Genetic Clues on Implantable Cardioverter-Defibrillator Placement in Young-Age Hypertrophic Cardiomyopathy: A Case Report of Novel MYH7 Mutation and Literature Review

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Background: Hypertrophic cardiomyopathy (HCM) is the second most common cardiomyopathy in childhood with a life-threatening risk. Implantable cardioverter-defibrillator (ICD) placement is recommended for early prevention if there are two or more clinical risk factors. Pediatric patients with HCM are at a higher risk of sudden cardiac death (SCD), but there are limited reports on indications for ICD implantation in children. Herein we describe the case of Myh7 mutation-induced HCM and cardiac arrest in a patient and evaluated information originating from genetic background to guide ICD administration.

Case Presentation: The patient was a girl aged 7 years and 8 months who had been diagnosed with cardiomyopathy in utero 8 years prior. She had had recurrent cardiac arrests within the last 4 years. Electrocardiography indicated abnormalities in conduction, and ST segment changes. Echocardiography indicated significant left ventricular hypertrophy and hypertrophic systolic interventricular septum. Cardiac magnetic resonance imaging depicted general heart enlargement with hypertrophy, and delayed enhancement in myocardium with perfusion defect was also evident. Whole exon sequencing identified a de novo c.2723T>C (p.L908P) heterozygous mutation in the MYH7 gene. MYH7 p.L908P predicted unstable protein structure and impaired function. The patient was scheduled for ICD implantation. There were no complications after ICD implantation, and she was discharged from hospital on the 10th day. Regular oral beta-blockers, amiodarone, spironolactone, and enalapril were administered, and she was required to attend hospital regularly for follow-up. During follow-up there were no cardiac arrests. Literature review of clinical prognoses associated with genetic mutations of MYH7, MYBPC3, TNNI3, TNNT2, and TPM1 in pediatric HCM patients with and without ICD implantation indicated that they were totally differently. Previous reports also indicated that gene mutations predicted earlier onset of cardiac hypertrophy, and increase likelihood of SCD.
Introduction

Hypertrophic cardiomyopathy (HCM) is the second most common myocardial disease in childhood, with an annual incidence of ∼0.24–0.47 per 100,000. Characterized by unexplained left ventricular hypertrophy (LVH), the typical histological manifestation is uneven distribution of myocardium. The causes of HCM are heterogeneous in children, and include congenital metabolic defects, chromosome-related syndromes, and neuromuscular diseases (1, 2). More than 1,400 rare variants in at least 8 sarcomere-related genes have been linked to HCM, with variations in the MYH7 and MYBPC3 genes the most common. Most cases of child-onset HCM are familial/hereditary however, and are caused by mutations in genes encoding the sarcomere, cytoskeleton, or desmosome protein (3).

Children with HCM are at greater risk of sudden cardiac death (SCD) and other adverse events (4). Both the European Society of Cardiology and the American Heart Association recommend implantable cardioverter defibrillators (ICDs) for early prevention if there are two or more clinical risk factors, including severe LVH, unexplained syncope, cardiac arrest, nonsustained ventricular tachycardia, and a family history of SCD (5, 6). However, there is no practical guideline for pediatric patients. Moreover, there is no genetic factor involved in analyzing the risks of pediatric HCM patients suffering SCD. Previous studies indicate that patients with gene mutations are more likely to experience poor outcomes (7). Herein we describe the case of a patient with de novo MYH7 mutation-induced HCM and recurrent cardiac arrest, then present related literature to assess the influence of genetic risk on early ICD intervention in pediatric HCM.

Case Presentation

Ethical Compliance

This report was approved by the Ethics Committee of the West China Second Hospital of Sichuan University (approval number 2014-034). Informed consent was obtained from the patient’s parents prior to performing whole exon sequencing, and for the inclusion of the patient’s clinical and imaging details in subsequent publications.

Medical History and Physical Examination

The patient was a girl aged 7 years and 8 months who had been diagnosed with cardiomyopathy in utero 8 years prior. She had had recurrent cardiac arrest attacks within the last 4 years (from 2015 to 2021). On each of these occasions she had been saved via immediate chest compressions and other cardiopulmonary resuscitation methods. Seizures had been observed two or three times per year, which were ∼2–3 min in duration. Her daily activity tolerance was limited, her breathing rate was 25–35 breaths/min, and her blood pressure was ∼95/55 mmHg. Arrhythmia and dull heart sound were detected. Pulmonary, abdominal, musculoskeletal system, and neurological examination results were unremarkable.

Imaging and Laboratory Examinations

Electrocardiography (ECG) revealed electrical axis deviation to the right, complete right bundle branch block (CRBBB), abnormal double atrium, ventricular hypertrophy, first-degree atrioventricular block, ST segment changes (lead I, aVL, and V3–V6 depression >0.5 mV) (Figure 1A). Notably however, ventricular tachycardia had been observed three times on a monitor and had failed to be recorded before electric cardioversion. Echocardiography have been performed by the same echocardiographer to make the data comparable, and the echocardiography pre-ICD implantation indicated significant LVH and hypertrophic interventricular septum (19 mm, Z-score = 5.64) at the end of diastole with normal left ventricular systolic function (62–71.6%) (Figure 1B). Cardiac magnetic resonance imaging demonstrated general heart enlargement with LVH. Delayed enhancement in the myocardium with perfusion defect were also detected, indicating microdiffusion disorder in myocardial tissue. Scattered flaky enhancement foci were evident in the myocardium, suggesting myocardial fibrosis (Figure 1C).

Initial laboratory tests revealed dramatic elevation of troponin I (> 50 μg/L, n.v. < 0.02 μg/L) and B-type natriuretic peptide (10,330.6 pg/mL, n.v. < 146 pg/mL) immediately after her first cardiac arrest at age 6. During follow-up before ICD implantation, the troponin I range was 0.15–20.32 μg/L and the B-type natriuretic peptide range was 478.2–8746.1 pg/mL.

Molecular Results

A peripheral blood sample was obtained from the patient in an ethylenediaminetetraacetic acid anticoagulant blood sample tube then stored at 4°C for < 6 h. DNA was extracted using the Blood Genome Column Medium Extraction Kit (Tiangen Biotech, Beijing, China) in accordance with the manufacturer’s instructions. Protein-coding exome enrichment was performed using the xGen Exome Research Panel v.1.0, comprising 429,826
individually synthesized and quality-controlled probes targeting 49.11 Mb of protein-coding regions (>23,000 genes) of the human genome. Whole-exon sequencing was performed using the NovaSeq 6000 platform (Illumina, San Diego, CA, USA), and the raw data were processed using FastP to remove adapters and filter out low-quality reads. Paired-end reads were aligned to the Ensembl GRCh38/hg38 reference genome using the Burrows-Wheeler Aligner. Variant annotation was performed in accordance with database-sourced minor allele frequencies (MAFs) and practical guidelines on pathogenicity issued by the American College of Medical Genetics. The annotation of MAFs was performed based on the 1000 Genomes, dbSNP, ESP, ExAC, Provean, Sift, Polypen2_hdiv, Polypen2_hvar, and Chigene in-house MAF databases using R software (R Foundation for Statistical Computing, Vienna, Austria). The sequencing data have been deposited in the GSA database (http://ngdc.cnbc.ac.cn/gsub/).

MutationTaster was used with R software to predict the pathogenicity of MYH7 c.2723T>C and assess the effects of this mutations on protein structure. Besides, according to the recent report from Lioncino et al., we also evaluated the related mutations of RASopathies, and the result was negative (8). There is no MYH7 protein crystal structure available. Modeling analysis was performed using SWISS-MODEL (https://swissmodel.expasy.org/) for the three domains with a 5tby.1.A template. The capability of the protein structure was estimated using Ramachandran plots (Figure 2A). Change in the free energy of the model was estimated using the mutation cutoff scanning matrix (mCSM) method (http://biosig.unimelb.edu.au/mcsm/). Site Directed Mutator (SDM, http://marid.bioc.cam.ac.uk/sdm2) was used to enable assessment of the effects of mutations on the stability of MYH7, and the DUET server was also used (http://biosig.unimelb.edu.au/duet/) to integrate mCSM and SDM to improve the overall prediction accuracy of the mutations under consideration. The signature vector that was ultimately generated was used to train the predictive classification and regression model for calculating the change in Gibbs folding free energy induced by the mutations. Missense3D (http://
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MYH7 Mutation and ICD Implantation

FIGURE 2 | Effects of MYH7 c.2723T>C mutation on molecular protein structure. (A) Ramachandran plots of MYH7 with and without p.L908P mutation. (B) SWISS-MODEL to predict the variant’s wild-type and mutated protein crystal structures using 5tby.1.A template, and structural changes identified in the helix. (C,D) The mCSM tool used to predict protein stability revealed a decline in Gibbs free energy, indicating an unstable protein structure associated with this mutation. (E) Missense3D analysis indicated that MYH7 p.L908P caused a structure clash.

Three types of calculation methods all demonstrated significant destabilizing change (mCSM, $-1.571$ Kcal/mol; DUET, $-2.044$ Kcal/mol; SDM, $-3.14$ Kcal/mol; Figure 2D). The Missense3D tool was also used to evaluate the molecular probity clash score. MYH7 p.L908P predicted obvious protein clash, with an elevated clash score $>18.00$ (Figure 2E).

Final Diagnosis and Treatment

After several examinations and molecular tests the child was diagnosed with HCM, ventricular tachycardia, and Stokes-Adams syndrome. Before ICD implantation she received captopril, beta-blockers, and amiodarone to control heart rhythm. Clopidogrel, spironolactone, and vitamin C were provided to improve heart function. Electrical cardioversion has been used to terminate ventricular tachycardia. In accordance with 2020 American College of Cardiology/American Heart Association HCM guidelines (9) the patient was scheduled for ICD placement after the diagnosis of HCM with the novel MYH7 mutation c.2327T>C, suffering several cardiac arrests accompanied by sustained ventricular tachycardia, and echocardiography demonstrating an interventricular septum thickness $>15$ mm.

After ICD implantation the patient suffered no complications and was discharged from hospital on the 10th day. Oral beta-blockers, amiodarone, and enalapril were then administered for regularity, and spironolactone had been provided at the 1st...
month post ICD implantation. In conjunction with the patient had been required to visit hospital strictly for follow-up. During the 1 year of follow-up period there was no recurrent cardiac arrest, and the ICD remained functional. The most recent ECG indicated sinus rhythm, CRBBB, LVH, and ST segment changes, and prolonged QT and QTc intervals. During the follow-up, Holters had been performed every 2 months, which were absence of ventricular tachycardia. Echocardiography indicated general hypertrophic changes in left and right ventricular hypertrophy at the end of diastole (interventricular septum 14 mm (Z-score = 4.22)), left ventricular posterior wall 9 mm (Z score = 2.90), right ventricular posterior wall 6 mm) and normal left ventricular systolic function = 64%.

**DISCUSSION**

HCM is the most common type of cardiomyopathy in children. It is associated with SCD and other adverse outcomes that are usually life-threatening such as severe heart failure, which lead to early death. A recent statement from Monda et al. demonstrated the HCM was the major cause of SCD among all kinds of cardiomyopathies (10). Besides, this statement emphasized the importance of genetic variants evaluation in preventing future SCD. Notably however, predicting such cardiac events in HCM patients remains challenging. Furthermore, the European Society of Cardiology and the American Heart Association developed a risk score system to guide the clinical management of HCM patients. Unfortunately there are no specific recommendations for preventing SCD in pediatric HCM patients, and no specific recommendations pertaining to ICD implantation in such patients. In view of this limitation several case series and reports have discussed this issue and suggested reasonable indications for ICD placement. Because the technique for ICD placement in pediatric patients is challenging and high-risk, the procedure involves several external considerations that do not apply in adults.

Next generation sequencing tests are rapid, and are widely used in both developed and developing countries to investigate genetic associations. Mathew et al. (5) reported that the primary genes affected were MYH7 in 35% and MYBPC3 in 49% in a pediatric cohort. MYH7 mutation-positive patients exhibited earlier disease onset and were at a higher risk of major adverse cardiac events (HR, 2.7, 95% CI 1.3–5.7). The risk of major adverse cardiac events was also higher in patients with multiple variants (n = 16; HR, 2.5, 95% CI 1.1–5.9), and de novo variant subsets revealed a higher risk (HR, 5.7, 95% CI 2.6–12.7). Ferradini et al. (11) reported that MYH7 was the dominant genetic site overlapping HCM and arrhythmogenic cardiomyopathy. To predict the risk of SCD among HCM patients, several predictive models had been reported. Recently, two groups reported two individual validated model of SCD in children. The research from Norrish et al. demonstrated the maximal wall thickness and left atrium as the most important indicator to predict 5-years risk of SCD (12). However, this article did not take pathogenic variant into the formula of risk calculation, and they found the family history was not related to the risk of SCD (12). Another research from Miron et al. revealed a validated model for SCD risk. In this model, it confirmed the pathogenic variant elevated the likelihood of experiencing SCD events (HR, 1.32 [95% CI, 1.00–2.12]) (7). Among the reported pathogenic variants, MYH7 and MYBPC3 were the most common mutations had been elucidated (7). So that, more detail evaluation of genetic variants, including the molecular function of mutated genes (structural proteins, metabolic molecules or calcium handling channel, etc.) should be taken into different or hierarchical considerations to predict risk of SCD and guiding the application of ICD implantation. This research highlight the importance of genetic analyses and significance of mutations in guiding the implantation of ICD. However, the implantation of ICD among high risk (>6%) population to save patients from SCD was not very satisfied, as only 1 patient may potentially be saved from SCD at 5 years among every 10 ICDs implanted in patients with 6% or more of a 5-year SCD risk (12). So that, the clinical outcomes of ICD application is mainly relied on the patient risk stratification. Analysis of the role of sarcomere genes in the pathogenesis of arrhythmogenic cardiomyopathy is recommended in arrhythmogenic cardiomyopathy patients who test negative for desmosomal mutations. In other research utilizing the International Sarcomeric Human Cardiomyopathy Registry (13, 14) the top three genetic variants indicating HCM onset were MYH7, MYBPC3, and Thin Filament. The average age at initial diagnosis was 40.1 ± 15.2 years however, thus corresponding pediatric information remains lacking. That research demonstrated that new-onset atrial fibrillation developed in 19% of HCM patients with sarcomere mutations, and compared with other sarcomere genes, patients with pathogenic or likely pathogenic variation in MYH7 had a higher rate of incident atrial fibrillation independent of clinical and echocardiographic factors. Accordingly, MYH7 mutation is a major indicator of arrhythmia in HCM patients, which called positive recommendation for ICD application. Besides, the mutations of above genes, a newest research from Lioncino et al. demonstrated the RASopathies was critical to underline the clinical outcomes HCM (8). So that, any HCM patients, especially for the children who had right ventricular hypertrophy involved, should be paid more attention to exclude RASopathies.

In recent years ICD interventions have proven effective for the prevention of cardiac arrest by monitoring and terminating ventricular fibrillation or malignant ventricular tachycardia. ICD therapy in children is associated with higher rates of complications than it is in adults however, necessitating complex consideration before proceeding with ICD implantation (7, 15, 16). Herein we attempted to evaluate the potential benefits of ICD implantation in pediatric patients. Literature review indicated that clinical prognoses associated with genetic mutations (MYH7, MYBPC3, TNNI3, TNNT2, and TPM1) in pediatric HCM patients with and without ICD implantation were totally different (17–20). Multiple studies indicate that in adults some gene mutations predict earlier disease onset and more severe phenotypes in HCM (21–25). Although gene mutations and phenotypes are heterogeneously influenced by modifier genes, environmental factors, and other influences (16), current evidence suggests that HCM patients with
TABLE 1 | Association between gene mutations and malignant events in children of hypertrophic cardiomyopathy.

| References | Targeted gene | Variants | Events | Age on onset | ICD implantation | Age on receiving ICD | Gender | Family history | ECG | Clinical outcomes |
|------------|---------------|----------|--------|--------------|------------------|---------------------|--------|----------------|------|------------------|
| Fernlund et al. | MYH7 | c.746G>A; p.R249Q | Cardiac arrest | 7 years | Yes | 12 years | Female | Positive | High risk by ECG-risk score | Alive |
| | ALPK3 | c.903del, p.I301Mfs*10 | Cardiac arrest | 14 years | Yes | 24 years | Male | Positive | Several episodes with non-sustained VT | Alive |
| Hwang et al. | MYH7 | c.2146G>A; p.G716R | Sudden cardiac death | Young ages | No | N.A. | 2 males and 1 female | Positive | Q wave in lead II and aVF | Ceased |
| Jeschke et al. | MYH7 | c.2155C>T; p.R719W | Cardiac arrest | 6.5 years | YES | 8.5 years | Male | Negative | Severe arrhythmia including VT | Alive |
| Lekanne Deprez et al. | MYBPC3 | c.2373_2374insG (maternally) and c.1624+1G>A (paternally) | Cardiac failure | 3 days | No | N.A | Female | Positive | First degree AVB, with deep QS complexes in the left precordial leads associated with T wave abnormalities | Ceased |
| | MYBPC3 | c.3288delA; p.E1096fs*92 (maternally) and c.2827C>T; p.Arg943X (Paternally) | Cardiac failure | 2 weeks | No | N.A | Male | Positive | Giant P waves, hardly any left sided activity in the precordial leads, and flattened T waves | Ceased |
| Maron et al. | TNNI3 | p.R162W (Homo) | Cardiac arrest | 17 years | Yes | 17 years | Female | Positive | Diffuse flattened T | Alive |
| Mori et al. | Compound mutations with MYBPC3 and MYH7 | MYBPC3 c.472G>A; p.V158M; MYH7 c.788T>C; p.V320M | Sudden cardiac death | Childhood | No | N.A | 6 children | N.A | N.A | Ceased |
| Van Driest et al. | TPM1 | c.610T>C; p.L185R | Cardiac arrest | 2.5/8/10 years | 2 cases received ICD | 2 years after diagnosis | 2 Males and 1 female | Positive | Ventricular fibrillation | 1 ceased case without ICD implantation | Alive |
| Monda et al. | TNNT2 | c.304C>T; p.A102T | Cardiac arrest | 11 years | Yes | N.A | Male | Positive | N.A | Alive |

ICD, implanted cardioverter defibrillator; N.A., not available; VT, ventricular tachycardia.

multiple variants are more likely to suffer malignant outcomes and SCD, potentially justifying early ICD implantation (26–29).

Systematic review indicates that ICD implantation is usually recommended in HCM patients with severe cardiac events. Notably however, several large cohort studies and meta-analyses suggest that the most common age range for receiving ICD implantation is ∼40–45 years. The current case of HCM was relatively rare in that the patient presented with severe arrhythmic attacks resulting in recurrent cardiac arrest. It was fortunate that death had not occurred prior to ICD placement. ICD placement was deemed urgent in this very young patient (aged 7.7 years). Given her very young age, we acquired all published reports detailing cases of ICD implantation in patients aged under 18 years that provided clear clinical and molecular results. This amounted to a total of seven reports describing 14 cases of patients suffering malignant cardiac events, and almost all of them involved a positive family...
history. Among them, two patients with compound MYBPC3 variants died soon after birth due to aggressive heart failure with HCM. Another 11 patients presented HCM phenotypes with MYH7, ALPK3, MYBPC3, TNNI3, TNNT2, and TPM1 variants. Age at ICD implantation ranged from 8.5 to 17.0 years. Unfortunately, SCD occurred in 5 of 5 children in whom the ICD placement procedure was not completed. Conversely, only 1 of 7 children (14.3%) died after successful ICD implantation (Table 1). So that, compared with the reports from Norrish et al., which revealed the ICD could only save 1 out of 10 HCM with high risk of SCD without genetic stratification, the patients with positive genetic variant might receive more benefits from ICD implantation according to literature review.

The present case and the associated literature review facilitated the derivation of the genetic clues for a potential future perspective for ICD placement, as the patients with genetic mutations associated with HCM and arrhythmia, especially MYH7 and MYBPC3 mutations might be benefit from early ICD implantation. Besides the screening for positive genetic variant, several indicators required to be clarified to demonstrate the risk stratification for SCD. The echocardiographic parameters, especially for left atrium and right ventricle; the onset age with or without syncope; and whether there were notable abnormal ECG changes. However, two studies provided a controversial results on the application of ECG in predicting SCD (31, 32). So further prospective studies are required to provide more evidences on SCD application indication among HCM children.

CONCLUSION
Variant burden and variant type contribute to the risk of adverse events in pediatric HCM patients. Early recognition and intervention are vital in such patients. We suggest that gene mutation could be considered as an potential indication for early ICD placement in pediatric HCM patients during standard risk stratification, but this requires further investigation.

DATA AVAILABILITY STATEMENT
The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: http://ngdc.cncb.ac.cn/gsub, GSA database.

ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the Ethics Committee of West China Second Hospital of Sichuan University (2014-034). And informed consent from the patient's parents prior to conducting the WES had been obtained, including the patient's clinical and imaging details in the manuscript for the purpose of publication. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)’ legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS
YH, KZ, and TW were the patient’s physicians. XL and JT reviewed the literature and contributed to manuscript drafting. JL and SL performed the mutation analysis. YL conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. YH and YL were responsible for the revision of the manuscript for important intellectual content. All authors issued final approval for the version to be submitted.

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