Journal of Human Genetics (2018) 63:1273–1276
https://doi.org/10.1038/s10038-018-0509-9

BRIEF COMMUNICATION

Clinical and genetic backgrounds of hypertrophic cardiomyopathy with mid-ventricular obstruction

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Received: 17 June 2018 / Revised: 18 August 2018 / Accepted: 22 August 2018 / Published online: 11 September 2018

Abstract

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy. This study aimed to reveal the clinical and genetic backgrounds of the unique HCM with mid-ventricular obstruction (HCM-MVO) subtype. We identified 34 patients with HCM-MVO in our cohort, and about half (47%) of these patients experienced adverse events. We analyzed 67 cardiomyopathy-associated genes in the patients. In total, 44% of patients with HCM-MVO carried the cardiomyopathy-associated genetic variant (CAGV) in 14 genes. Only 21% of patients carried HCM-associated CAGVs in major sarcomere-encoding genes, while 18% of patients carried CAGVs in dilated cardiomyopathy/arrhythmogenic right ventricular cardiomyopathy-associated genes. CAGVs were more frequent in patients with asymmetric septal hypertrophy (ASH) than in those without ASH. These findings suggest that HCM-MVO is a high-risk group and may have different etiologies from typical HCM.

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy, diastolic dysfunction, and myofibrillar disarrays in the ventricle. HCM is a major cause of sudden cardiac death during young adolescence [1]. Several groups have reported that patients with the unique HCM with mid-ventricular obstruction (HCM-MVO) subtype have worse outcomes than patients with common type of HCM [2, 3]. However, genetic studies of HCM-MVO are lacking. Therefore, we investigated the clinical and genetic backgrounds of patients with HCM-MVO in Japan.

This study was approved by the ethics committees of local institutional review boards. All patients were diagnosed with HCM following ACCF/AHA guidelines by ultrasound cardiography (UCG) (EPIQ 7 G, Philips Healthcare, Andover, MA, USA); HCM-MVO was diagnosed by a mid-ventricular peak pressure gradient of ≥30 mmHg [1–3]. Left ventricular (LV) wall thickness and LV ejection fraction (LVEF) were measured by the modified-Simpson method. The clinical follow-up duration was 3 years.

Genomic DNA was purified from peripheral blood of patients with HCM-MVO and analyzed using the Ion Torrent PGM™ system (Thermo Fisher Scientific, Carlsbad, CA, USA) for variants in 67 known cardiomyopathy-associated genes associated with secondary cardiomyopathy (*ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CALR3, CAV3, CRYAB, CSRP3, DES, DOLK, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FHL2, FHOD3, FKTN, GAA, GATAD1, GLA, ILK, ISL1, JPH2, JUP, LAMA4, LAMP2, LDB3, LMNA, MTO1, MURC, MYBPC3, MYH6, MYH7,*

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Table 1 Clinical and genetic profiles of patients with HCM-MVO carrying cardiomyopathy-associated genetic variants (CAGVs)

a. Clinical background of HCM-MVO patients carrying CAGVs

Patient No.	Sex	Age at diagnosis	FH of HCM	ICD/ SD	NYHA	ASH	APH	Apical aneurysm	IVS-mid/ LVWT max	LVEF (%)	PG max (mmHg)
1	M	60	Y	I	I	Y	—	Y	20	63	36
2	M	65	—	—	I	Y	—	Y	19	61	44
3	F	59	Y	—	I	Y	—	—	18	71	34
4	F	52	—	D	III	Y	—	Y	22	55	36
5	M	74	Y	I	I	Y	—	Y	24	42	36
6	M	51	—	—	I	Y	—	—	16	65	41
7	M	74	—	—	II	Y	—	Y	18	63	34
8	M	45	Y	I	II	Y	—	Y	17	56	34
9	F	68	—	—	I	Y	—	Y	23	70	31
10	M	22	Y	I	I	Y	—	Y	17	72	44
11	M	84	—	—	II	—	Y	—	15	69	34
12	M	62	Y	—	I	Y	—	—	15	66	67
13	F	68	—	I	II	Y	—	—	23	74	41
14	F	79	Y	—	III	Y	—	—	18	55	31
15	F	50	Y	—	I	Y	—	—	16	79	38
HCM-MVO carried CAGV	40% (Female)	61 ± 16	53%	40%	[a]	93%	7%	53%	19 ± 3.0	64 ± 9.4	39 ± 8.9
Total HCM-MVO	41% (Female)	62 ± 13	35%	47%	[b]	67%	32%	56%	18 ± 2.9	63 ± 11	40 ± 15

b. CAGVs identified in patients with HCV-MVO

Patient No.	CAGV	TG (MAF)	ExAc (MAF)	HGVD (MAF)	ClinVar	ACMG
1	*DSP* Arg1537His	None	0.0033%	None	NA	LP
	JUP Arg540Cys	None	0.003%	None	NA	LP
2	*FHOD3* Arg516Gly	None	None	None	NA	LP
3	*GLA* Tyr184Asn	None	None	None	NA	LP
4	*GLA* Cys174Arg	None	None	None	NA	LP
5	*MYBPC3* Arg1073Pro	None	None	None	NA	LP
6	*MYBPC3* Arg1205Trp	None	None	None	Conflicting	LP
	MYPN Pro826Thr	0.020%	None	0.045%	NA	LP
7	*MYBPC3* Gly988Arg	None	0.0033%	None	NA	LP
8	*MYBPC3* Tyr1100 fs	None	None	None	LP	P
9	*MYH7* Arg870Cys	None	0.0008%	0.045%	LP	LP
10	*MYH7* Arg249Glu	None	None	None	P	P
11	*NEBL* Ala477Pro	None	0.0016%	None	NA	LP
12	*PRDM16* Arg232Cys	None	0.0034%	None	NA	LP
13	*PRKAG2* His500Tyr	None	None	None	NA	LP
14	*TMEM43* Ser193 Leu	None	None	None	NA	LP
	ILK Arg241Trp	None	0.001%	None	NA	LP
	NEBL Phe354Leu	None	None	None	NA	LP
15	*TNNT2* Phe122Ile	None	None	0.045%	P	LP
	TTN Glu4667*	None	None	None	NA	P

Patient numbers are consistent between tables a and b

HCM-MVO hypertrophic cardiomyopathy with mid-ventricular hypertrophy, *M* male, *F* female, *Y* yes, *FH* family history, *SD* sudden death, *ICD* implantable cardioverter defibrillator, *I* implanted ICD, *D* death, *NYHA* New York Heart Association classification, *ASH* asymmetric hypertrophy, *APH* apical hypertrophy, *IVS* interventricular septum, *LVWT max* maximum left ventricular wall thickness, *LVEF* left ventricular ejection fraction,

PG max maximum pressure gradient, *TG* 1000 genome project, *MAF* minor allele frequency, *ExAc* exome aggregation consortium, *HGVD* human genetic variation database, *ACMG* the American College of Medical Genetics and Genomics standards and guidelines, *NA* not applicable, *LP* likely pathogenic, *P* pathogenic

Genes (ENSP number) with CAGV: *DSP* Desmoplakin (ENSP00000369129), *JUP* Junction Plakoglobin (ENSP00000393931), *FHOD3* Formin Homology 2 Domain Containing 3 (ENSP00000257209), *GLA* α-Galactosidase (ENSP00000218516), *MYBPC3* Cardiac Myosin Binding Protein C (ENSP00000382193), *MYPN* Myopalladin (ENSP00000351790), *MYH7* Cardiac Myosin Heavy Chain (ENSP00000347507), *NEBL* Nebulette (ENSP00000366326), *PRDM16* PR Domain Containing 16 (ENSP00000426975), *TMEM43* Transmembrane Protein 43(ENSP00000303992), *ILK* Integrin Linked Kinase (ENSP00000299421), *TNNT2* Cardiac Troponin T(ENSP00000387874), *TTN* Titin (ENSP00000354117)

[a]I, 60%; II, 27 %; III, 13%; IV, 0%

[b]I, 62%; II,24%; III, 12%; IV, 0%

MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, OBSCN, PKP2, PLN, PRDM16, PRKAG2, PSEN1, PSEN2, RBM20, SCN5A, SDHA, SGCD, TAZ, TCAP, TGFB3, TIEG1, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, and *VCL*) [4]. Variants were filtered using a minor allele frequency threshold of less than 0.002 (0.2%) in the following variant databases: 1000 genomes project, exome aggregation consortium (ExAC), and the human genetic variation database, specific to the general Japanese population [4–7]. Filtered variants were confirmed by Sanger sequencing and in-silico analysis. Variants classified as "pathogenic" or "likely pathogenic" according to the American College of Medical Genetics and Genomics standards and guidelines were defined as cardiomyopathy-associated genetic variant (CAGV) in this study [4, 8]. Differences among patient groups were evaluated using the Student's *t*-test and Fisher's exact test implemented in JMP version 13.0 (SAS Institute Inc., Cary, NC, USA). A value of $p < 0.05$ was considered statistically significant.

We identified 34 patients with HCM-MVO in our cohort. About half (47%, 16/34) of the patients with HCM-MVO experienced adverse events; 41% (14/34) received ICD implantation, and 5.8 % (2/34) died within the 3-years of follow-up period. In UCG, 67% (23/34), 32% (11/34), and 56% (19/34) patients showed asymmetric septal hypertrophy (ASH), apical hypertrophy (APH), and LV aneurysm, respectively. LVEF was lower in patients with implanted ICD or those who died than in patients without ICD ($56 \pm 11\%$ vs $68 \pm 6.4\%$; $p = 0.0004$), and maximum LV wall thickness was greater for patients with implanted ICD or those who died than for patients without ICD (19 ± 3.4 mm vs 17 ± 2.1 mm; $p = 0.035$).

A total of 44% (15/34) patients with HCM-MVO carried CAGVs in 14 genes; of these, 67% (8/12) of patients had a family history of HCM and 32% (7/22) had no apparent family history of HCM (Table 1). In total, 20 CAGVs were detected; all variants had frequencies of less than 0.005% in the ExAc database (Table 1). Additionally, 32% (11/34), 8.8% (3/34), and 2.9% (1/34) of patients carried single, double, and triple CAGVs, respectively. Only 21% (7/34) of patients carried HCM-associated CAGVs in major sarcomeres-encoding genes (5.9% (2/34) in *MYH7*, 12% (4/34) in *MYBPC3*, and 2.9% (1/34) in *TNNT2*), while numerous studies have revealed that approximately half of the patients with common types of HCM carried CAGVs in major sarcomeres-encoding genes (Table 1) [1, 9, 10]. Moreover, 5.9% (2/34) of patients with HCM-MVO carried CAGVs in *GLA*, which encodes α-galactosidase; both exhibited low α-galactosidase activity. One patient with *GLA* Tyr184Asn began treatment with α-galactosidase and another patient with *GLA* Cys174Arg died due to heart failure before starting therapy. Detailed information about patients with HCM, carrying CAGVs in *GLA* will be reported in a subsequent paper. Additionally, 18% (6/34) of patients carried CAGVs in dilated cardiomyopathy (DCM)/arrhythmogenic right ventricular cardiomyopathy (ARVC)-associated genes, i.e., *DSP*, *JUP*, *NEBL*, *FHOD3*, *MYPN*, *PRDM16, TMEM43*, *ILK*, and truncation of *TTN*, but did not manifest low LVEF as in DCM (Table 1). CAGVs were more frequent in patients with ASH (13/23) than in those without ASH (1/11) ($p = 0.005$). CAGVs were less frequent in patients with APH than in those without APH (9% vs 57%, $p = 0.005$); therefore, genes other than those examined in this study may be associated with APH.

In summary, patients with HCM-MVO show a high rate of adverse events, due to which HCM-MVO is considered a high-risk group of HCM. The CAGVs in patients with HCM-MVO may tend to be found less frequently in sarcomere-encoding genes and more frequently in DCM/ARVC- associated genes, and these results differ from those reported by accumulated genetic studies of patients with typical HCM [1, 9, 10]. These findings suggest that HCM-MVO may have a different etiology from that of typical HCM and may be more arrhythmogenic. In addition, CAGVs were more frequent in HCM-MVO patients with ASH than in those without ASH, which may have developed from apical hypertrophy. This finding suggests that HCM-MVO with ASH and that without ASH also have different etiologies. To characterize each variant more accurately and explore the mechanism of HCM-MVO development, genetic studies on a larger number of patients, comparing CAGV of HCM-MVO to that of typical HCM, and in vitro or in vivo functional analysis for each variant are required.

Acknowledgements We would like to thank Yukiko Ueda and Chinami Sonobe for their excellent technical assistance with respect to NGS. We also thank Akiko Ito, Reiko Makitani-Ishida, and Toyo Fukui for technical assistance with respect to Sanger sequencing. This work was supported by the Japan Society for the Promotion of Science KAKENHI grant number 258606625 (N.I.), 26460407 (T.H.), 17K08684 (T.H.), 15K15095 (A.K.), 16H05296 (A.K.), a grant from The Institute of Seizon and Life Science (T.H), and Nanken-Kyoten, Tokyo Medical and Dental University (TMDU).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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