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ORIGINAL PAPER

Genetic basis of hypertrophic cardiomyopathy in children

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Abstract

Background Previous investigations assessing the genetic cause of pediatric hypertrophic cardiomyopathy (HCM) found underlying genetic mutations in 50–60% of cases. The purpose of our study was to analyze whether this number can be augmented by applying next-generation sequencing and directing further diagnostics by discussing unsolved cases in a multidisciplinary board.

Methods and results 42 patients with the diagnoses of HCM made before age 18 years were treated in our center from 2000 to 2016. Genetic analysis was performed in 36 subjects, a genetic defect was detected in 29 (78%) patients. 15 individuals (42%) had pathogenic variants in genes encoding sarcomere proteins, and 5 (14%) in genes coding for components of the RAS/MAPK signaling pathway. 4 subjects (11%) had mutations in the GAA gene (Pompe disease), and 3 (8%) had Frataxin repeat expansions (Friedreich's ataxia). One patient each showed a mutation in BAG3 and LMNA. Discussion of unsolved HCM cases after performing next-generation sequencing (28 genes) in an interdisciplinary board unraveled the genetic cause in 9 subjects (25%).

Conclusion A definite genetic diagnosis can be reached in nearly 80% with HCM of childhood onset. Next-generation sequencing in conjunction with a multidisciplinary cooperation can enhance the diagnostic yield substantially. This may be important for risk stratification, treatment planning and genetic counseling.

Keywords Hypertrophic cardiomyopathy · Children · Next-generation sequencing

Introduction

Hypertrophic cardiomyopathy (HCM) is morphologically characterized by hypertrophy of the left ventricle, not secondary to other conditions causing left-ventricular wall thickening such as severe hypertension, aortic stenosis, or any other cardiac disease. HCM is the most common form of the inherited cardiomyopathies with a prevalence of 1:500 and constitutes an important cause of sudden unexpected death in adolescents and young adults [14, 20].

Hypertrophic cardiomyopathy may manifest at any time from infancy to old age, but in the majority of patients symptoms do not set in before adolescence. About 50–60% of patients manifesting during adolescence or later harbor genetic defects in cardiac sarcomere proteins [6], with mutations in the beta myosin heavy chain (MYH7) and in the myosin binding protein (MYBPC3) accounting for the major part of them [13]. In the remaining, HCM is assumed to be caused by pathogenic variants in genes not specifically related to cardiac sarcomere function. Multisystemic conditions with HCM include neuromuscular diseases, disorders of the RAS/MAPK signaling pathway, lysosomal storage diseases, and disorders of energy metabolism [16]. Mutations in genes causing HCM are inherited mostly in an autosomal dominant pattern, with the exceptions of autosomal-recessive Pompe disease and Friedreich's ataxia.

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Data about the genetic basis of HCM with onset during infancy and childhood are sparse. In children, the number of cases resulting from defects of sarcomere genes is assumed to be lower compared to older patients [18]. Therefore, the diagnostic work-up is more complex, and may necessitate an interdisciplinary approach to unravel the cause underlying HCM.

Identifying the underlying genetic defect can be essential for individual therapy planning and genetic counseling of families [2, 5, 11, 19]. Thus, the aims of this study were to determine which genetic defects caused HCM in children regularly seen in our institution, and to analyze whether a multidisciplinary collaboration involving pediatric cardiology, neuropediatric, neuropathologic, and genetic specialists helps to increase the rate of underlying disease categories and the genetically solved cases.

Methods

We reviewed the database of the Pediatric Heart Center Giessen for patients with a diagnosis of HCM (age at diagnosis < 18 years) seen at least twice in our center from 2000 to 2016. Hypertrophic cardiomyopathy was defined by otherwise unexplained septal and/or free wall hypertrophy (z score > 2). This retrieved 42 subjects. Two of these individuals had died without having any genetic screening, and four families refused genetic testing. Therefore, 36 patients were eligible for further analysis. The study was approved by the ethics committee of the University of Giessen. Written informed consent was obtained from the patients and/or their parents according to study protocols approved by our institutional review board.

In a first step, we evaluated the data of patients in whom a definite genetic defect had already been established. In a second step, a genetic screening for mutations in genes known to cause HCM was either performed for the first time or updated. In brief, genomic DNAs were analyzed by next-generation sequencing (NGS) using a custom design based on an Agilent SureSelect^{QXT} solution-capture enrichment strategy (Agilent, Santa Clara, CA, USA). Targeted sequencing capture probes were custom designed using the specific online tool (SureDesign) provided by Agilent to identify disease-causing mutations in 28 cardiomyopathy-causing genes:

ACTC1 (NM_005159.4), *ACTN2* (NM_001103.2), *ANKRD1* (NM_014391.2), *CALR3* (NM_145046.4), *CASQ2* (NM_001232.3), *CAV3* (NM_033337.2), *CRYAB* (NM_001885.2), *CSRP3* (NM_003476.3), *DES* (NM_001927.3), *JPH2* (NM_020433.4), *LDB3* (NM_007078.2), *MYBPC3* (NM_000256.3), *MYH6* (NM_002471.3), *MYH7* (NM_000257.2), *MYL2* (NM_000432.3), *MYL3* (NM_000258.2), *MYLK2* (NM_033118.3), *MYOZ2* (NM_016599.3), *MYPN* (NM_032578.3), *NEXN* (NM_144573.3), *PLN* (NM_002667.3), *PRKAG2* (NM_016203.3), *TCAP* (NM_003673.3), *TNNC1* (NM_003280.2), *TNNI3* (NM_000363.4), *TNNT2* (NM_001001430.1), *TPM1* (NM_001018005.1), *VCL* (NM_014000.2).

In a third step, all relevant data of the remaining subjects were extracted from their medical records, and the findings were discussed in interdisciplinary team meetings with specialists from the departments of Neuropathology (AS), Child Neurology (AH), and Genetics (MZ,CM). If appropriate, patients were re-examined by one of these specialists and/or additional examinations were initiated to further delineate the exact phenotype. Thereafter, a targeted genetic testing was initiated in some patients.

Results

HCM was diagnosed in 12 patients (29%) within the first year of life, in 14 (33%) between 1 and 6 years, and in 16 (38%) thereafter (7–18 years). Patient data, genetic findings and additional clinical features of the study cohort are shown in Table 1. The underlying conditions causing HCM in relation to age at diagnosis are presented in Table 2.

15 patients (42%) harbored mutations in genes coding sarcomere proteins. Among them, 7 had pathogenic variants in MYBPC3, 5 in MYH7, 2 in TNNI3, and 1 in MYH6. 5 subjects were shown to have mutations in genes (RIT1, RAF1, PTPN11) involved in RAS-MAPK signaling. 5 subjects were compound heterozygous or homozygous for mutations in the GAA gene, prompting the diagnosis of infantile Pompe disease. A GAA-repeat expansion in the FXN (Frataxin) gene was found in three subjects and led to the diagnosis of Friedreich's ataxia. In one individual, a mutation in the LMNA gene was found, and one subject with myofibrillar myopathy was shown to have a defect in the BAG3 gene. Overall, a definite genetic diagnosis could be established in 29 patients (78%). Genetic testing of parents and other family members for the specific mutation detected in the index patient is routinely advised in our institution. A familial autosomal dominant form of HCM was diagnosed in six families. In addition, all parents of patients with autosomal-recessive mutations turned out to be heterozygous carriers.

When looking through the medical files at start of this study, a genetic diagnosis had already been established in 16 patients (44%). An extended screening for mutations in HCM causing genes in the remaining patients unraveled the genetic defect in four subjects (11%) only, whereas an interdisciplinary discussion prompting additional genetic examinations solved the genetic basis in further nine individuals (25%). In one case, a variant of unknown significance (VUS) was detected and communicated to the parents, but it was

Table 1 Synopsis of 42 patients with HCM manifesting before age of 18 years

Patient	Age at diagnosis (years)	BNP (pg/ml)	IVS (d) *z* score	IVS (s) *z* score	LVOTO (l = present)	NYHA classification	Gene	Mutation	AMCG classification	Additional clinical features
1	0.2	3442	4.71	4.29		3	GAA	c.236_246del (p.Pro79Argfs*12) c.236_246del (p.Pro79Argfs*12)	Path.	Muscular hypotonia and muscle weakness, CK elevation
2	8.7	2	1.46	1.76		1				Attention defecit disorder
3	10.8	1068	7.37	0.00	1	1	MYH7	c.2334C>G p.(Asp778Glu)	Likely path.	
4	0.5	3924	7.68	6.42		3	GAA	c.307T>G (pCys103Gly) c.307T>G (pCys103Gly)	Path.	Muscular hypotonia and muscle weakness, CK elevation
5	0.0		1.65	0.48		4				
6	8.3	5614	6.65	6.36		1				
7	0.1	56	6.01	6.45	1	1	GAA	c.794delG (p.Ser265Ilefs*3) c.1933G>A (p.Asp645Asn)	Path.	Muscular hypotonia and muscle weakness, CK elevation
8	1.0	4665	3.03	2.44		3	MYBPC3	c.2373dupG p.(Trp792Valfs*41) c.2078insA p.(A694Gfs*43)	Path.	
9	0.4	18	2.42	1.82		1	GAA	c.2078insA p.(A694Gfs*43)	Path.	Muscular hypotonia and muscle weakness, CK elevation
10	13.6		−0.42	−0.58		2	MYH7	C.5380C>A p.(Gln1794Lys)	Likely path.	Epilepsy
11	0.1	720	3.00	2.70		2	RIT1	C.170C>G p.(Ala57Gly)	Path.	
12	12.8	1886	7.66	5.66	1	2	PTPN11	c.1391G>C p.(Gly464Ala)	Path.	Deafness, scoliosis, mental retardation
13	17.4	160	2.75	−0.93	1	1	TNN13	c.484C>T p.(Arg162Trp)	Path.	
14	4.6	1476	3.10	3.06		2	BAG3	c.626C>T p.Pro209Leu	Path.	Muscle weakness, nocturnal hypoventilation
15	13.9	640	3.74	3.93	1	1	MYBPC3	c.2067+1G>A	Path.	Hearing impairment
16	14.8	791	7.86	7.43	1	1	MYBPC3	c.1433>Tp.(His510Asp)	VUS	
17	0.2	3315	5.28	5.37		4	PTPN11	c.1528C>G p.(His510Asp)	Path.	Deafness, developmental delay
18	0.3	441	3.87	3.96	1	1				
19	5.2	251	1.95	0.62		1	MYH7	c.2302G>A p.(Gly768Arg)	Path.	
20	3.2	52	3.35	3.40		1				
21	12.9		0.00	0.00	1	1				
22	11.0	403	9.33	9.11		1	MYBPC3	c.2441_2443delAGA p.Lys814del	Path.	
23	3.4		8.00	0.00		1	MYBPC3	c.2441_2443delAGA p.Lvs814del	Path.	
24	3.0	15	0.76	0.55		1				
25	3.5		6.15	6.31		1	MYBPC3	c.790dupG p.Asp264Glyfs*	Path.	

Table 1 (continued)

Patient	Age at diagnosis (years)	BNP (pg/ml)	IVS (d) *z* score	IVS (s) *z* score	LVOTO (l = present)	NYHA classification	Gene	Mutation	AMCG classification	Additional clinical features
26	3.3		−0.33	0.17		3	LMNA	c.1411C>T (p.Arg471Cys)	Path.	Muscle weakness, progeria-like appearance, asymmetric contractures
27	7.2	3	4.23	3.61		2				Muscle weakness
28	7.6	17	1.87	2.08		1	MYH6	c.2929-2A>C	Likely path.	
29	0	6149	4.76	4.58	1	1	RAF1	c.770C>T p.(Ser257Leu)	Path.	Deafness, profound muscular hypotonia
30	9.3	69	2.03	1.40		1	FXN	GAA-repeat expansion	Path.	Scoliosis, ataxia
31	10.4	38	2.32	2.45		1	FXN	GAA-repeat expansion	Path.	Scoliosis, ataxia
32	15.7		3.48	0.00		1				
33	0.0	214	3.92	4.35	1	2	RAF1	c.770C>T p.(Ser257Leu)	Path.	Short stature, unilateral ptosis, dysmorphic features
34	2.4	2369	5.27	2.99	1	1				
35	3.5		5.41	5.82		1				
36	7.6		1.86	1.27		1				
37	9.5	51	4.00	3.78		2	FXN	GAA-repeat expansion		Scoliosis, mild ataxia
38	4.2		4.22	4.48		1				Developmental delay, facial dysmorphia
39	5.7	1563	7.12	6.71		2	MYBPC3	c.1765C>A p. (Arg598Ser)	Path.	
40	0		1.63	1.45		1	MYH7	c.1357C>Tp. (Arg453Cys)	Path.	
41	5.2	15	0.34	−0.76		1	TNN13	c.422G>A p. (Arg141Gln)	Path.	
42	15.9		0.82	0.01		1	MYH7	C.48320T p.(Ala1611Val)	Path.	

Patients 5 and 18 died before extended genetical screening; patients 4, 24, 32 and 38 refuse genetical screening

BNP brain natriuretic peptide, *IVS* interventricular septum, *LVOTO* left-ventricular outflow tract obstruction

Table 2 Genetic finings in 36 patients with HCM in relation to age

	Age (years)			
	0 ≤ 1 years ($n=10$) 28%	1 ≤ 6 years ($n=7$) 19%	6–18 years ($n=19$) 53%	Total ($n=36$)
Cardiac sarcomere proteins	2	5	8	15 (42%)
RAS/MAPK signaling pathway disorder	4		1	5 (14%)
Pompe disease	4			4 (11%)
Friedreich's ataxia			3	3 (8%)
Others		2		2 (6%)
No mutation found			7	7 (19%)

made clear that these genetic findings could not be used for genetic counseling or therapeutic decisions.

In two patients, a thorough neurological examination disclosed dysmetria and an ataxic gait, while neurophysiological testing revealed abnormalities consistent with Friedreich's ataxia, which was confirmed by genetic testing. HCM in conjunction with muscular hypotonia and CK elevation led to the diagnosis of infantile Pompe disease in two subjects. Additional clinical symptoms (e.g., deafness, short stature, dysmorphic features) prompted the tentative diagnosis of a RAS/MAPK signaling pathway disorder in 3 subjects, while clinical features such as progeria-like appearance in one individual and unexplained nocturnal hypoventilation together with mild proximal myopathy in another, finally led to detection of a mutation in the LMNA and BAG3 gene, respectively.

The potential impact of such an interdisciplinary approach is exemplified by patient 12 (Table 1; Fig. 1). This boy of Arab descent was diagnosed with HCM at the age of 12. Additional clinical features included deafness, mild mental retardation, and short stature. Moreover, a progressive scoliosis evolved from the age of 10, and a detailed clinical examination showed three small lentigines. After discussing the patient's clinical features in the interdisciplinary round, the tentative diagnosis of a RAS/MAPK signaling pathway disorder, especially Noonan syndrome with multiple lentigines (NSML), was made. This was subsequently confirmed by demonstrating a typical mutation in the PTPN11 gene. On the basis of this test result, we started a therapy trial with everolimus on a compassionate use basis, which was terminated after 6 months due to progression of left-ventricular outflow tract obstruction and recurrent oral infections. Instead, a surgical resection of the left-ventricular outflow tract obstruction was performed. A histological analysis of the resected cardiac tissue showed substantial remodeling, eventually explaining why everolimus treatment had failed (Fig. 2).

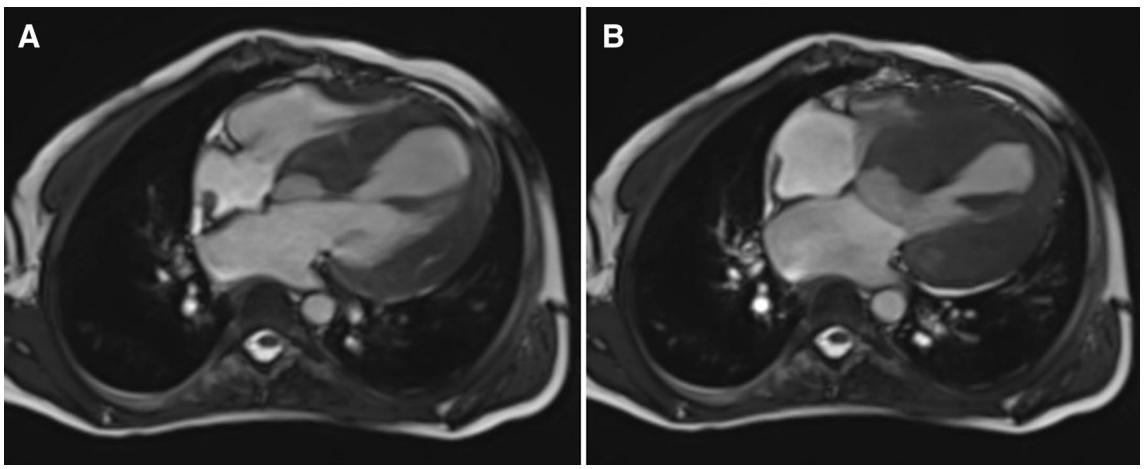

Fig. 1 The MRI of a 14 year old child with a hypertrophic cardiomyopathy caused by a Noonan syndrome with lentigines in **a** diastolic and **b** systolic four-chamber view is depicted

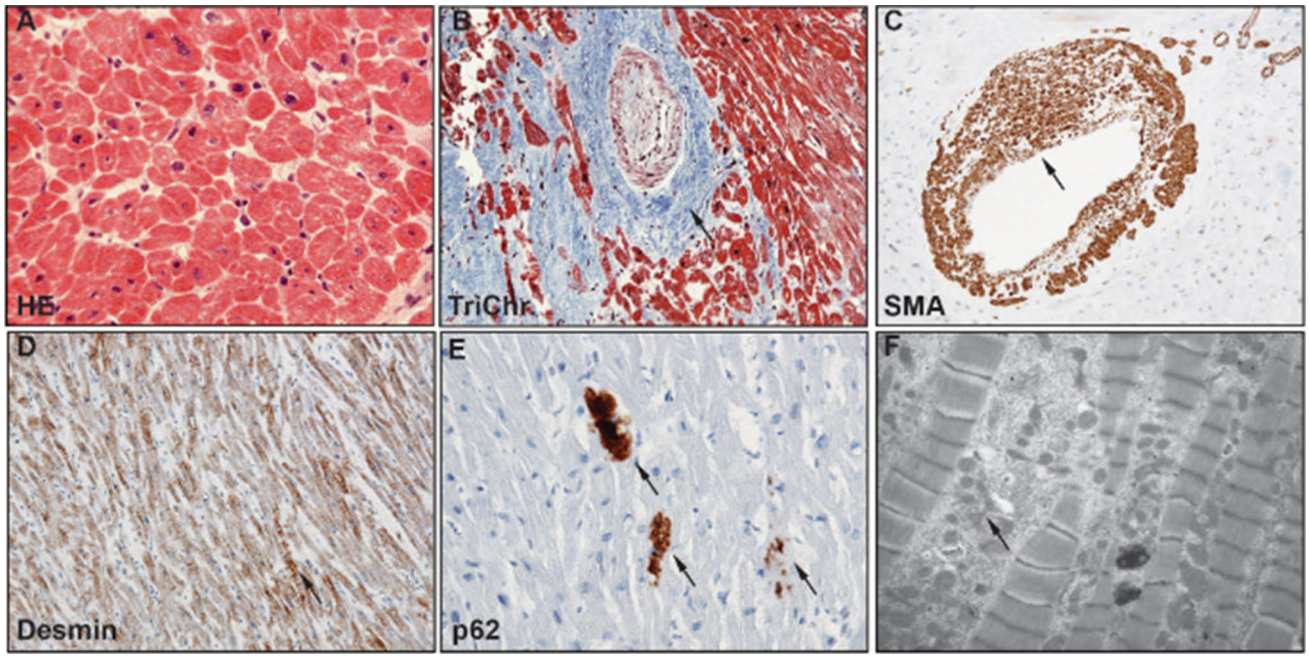

Fig. 2 Histological findings on a heart explant from the same child. **a** H&E stained cryosections show hypertrophic and atrophic cardiomyocytes and hyperchromatic nuclei. **b** Interstitial and perivascular fibrosis (blue) is shown by Azan-Mallory trichrome stain. **c** Immunohistochemistry with antibodies against smooth muscle actin (SMA) shows thickening of the endothelial cells (arrow). **d** Antibody against Desmin show myofiber disarray with granular deposits in some fibers (arrow). **e** In some cardiomyocytes autophagy is increased demonstrated by antibodies against p62. **f** Electron microscopy with myocardial disarray and focal accumulation of mitochondria (arrow) (**a** cryosection, **b–f** paraffin sections; Magnification: **b–d** ×200, **a, f** ×400, **g** ×4400)

Discussion

We investigated which genetic defects caused HCM in subjects attending the Pediatric Heart Center Giessen between 2000 and 2016. The major findings of this study were, that the genetic cause of HCM could be solved in about four-fifth of children, that about one-half of patients had mutations in genes causing multisystemic diseases, and that a multidisciplinary assessment enhanced the diagnostic yield substantially.

The National Heart, Lung and Blood Institute research group for HCM in the United States, stated that at least 50% of adult HCM cases can be traced to a specific genetic cause [6]. In line with this, sequencing of nine genes (including MYH7 and MYBPC3) in 197 French subjects with familial or sporadic HCM revealed a disease-causing mutation rate of 60%, with MYH7 and MYBPC3 accounting for 80–85% of cases with identified mutations [17]. Similarly, a UK study performing high-throughput sequencing of 41 cardiovascular genes in 223 unrelated patients with an average age of 46 years at diagnosis of HCM revealed genetic variants in 64% of patients (excluding sequence variants in the highly variably expressed titin gene) [12]. As in these adult studies, sarcomere gene mutations represented the greatest single category in our cohort (52%). Of note, HCM due to sarcomere protein defects were caused by mutations in four genes only (MYBPC3, MYH7, TNNI3 and MYH6). The rate of sarcomere protein mutations determined in the present investigation is also similar to the percentage of 54% reported by Morita et al., when testing 84 subjects with HCM manifesting before 15 years of age for mutations in 8 sarcomere and 2 non-sarcomere genes [15].

Compared to adults, information about the genetic basis of HCM manifesting in the pediatric age range is limited. Only two larger epidemiological studies investigated the etiology of HCM, but were not specifically focused on revealing the genetic basis [4, 16]. Nugent and the National Australian Childhood Cardiomyopathy Study Group reported the data of 80 children presenting with HCM until the age of 10, but did not give detailed information about the results of genetic testing [16]. By excluding subjects with progressive neuromuscular diseases and inborn errors of metabolism, a diagnosis of Noonan syndrome was made in 23 subjects (29%), while 1 patient each was affected by Costello, Beckwith–Wiedemann, and Fukuyama syndromes. 17 individuals (21%) had familial HCM, and 2 were found to have a myocardial respiratory chain enzyme deficiency. Collectively, the etiology could be elucidated in 58% of patients. Colan et al. [4] reported findings from the Pediatric Cardiomyopathy Register assessing data of 855 patients from Canada and

the US, who presented with HCM in the first 18 years of life. 74.2% of the patients were classified as idiopathic HCM, 8.7% had inborn errors of metabolism, 9% had malformation syndromes and 7.5% had neuromuscular disorders.

The findings of both studies are in principal agreement with the rates for neuromuscular disorders (14%), metabolic diseases (11%), and disorders of the RAS/MAPK signaling pathway (14%) determined in the present study. While Pompe disease was the predominant metabolic cause, Friedreich´s ataxia and Noonan syndrome accounted for most of the cases within the groups of neuromuscular disorders and disturbed RAS/MAPK signaling, respectively.

Previous studies related to HCM manifesting in children either screened for specific mutations only [15], did not assess genetic testing findings at all [1, 3, 4, 9, 16, 21, 22], or excluded certain diseases [3, 9, 22], thus leading to a substantial rate of idiopathic HCM cases or biased results. Our study design differed from that of these former investigations since we did not restrict our approach to specific genetic analyses. Instead we performed additional genetic testing after careful interdisciplinary re-evaluation, when targeted next-generation sequencing for sarcomere gene mutations was negative, with the specific aim to solve as much cases as possible.

Identifying the genetic defect in an individual with HCM can be important for estimation of prognosis [11], and genetic counseling and may also have implications for treatment. For some metabolic diseases and malformation syndromes, specific therapies have been approved within the last years, while in others drug trials are currently underway, or the results of animal studies give rise to hopes for treatment in the nearer future. For example, approval of enzyme replacement therapy in Pompe disease has substantially improved the outcome of infants with HCM due to acid alpha-glucosidase deficiency, while the effects of treatment with idebenone for patients with Friedreich's ataxia are studied [10]. In addition, improved understanding of the RAS/MAPK signaling cascade has identified new components causing cardiac diseases such as RIT1. Moreover, animal studies have revealed that specific mutations in PTPN11, associated with Noonan syndrome with multiple lentigines, result in HCM by activating the AKT/mTOR pathway. In mice, this form of HCM is responsive to treatment with rapamycin, allowing to discuss individualized medical trials on a compassionate use basis as performed in one subject of our cohort [7, 8].

Panels analyzing genes associated with HCM should also focus on multisystemic conditions when applied in infants and younger children. In retrospect, the commercially available panel used in this study seemed not very well-suited for our cohort since it was adapted from the experience made in the adult population. In addition, this panel included 28 genes, which is still a limited number. A larger panel including candidate genes such as taffazin could be meaningful. Moreover, whole exome or even genome sequencing should be considered in any child with an unequivocal diagnosis of HCM after negative panel diagnostics.

This study has important shortcomings, as it is a single center study and the sample size is rather small, thereby limiting generalization of the results.

In conclusion, the present study is the first analyzing comprehensively sarcomere and non-sarcomere mutations in a cohort of pediatric HCM patients. Somewhat unexpected, we were able to resolve the underlying mutation in almost 80% of patients. In line with others, sarcomere protein mutations were rarer than in the adult population, whereas mutations in genes causing multiystemic diseases were rather frequent. Because of the broad differential diagnosis in childhood, a multidisciplinary assessment is recommended for further outcome studies for patients with HCM.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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