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EDITORIAL COMMENT

# Why Should Cardiologists Consider Genetic Testing for Hypertrophic Cardiomyopathy?*

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Although it has been more than a decade since the official announcement of the complete sequencing of the human genome, the impact of this monumental achievement on clinical practice has so far fallen short of expectations. Many thought that medicine in the "post-genome era" would quickly develop into highly personalized care, with targeted therapies based on individual mutations. Impatient critics have suggested that the cost and effort spent on human genome sequencing were unnecessary or unwarranted. But as we all know, changes in medical practice typically take a long time. Its ultimate success relies not only on improved diagnosis but also on treatments for genetically predisposed people to prevent disease.

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Toward that goal, in this issue of *JACC: Heart Failure*, Ho et al. (1) report results of a pioneering study that was focused on prevention of hypertrophic cardiomyopathy (HCM) among individuals with a sarcomere gene mutation. Thirty-nine participants 5 to 39 years of age were randomized on the basis of a pathogenic (or likely pathogenic) mutation, family history of HCM, and normal left ventricular (LV) wall thickness by echocardiography. Treatment was allocated 1:1 in a double-blinded fashion, with 18 receiving diltiazem, 20 receiving placebo, and 1 dropping out before treatment. The diltiazem dosing was substantial, with target dose of 360 mg/day for adults or 5 mg/kg/day for children. Although there was no difference in the low number who were diagnosed with overt HCM (2 in each group, or 10% overall) during a median follow-up of 25 months, diltiazem treatment was associated with improvement in certain subdiagnostic manifestations, such as change in LV wall thickness and left ventricular end-diastolic diameter (LVEDD). Somewhat surprisingly, blood pressures were not significantly different in the 2 cohorts. The study included a commendable range of 25 different mutations among the top 3 genes in which mutations cause HCM: *MYH7*, *MYBPC3*, and *TNNT2*. Intriguingly, the results for the subgroup with *MYBPC3* mutations were much more remarkable, with improvements in LV wall thickness and E/E′ by echocardiogram, LV mass by cardiac magnetic resonance imaging (MRI), and serum troponin I levels among this cohort treated with diltiazem. None of the participants who developed HCM during this study had *MYBPC3* mutations. The investigators must have been disappointed by the high number of people who declined participation. Among 103 individuals who were screened, 48 declined, "primarily from concerns about taking a daily medication or keeping study visits." This stands in stark contrast to studies of advanced heart failure, when those who are affected by the condition have far greater motivation to identify new treatments. Although this raises questions about the potential for larger multicenter trials to meet anticipated enrollment for prevention of HCM, it may simply reflect the small number of centers where this trial was performed, compared with larger multicenter efforts like the National Institutes of Health–funded VANISH trial (Valsartan for Attenuating Disease Evolution In Early Sarcomeric HCM; NCT01912534).

Should you start treating people with a sarcomere mutation and without pathologic LV hypertrophy with diltiazem to prevent development of HCM? As the

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authors recommend, "This novel strategy merits further exploration." The clinical trial was largely based on the success of this approach in cells and mice with alpha-myosin heavy chain mutation p.Arg403-Gln (2,3). Diltiazem treatment reduced hypertrophy and fibrosis in mutant mice and limited the hypertrophic response to other medications disrupting the normal calcium homeostasis. Dysregulation of calcium has been studied extensively in HCM, mediating fibrosis, diastolic dysfunction, and arrhythmia (4,5). A more direct association between myosin binding protein C (MyBP-C) deficiency and calcium sensitivity was shown with extraction studies, wherein an antibody was used to selectively remove MyBP-C from skinned rat cardiac trabeculae, and its loss led to a reversible increase in calcium sensitivity (6).

What about other treatments to prevent HCM? Investigating myocardial fibrosis in murine models of HCM, Teekakirikul et al. (7) showed increased expression of several TGF-β-responsive genes, including periostin. Subsequent studies with periostin-null mice helped these investigators conclude that periostin contributed to, but was not essential for, pathologic remodeling in HCM (7). Moving upstream in the pathogenesis, therapies targeting TGF-β next demonstrated remarkable efficacy in reducing cardiac fibrosis and nonmyocyte proliferation in the murine models of HCM. This included selective angiotensin II type 1 receptor blockade, which had previously been shown to be beneficial in a murine model of Marfan syndrome (8). Accordingly, the VANISH trial seeks to enroll 300 people with either preclinical HCM (LV wall thickness <12 mm in subjects ≥18 years of age or *Z* score <3 in those <18 years of age) or early overt HCM (LV wall thickness 12 to 20 mm in subjects ≥18 years of age or *Z* score ≥3 and <10 in those <18 years of age) to receive valsartan or placebo, with a primary outcome measure that involves a composite assessment of myocardial injury, hemodynamic stress, collagen metabolism, functional capacity, myocardial fibrosis, cardiac morphology, and cardiac function, combined into a single composite score. Other novel strategies targeting fibrosis may also be warranted, such as microRNAs and antisense oligonucleotides, as the molecular pathogenesis is ironed out in greater detail (9–11).

Of course, any approach for prevention of HCM requires pre-symptomatic genetic data in those who are at risk. This begins with identification of a family member with a clear diagnosis of HCM and clinical genetic testing (12). HCM programs throughout the world are including clinical sarcomere gene sequencing for this condition (13–15). Improvements in technology are rapidly lowering costs and expanding the number of genes in which analysis is routinely performed. Although early approaches often included only the top 3 to 5 genes in which mutations cause HCM, it is now arguably more efficient to include many more genes with next-generation DNA sequencing. Even more comprehensive approaches, such as whole exome or whole genome sequencing, will inevitably become routine in clinical practice for evaluation and management of inherited heart diseases in the near future (16). If needed, additional impetus for genetic testing can be found in legal cases in which courts have determined that our responsibility as healthcare providers extends beyond our patients to their relatives who are at risk (17).

With the increased clinical use of genotyping for cardiomyopathy, discovery of a therapy to prevent HCM would be welcomed by many health care providers and families who have watched this condition develop in multiple generations. As our understanding of the pathogenesis of HCM and other forms of cardiomyopathy continues to improve, it is easy to envision a time in the near future when these conditions are readily prevented or halted in their early stages.

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