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EDITORIAL COMMENT

Variable Penetrance in Hypertrophic Cardiomyopathy

In Search of the Holy Grail*

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Hypertrophic cardiomyopathy (HCM) is an inherited primary myocardial disorder that most commonly leads to isolated left ventricular hypertrophy (1). HCM is a common disorder occurring in at least 1 in 500 people (2). Patients with HCM display significant clinical heterogeneity that ranges from no symptoms and normal life expectancy to premature morbidity and mortality related to heart failure, life-threatening arrhythmias, and sudden cardiac death (1,3). Studies over the last 30 years have identified HCM as predominantly an autosomal dominant disorder caused by disease-causing variants in genes encoding the sarcomere proteins critical for contractile function (4). The 2 most common disease genes implicated are the *MYBPC3* and *MYH7* genes. Disease-causing variants in these 2 genes account for 70% to 80% of all genotype-positive HCM patients (5). Although the genetic architecture of HCM has been well established as a "disease of the sarcomere," how a variant in a sarcomere gene leads to such a diverse and complex clinical phenotype presenting at different ages, even within families, remains less well understood. Furthermore, with the increased application of cascade screening and presymptomatic genetic testing, a growing group of "variant carriers" has emerged for whom guidelines regarding counseling and clinical management remain unclear.

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In this issue of the *Journal*, Lorenzini et al. (6) report on the incidence of a new HCM diagnosis and major adverse events in 285 asymptomatic, phenotype-negative individuals from 156 families who carried likely pathogenic or pathogenic variants in sarcomere genes, followed-up for a median of 8 years. In a multivariable model adjusted for age and stratified for cardiac magnetic resonance (CMR) imaging, the independent predictors of HCM development were male sex (hazard ratio [HR]: 2.91; 95% confidence interval [CI]: 1.82 to 4.65) and abnormal electrocardiogram (ECG) (HR: 4.02; 95% CI: 2.51 to 6.44), while *TNNI3* pathogenic variant carriers had the lowest risk (HR: 0.19; 95% CI: 0.07 to 0.55 compared with *MYBPC3* carriers). The main conclusion of the study was that approximately 50% of those who carry likely pathogenic or pathogenic variants in sarcomere genes develop HCM over 15 years of follow-up and become prone to disease complications. Specifically, male sex and an abnormal ECG were associated with a higher risk of developing HCM, and CMR imaging was found to be beneficial in the identification of new HCM diagnoses.

This retrospective study provides valuable clinical and genetic data to clarify the important clinical challenge of understanding disease penetrance in at-risk individuals who carry likely pathogenic or pathogenic sarcomere variants in HCM disease genes but who are yet to develop clinical disease, namely left

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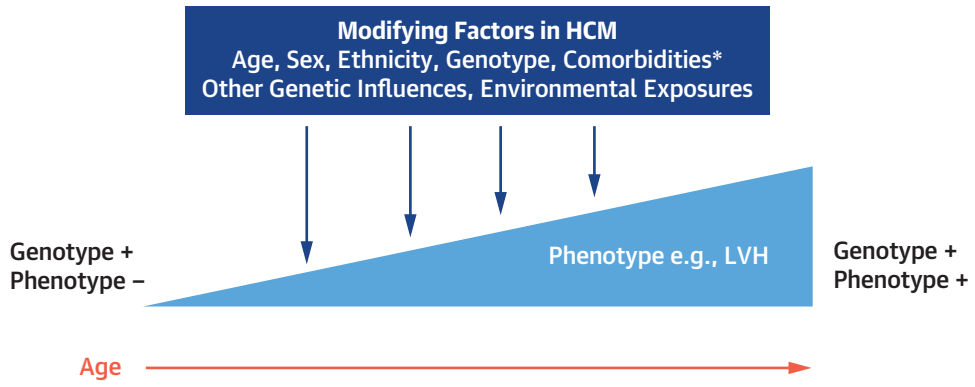
FIGURE 1 Factors That May Influence Penetrance in HCM Patients



*Comorbidities include hypertension, obesity, diabetes, and obstructive sleep apnea. + = positive; – = negative; HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy.

ventricular hypertrophy. This is highlighted by the widely variable phenotype development of HCM observed in clinical practice where some at-risk individuals who carry likely pathogenic or pathogenic variants never develop clinical HCM (nonpenetrant), some develop HCM very early in life as children (fully penetrant), while others may or may not develop clinical HCM during their adult years (variable penetrance). Understanding the natural history of these gene variant carriers of HCM is essential as it informs important clinical decisions related to frequency of clinical screening at different age groups, and the consideration of screening tests beyond an ECG and 2-dimensional echocardiogram.

The current study builds on data previously reported in smaller HCM cohorts (6–8). The power of the current larger dataset has enabled key factors to be identified as predictors of HCM penetrance, including male sex, an abnormal ECG, and genetic subtype. This provides more clinical tools to predict which sarcomere gene variant carriers are more likely to develop clinical HCM. A further important finding in the current study was the observation that disease expression occurred even in children younger than 10 years. These findings, coupled with a recent study that reported one-third of 524 children who underwent screening for HCM had clinical HCM (9), support the notion that clinical screening for HCM should perhaps commence at an earlier age than is currently recommended (10), taking into account the potential benefits and harms of screening in children (11).

A holy grail in the HCM field relates to why there is such variable penetrance in patients. Why do some individuals who carry likely pathogenic or pathogenic variants in sarcomere genes never develop clinical disease and are asymptomatic throughout life, whereas others develop clinical disease early in life, with severe left ventricular hypertrophy, and clinical outcomes that include life-threatening arrhythmias, heart failure, need for transplantation, and sudden cardiac death? The current study, combined with studies by research groups worldwide over 3 decades, suggest that penetrance in HCM is likely determined by a number of other environmental and genetic influences, in addition to the primary disease-causing sarcomere variant (**Figure 1**). These contributing factors include sex differences, background ethnicity, presence of comorbidities such as hypertension and obesity, the primary disease-causing genotype, and secondary genetic factors that may confound or modify the primary disease-causing sarcomere variant, leading potentially to both prevention and exacerbation of the clinical phenotype. In the current study, male sex and genotype (*TNNI3* vs. *MYBPC* gene variants) were 2 of the predictors of development of HCM, and consistent with previous studies suggesting both sex and genotype influences (9,12–14).

What are the implications of the current study for the clinician looking after HCM patients? First and foremost, this study reminds the clinician that HCM has a wide clinical spectrum with variable penetrance, meaning that disease can develop at any age from early childhood to late adulthood. Second, it demonstrates that the humble ECG and 2-dimensional echocardiogram remain the foundational screening tools in patients at risk of HCM. However, newer additional approaches such as CMR imaging are improving both diagnostic and prognostic

capacity by providing more detailed phenotype assessment and earlier detection of changes in HCM (15). Finally, this study reinforces the importance of genetic testing in HCM, both in the identification of the disease-causing variant in the individual, and in cascade genetic testing in at-risk family members. Future studies to elucidate the factors influencing penetrance in HCM will benefit from multicenter, collaborative, and prospective efforts, including both established and new HCM registries in both sex-balanced and ethnically-diverse populations. Although big data is important, the power of studying individual families remains a cornerstone of HCM research, with the ultimate goal to improve the care of individual patients and their families with HCM.

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