarcomeric causes. It was previously thought that sarcomeric causes are not a typical finding during childhood, but recent data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) and other studies have shown that childhood-onset sarcomeric HCM is common and has a worse prognosis compared with adult-onset HCM.<sup>1–4</sup> However, in the European Society of Cardiology (ESC) guideline on HCM, clinical screening and/or genetic testing is usually only recommended from the age of 10 years onwards.<sup>5</sup>

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## Timeline

09.06.2021, 9 years, 1 month	Family screening by a local paediatric cardiologist Suspicion of HCM
05.07.2021, 9 years, 2 months	Referral to the paediatric cardiomyopathy clinic Diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) by electrocardiogram (ECG) and echocardiography
06.08.2021, 9 years, 3 months	Further diagnostics including: cardiovascular magnetic resonance imaging, exercise testing, Holter ECG Risk assessment Patient was started on beta-blocker Referral to human genetics Patient is scheduled for regular follow-up visits in the paediatric cardiomyopathy clinic

## Case presentation

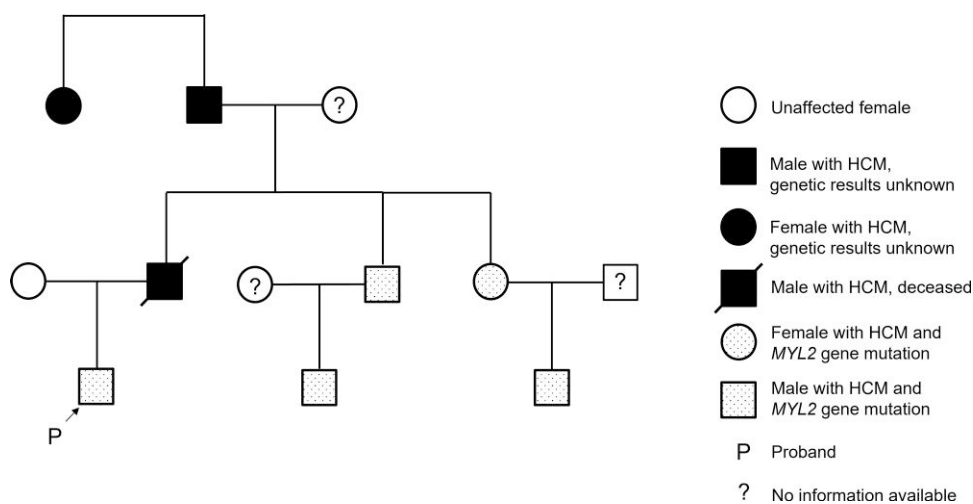
Family screening in a 9-year-old boy by a local paediatric cardiologist suggested a possible diagnosis of familial HCM and he was referred to our paediatric cardiomyopathy clinic. His father suffered from HCM and died 6 years ago in his 3rd decade due to a stroke. The paternal grandfather of the proband and his sister were also diagnosed with HCM. Other affected family members included a paternal uncle and his son as well as a paternal aunt and her son. Genetic testing of the latter family members revealed a mutation in the *MYL2* gene (*MYL2*, c.487G > A [p.(Glu163Lys)])—(Supplementary material online). The mutation was classified as likely pathogenic after reviewing mutation type together with a search in scientific databases and literature. More detailed information was not available. A family pedigree is shown in Figure 1.

Clinically, he was well and asymptomatic with no signs of congestive heart failure and no history of syncope. His weight was 44.6 kg (93rd centile) and height was 150.5 cm (94th centile); heart rate was 60 b.p.m. and

right arm blood pressure was 111/67 mmHg with a mean arterial pressure of 83 mmHg. On auscultation, a 2/6 systolic murmur in the 3rd intercostal space at the left sternal edge was audible. The ECG demonstrated discordant negative T-waves in Lead III and deep S-waves in the septal and anterior leads (Figure 2) but based on these ECG findings solely and according to recent international recommendations in athletes, the patient would not have been considered for echocardiography.<sup>6</sup> N-terminal pro-hormone of brain natriuretic peptide level was 434 ng/L (normal range <112 ng/L). The echocardiogram showed asymmetric septal hypertrophy (maximal wall thickness 18 mm) of the left ventricle (LV) with mild flow acceleration in the mid-LV cavity (peak systolic velocity 2.6 m/s) consistent with HOCM (Supplementary material online, Movie clips 1–4). There was no systolic anterior movement (SAM) and no mitral regurgitation. Cardiovascular magnetic resonance was performed and confirmed the diagnosis of HOCM with a maximum wall thickness of 19 mm at the midventricular inferoseptal and inferior level (Figure 3). Left ventricle systolic function was hyperdynamic with LVEF of 80%. Late gadolinium enhancement (LGE) imaging showed an area of patchy LGE at the level of the maximal LV wall thickness (Figure 4). The right ventricle was small for the patients' age, functioning well, and not hypertrophied. Holter monitoring did not demonstrate significant arrhythmias. Cardiopulmonary exercise testing was carried out for functional and prognostic assessment<sup>7</sup> and showed a reduced exercise capacity for his age with a peak oxygen uptake of 28 mL/kg/min (<3rd centile).<sup>8</sup> Genetic counselling and testing were performed and showed that he carries the likely pathogenic familial variant in the *MYL2* gene.

Risk assessment for the primary prevention of sudden cardiac death was performed using the newly developed HCM Risk-Kids calculator.<sup>9</sup> The estimated risk of sudden cardiac death at 5 years was 7.5%. A team discussion regarding the indication for implantation of an implantable cardioverter-defibrillator (ICD) took place considering genetic findings, family history, and results from the HCM Risk-Kids calculator.<sup>9</sup> The decision was made to recommend ICD implantation and to discuss this with the patient and his mother. In addition, the patient was advised to avoid competitive sporting activities and to have a regular fluid intake. He was allowed to participate in low to moderate recreational activities. Beta-blockade with bisoprolol was started for treatment of the left ventricular outflow tract obstruction.

The patient is under frequent follow-up in the paediatric cardiomyopathy clinic and is clinically well with no evidence for arrhythmias and no decrease in exercise capacity as shown by recent Holter monitoring and cardiopulmonary exercise testing.



**Figure 1** A three-generation pedigree together with explanations of the symbols is shown.



**Figure 2** 12-Lead electrocardiogram at first presentation. This showed sinus rhythm at 60–65 b.p.m. and a QRS axis of  $+90^\circ$ . There were negative T-waves in Lead III and deep S-waves in the septal and anterior leads.

## Discussion

Hypertrophic cardiomyopathy is a heart muscle disease that is often caused by disease-causing variants in sarcomere protein genes ('sarcomeric HCM') and more rarely by 'non-sarcomeric' causes such as RASopathy syndromes, neuromuscular diseases, inherited errors of metabolism, lysosomal storage diseases, and mitochondrial diseases.

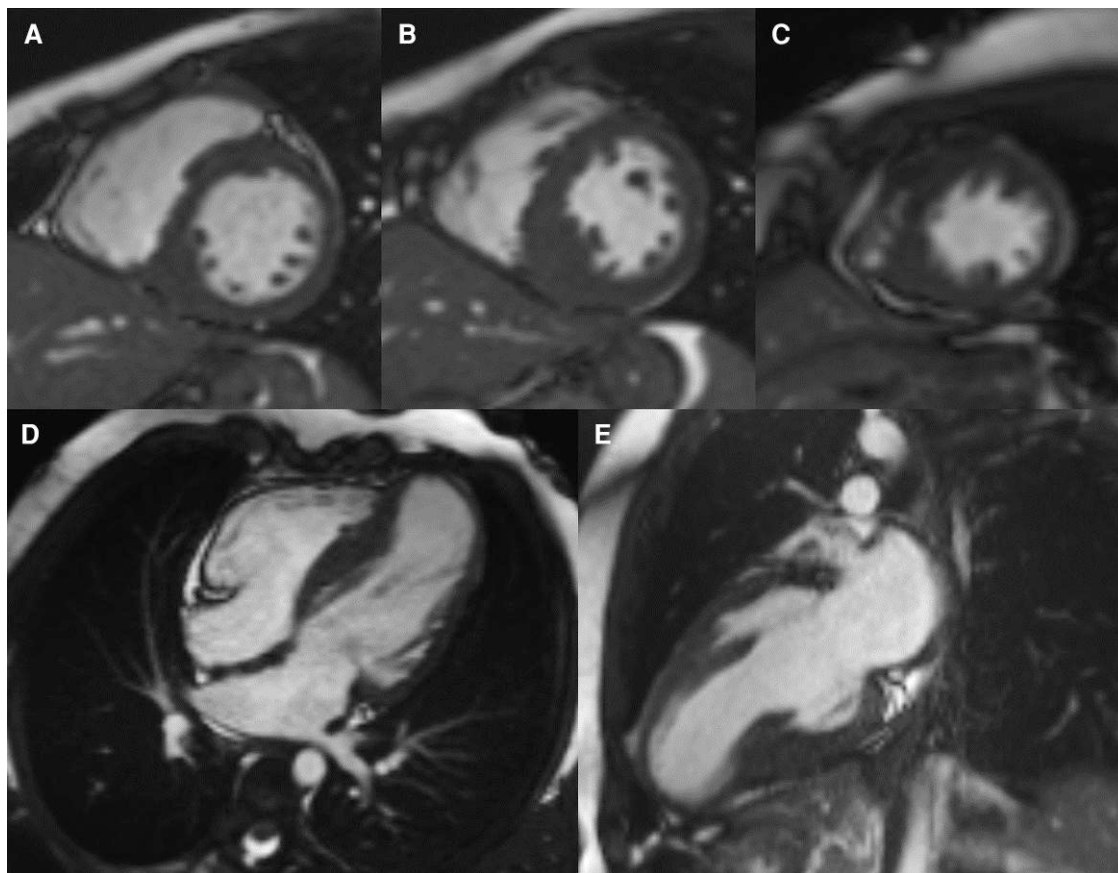
In children, HCM is a more heterogeneous and rare group of disorders with an incidence of 0.32–0.47/100 000.<sup>10,11</sup> In the past it was thought that sarcomeric protein mutations rarely cause a HCM phenotype during childhood, however, several studies have shown that sarcomeric HCM is common in children with a reported frequency between 43 and 63% in childhood-onset disease.<sup>1,3,4</sup> Recent data suggest that ~10% of children from HCM families are phenotype-positive on echocardiography and that ~50% of them are younger than 10 years of age<sup>12</sup> but detailed information about the onset of transition from an apparently normal myocardium to an HCM phenotype is lacking. The same group found that adverse events start occurring already in the paediatric age group.<sup>12,13</sup> In addition, a diagnosis made in infancy as well as childhood-onset sarcomeric HCM together with inborn errors of metabolism are associated with increased mortality and a higher rate of arrhythmic and heart failure events.<sup>1,14,15</sup>

The latest ESC guidelines for HCM and ESC position statement on genetic counselling and testing recommended that clinical and/or genetic testing should be considered in first-degree relatives from the age of 10 (-12) years onwards (Table 1).<sup>5,16</sup> An exception is made for those families with early-onset disorders (e.g. RASopathy syndromes, inborn errors of metabolism, multiple sarcomere mutations), malignant family history in childhood, for children with cardiac symptoms or children who are involved in demanding physical activities.<sup>5</sup>

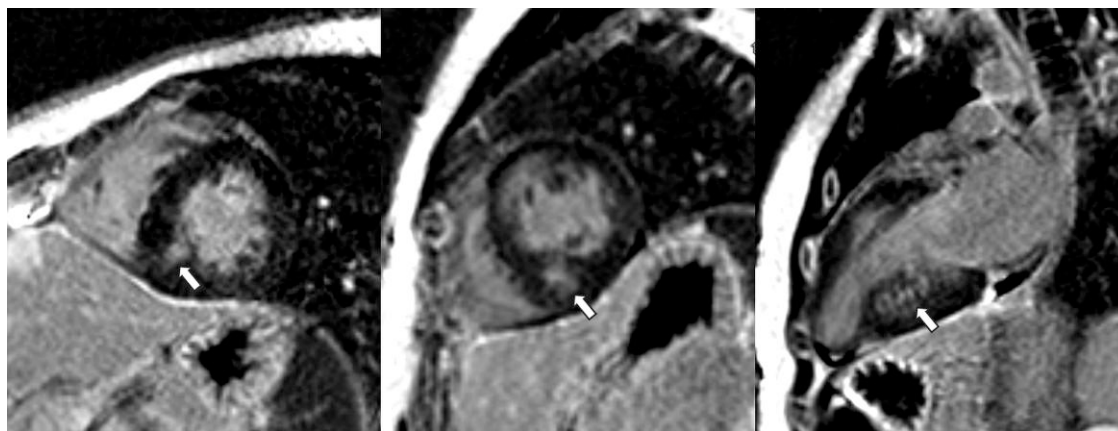
Within the family of the presented patient, several members had a diagnosis of HCM. Furthermore, genetic testing in the family showed

a mutation in the *MYL2* gene with the exchange of glutamate with alanin in the myosin regulatory light chain 2 was already described as pathogenic in the literature when the first genetic testing results within the patients family were available. However, following strictly the ESC guideline and position statement,<sup>5,16</sup> clinical screening would probably not have been performed before the age of 10 years or later although the patient was already affected by a significant HCM phenotype.

The recent guideline from the American Heart Association (AHA) and American College of Cardiology (ACC) has a different point of view on family screening in paediatric first-degree relatives of HCM patients.<sup>17</sup> They recommended screening with ECG and echocardiography in children and adolescents from genotype-positive families, and families with early-onset disease at the time of HCM diagnosis as well as in all other children and adolescents at any time after HCM diagnosis but no later than puberty.<sup>17</sup> That early family screening might be indeed clinically important was shown in a recent study that retrospectively analysed data from more than 500 children that underwent clinical family screening.<sup>14</sup> The authors were able to show that a third of children that were diagnosed with phenotype-positive HCM and 41% of patients who experienced a major cardiac event (death, sudden cardiac death as well as need for myectomy, ICD insertion, transplantation) were younger than 10 years of age.<sup>12</sup> The same group could show that event rates are not different than in adults suggesting that early screening might be beneficial in detecting significant early-onset HCM.<sup>12,13</sup> Another study by Norrish *et al.* showed that a diagnosis of HCM is made in ~5% of first-degree child relatives from 8% of families with the majority of diagnoses (72%) is made in preadolescence.<sup>18</sup> However, the monetary and emotional costs of early screening but also the emotional and financial costs of a missed diagnosis have to be considered.<sup>12,19,20</sup> In this context, Semsarian *et al.* pointed out the importance of clinical judgement. They suggest that rather applying specific age criteria for family



**Figure 3** Cardiovascular magnetic resonance short axis (A–C), four-chamber (D), and two-chamber (E) cine images illustrating the asymmetric left ventricular hypertrophy mainly affecting the inferoseptal and inferior wall.



**Figure 4** Late gadolinium late enhancement showing the area of late enhancement (arrows).

screening, families should be assessed in their individual clinical situation paying attention to risk features and risk tolerance.<sup>20</sup>

The presented case fulfils the recommendations and current statements from the ESC<sup>5,16</sup> and the AHA/ACC guideline<sup>17</sup> which, however, need to be applied in each patient's individual clinical context.

Based on studies showing that recent sarcomeric protein mutations in children are common and the results from the SHaRe highlighting that childhood-onset HCM are associated with a higher risk of life-threatening ventricular arrhythmias, and a greater need for advanced heart failure therapies,<sup>1–4</sup> we believe that family screening should be

**Table 1 Recommendations for clinical screening from the 2014 ESC guidelines on diagnostics and management of hypertrophic cardiomyopathy<sup>2</sup>**

Recommendation	Class of recommendation	Level of evidence
In first-degree child relatives aged 10 or more years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1–2 years between 10 and 20 years of age, and then every 2–5 years thereafter.	II A	C
When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical, or genetic testing of first-degree child relatives before the age of 10 years may be considered.	II B	C

Class II recommendation: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class II A: weight of evidence/opinion is in favour of usefulness/efficacy. Class II B: usefulness/efficacy is less well established by evidence/opinion. Level of evidence C: consensus of opinion of the experts and/or small studies, retrospective studies, registries.

offered to all first-degree relatives at the time of diagnosis without age limit but clinicians should also pay attention to risk features and risk tolerance of the individual family.<sup>20</sup>

## Conclusion

Recent studies together with our case suggest that significant familial/sarcomeric HCM is not uncommon in children and should be diagnosed early for prognostic reasons. Clinicians should consider offering family screening to first-degree paediatric family members at the time of diagnosis.

## Lead author biography



Inga Voges is a consultant in paediatric and adult congenital heart disease at the University Hospital Schleswig-Holstein in Kiel (Germany) with expertise in cardiovascular MR and further special interest in paediatric cardiomyopathies. She is the secretary of the Association for European Paediatric and Congenital Cardiology imaging working group and a member of the paediatric and congenital heart disease executive committee of the SCMR. Dr Voges is highly involved in clinical research in the field of congenital

heart disease and Cardiovascular MR imaging.

## Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.

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