JACC: ADVANCES VOL. 4, NO. 2, 2025

BRIEF REPORT

Longitudinal Evaluation of Genetic Hypertrophic Cardiomyopathy Penetrance and Transition to Disease in an Academic Biobank

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Hypertrophic cardiomyopathy (HCM) is a myocardial pathology characterized by left ventricular (LV) hypertrophy disproportionate to loading conditions. The increasing use of genomic sequencing has allowed the identification of individuals carrying variants predicted to be pathogenic (P) or likely pathogenic (LP) of HCM. Not all individuals with HCM-associated P/LP alleles exhibit clinical manifestations at the time of genetic testing.[1-3] However, whether such individuals carrying P/LP HCM variants discovered in a genome-first context subsequently develop progressive endophenotypes indicative of HCM remains unknown. Increased use of next-generation sequencing in asymptomatic populations merits a need to understand both screening and surveillance. Here, we leveraged the Mass General Brigham Biobank (MGBB), a health care-associated genotyped biobank with serial clinically performed TTE imaging to determine phenotype conversion rates of adults carrying HCM P/LP variants identified via biobank testing.

What is the clinical question being addressed?
Whether adults carrying P/LP HCM variants discovered in a genome-first context have progressive HCM endophenotypes remains unknown.

What is the main finding?
Longitudinal transthoracic echocardiography imaging of genotyped individuals in the MGB Biobank revealed 0% phenotype conversion rate in phenotype-negative carriers of P/LP HCM variants.

MGBB consists of 36,417 consenting participants with mean age 55 ± 17 years and 54% (19,721/36,417) female sex, for whom Illumina Infinium Multi-Ethnic Genotyping array data are linked to clinical data. A Sanger verification step was performed on samples that yielded P/LP variants prior to genotype return of results.[4] The primary images of the earliest—and for those with multiple echocardiograms also the latest—TTE were unblinded and reviewed for posterior wall (PW), interventricular septum (IVS), apical thickness, and overall LV morphology. Phenotype-positive status was defined by a wall thickness of at least 13 mm per 2024 American Heart Association/American Cardiology College/American Medicine Society for Sports Medicine/Heart Rhythm Society/Pediatric and Congenital Electrophysiology Society/Society for Cardiovascular Magnetic Resonance guidelines. Electrocardiograms were reviewed for electrocardiographic

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101520

ABBREVIATIONS AND ACRONYMS

HCM = hypertrophic cardiomyopathy

IVS = interventricular septum

LV = left ventricle

MGBB = Mass General Brigham Biobank

P/LP = pathogenic/likely pathogenic

PW = posterior wall

SD = standard deviation

features of HCM, including left ventricular hypertrophy, apical T-wave inversion, and anterolateral Q waves.

HCM variants deemed P/LP per American College of Medical Genetics and Genomics criteria were identified in 0.1% (42/36,417) participants with mean age 50.0 ± 16.6 years, an estimated prevalence comparable to that of other genotyped biobanks with similar age ranges.[1] Comparable to prior reports, the most common HCM variants identified in the MGBB were in myosin-binding protein c (*MYBPC3*) (0.05%, 19/36,417) and myosin heavy chain 7 (*MYH7*) (0.04%, 16/36,417), while a minority possessed mutations in cardiac troponin T (*TNNT2*) (0.003%, 1/36,417), *TNNI3* (0.008%, 3/36,417), and myosin light chain 3 (*MYL3*) (0.008%, 3/36,417). Among the 42 genotype-positive individuals in the MGBB, 55% (23/42) were phenotype-positive by TTE with mean posterior wall thickness and IVS of 11 ± 3 mm and 17 ± 5 mm, respectively (Table 1). Whereas, 45% (19/42) were phenotype-negative with mean PWT and IVS of 9 ± 2 mm and 9 ± 2 mm. There were no patients with echocardiographic features or EKG findings consistent with apical HCM or subclinical HCM, respectively.

TABLE 1 TTE Measurements of Genotype-Positive Patients With HCM

	Phenotype Negative	Phenotype Positive
MGBB cohort characteristics of 42 genotyped individuals with HCM variant		
Total population, N	19	23
Female	6 (31)	7 (30)
Mean age, y	52.9 (17)	47.5 (16)
Mean PWT, mm	9 (2)	11 (3)
Mean IVS, mm	9 (2)	17 (5)
EKG abnormalities	0 (0)	12 (52)
MGBB cohort characteristics of 26 genotyped individuals with HCM variant and serial TTE measurements		
Total population, N	10	16
Female	9 (90)	6 (38)
Mean age, y	45.7 (23)	50.6 (16)
Median follow-up duration, y	10 (7-15)	8 (2-13)
Median number of serial TTE	3 (2-4)	5 (4-9)
MYBPC3	5 (50)	5 (31)
MYH7	2 (20)	9 (56)
TNNI3	2 (20)	0
TNNT2	0	1 (6)
MYL3	1 (10)	1 (6)
TTE measurements of genotype-positive individuals with serial TTE measurements		
Mean initial LVEF, %	65 (17)	67 (11)
Mean initial PWT, mm	8 (2)	11 (2)
Mean maximal PWT, mm	8 (2)	13 (4)
Mean percent increase PWT, (95% CI)[a]	4 (−16 to 24)	25 (5-44)
Mean initial IVS, mm	9 (2)	18 (5)
Mean maximal IVS, mm	10 (1)	22 (5)
Percent increase IVS, (95% CI)[a]	13 (−4 to 30)	26 (3-50)
Mean initial IVS: PWT	1.1 (0.1)	1.7 (0.5)
Mean maximal IVS: PWT	1.2 (0.2)	1.8 (0.6)
Mean percent increase IVS:PWT, (95% CI)[a]	11 (−2 to 25)	7 (−16 to 30)
Mean of maximal IVS by genotype		
MYBPC3, mm	9 (2)	32 (7)
MYH7, mm	11 (2)	30 (4)
TNNI3, mm	11 (1)	NA
TNNT2, mm	NA	22 (NA)
MYL3, mm	7 (1)	17 (NA)

Values are n (%) or median (IQR) unless otherwise indicated. [a]95% CIs were derived from paired *t*-tests given the small sample size.

HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; LVEF = left ventricular ejection fraction; MGBB = Mass General Brigham Biobank.

To evaluate the phenotype conversion rate of adults carrying P/LP variants of HCM, the MGBB was subgrouped for individuals who carried P/LP HCM variants and underwent at least 2 serial TTE studies, which included 26 genotype-positive individuals. At the time of initial TTE, 62% (16/26) were phenotype positive, with mean age of 50.6 ± 16 years. This group was followed for median follow-up duration of 8 (IQR: 2-13) years, including median number of 5 (IQR: 4-19) TTE studies. The remaining 38% (10/26) of patients were phenotype-negative at the time of initial TTE, with mean age 45.7 ± 23 years. This group was followed for median follow-up duration of 10 (IQR: 7-15) years, including median number of 3 (IQR: 2-4) TTE studies.

At the time of initial TTE, the phenotype-positive group had a mean PWT and IVS of 11 ± 2 mm and 18 ± 5 mm, respectively (Table 1). The phenotype-negative group had a mean PWT and IVS of 8 ± 2 mm and 9 ± 2 mm, respectively. IVS or PWT in genotype-positive, phenotype-negative individuals did not significantly increase over time, indicating a 0% phenotype conversion rate over a median 10 [IQR: 7-15] years of follow-up (Table 1). EKG and TTE images were negative for subclinical or apical variants of HCM in this population. In contrast, individuals who were phenotype-positive at the initial TTE exhibited a distinct pattern of progressively thickening PW (25% increase, 95% CI: 5-44) and IVS (26% increase, 95% CI: 3-50) over median follow-up of 8 [IQR: 2-13] years. Though there is an enrichment of females in the phenotype-negative group (90%, 9/10) compared to phenotype-positive group (38%, 6/16), IVS and PWT continued to thicken only among phenotype-positive patients, when adjusted by gender.

Taken together, the MGBB allows for the evaluation of primary TTE images serially obtained in genotyped individuals. Our study suggests that phenotype-negative adults with newly detected

P/LP HCM variants may remain phenotype-negative if an initial TTE shows normal PWT or IVS thickness, while those who are phenotype-positive may continue to manifest additional LV hypertrophy. Limitations include a small sample size inherent to the scarcity of Mendelian alleles in selected populations. Furthermore, given that approximately half of genotype-negative participants lacked serial TTE, there is a possibility of a selection bias. Other limitations include the differences in the number of TTEs performed in each group, which may affect estimated differences in maximal wall thickness. Future investigation into the phenotype conversion rate in adults with increased sample sizes and longer follow-up studies, and modifying factors, may provide deeper insights into the natural progression of the disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Zawatsky has received personal fees from Color Genomics to Chair the NIH All of Us Genetic Counseling Resource Advisory and Advocacy Board, Atria, Harvard Catalyst. Dr Fifer has received research grants from Bristol Myers Squibb and Novartis; and has received personal fees from Viz.ai, Bristol Myers Squibb, Cytokinetics, and Edgewise. Dr Tower-Rader has received research grants from Bristol Myers Squibb and Cytokinetics. Dr Green has received personal fees from Allelica, Atria, Fabric, Genomic Life, and Juniper Genomics; and is co-founder of Genome Medical and Nurture Genomics. Dr Natarajan has received research grants from Allelica, Amgen, Apple, Boston Scientific, Genentech/Roche, and Novartis; personal fees from Allelica, Apple, AstraZeneca, Blackstone Life Sciences, Creative Education Concepts, CRISPR Therapeutics, Eli Lilly & Co, Foresite Labs, Genentech/Roche, GV, HeartFlow, Magnet Biomedicine, Merck, and Novartis; scientific advisory board membership of Esperion Therapeutics, Preciseli, TenSixteen Bio, and Tourmaline Bio; scientific co-founder of TenSixteen Bio; holds equity in MyOme, Preciseli, and TenSixteen Bio; and spousal employment at Vertex Pharmaceuticals, all unrelated to the present work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS cardiovascular disease, genetics, hypertrophic cardiomyopathy, penetrance