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What Is the True Prevalence of Hypertrophic Cardiomyopathy?

In a recent paper by Semsarian et al. (1), several arguments are presented indicating that the prevalence of clinically expressed and hypertrophic cardiomyopathy (HCM) gene carriers has been greatly underestimated and could be as high as 1:200. This updated frequency estimate was primarily on the basis of a genetic analysis, published in 2012, that demonstrated 22 of 3,600 participants from the Framingham Heart Study and Jackson Heart Study cohorts had likely pathogenic or pathogenic sarcomeric gene variants (2). Although Semsarian et al. (1) stated that the variants were classified "using stringent criteria for pathogenicity," it is important to note that since 2012, there have been significant advancements in the tools to aid in variant classification (i.e., determining whether a variant is benign or pathogenic).

Technological advances have allowed us to more comprehensively and efficiently interrogate human genomes, and there are a number of large-scale efforts, such as the Exome Sequencing Project and Exome Aggregation Consortium, which have been publishing genomic data and variant frequencies from very large populations stratified by ethnicity. These large-scale efforts are important for variant classification because they provide population minor allele frequencies that, when used in concert with disease prevalence estimates, may push a variant into a benign or pathogenic category. Furthermore, databases such as ClinVar (3) and Human Genome Mutation Database make it easier for us to access variant classifications and publications by different clinical laboratories and groups. Variant data, from even just a few short years ago, should be reviewed through the lens of these new resources, and revisited accordingly, in this rapidly changing landscape.

As such, we took a closer look at the 22 variants classified as pathogenic or likely pathogenic by Bick et al. (2). The vast majority (20 of 22) of these variants were missense variants, which tend to be less straightforward to classify. Interestingly, only 4 of the 22 individuals actually expressed HCM (but were not specified by Bick et al. [2]). Utilizing our criteria for variant classification, which is largely on the basis of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology 2015 guidelines for variant interpretation (4) and utilizes databases and resources listed in the preceding text, only 6 of these variants could be confidently classified as likely pathogenic or pathogenic (i.e., 6 of 3,600, or approximately 1:600 HCM gene carrier frequency). In viewing ClinVar data, we observed that the Harvard Laboratory for Molecular Medicine (whom participated in the original Bick et al. [2] variant classification) currently classifies 12 of the 22 variants as variants of uncertain significance (equating to an HCM gene carrier frequency of 1:360).

Assessment of these 22 variants illustrates the somewhat subjective and rapidly evolving nature of genetic variant classification. After applying contemporary variant classification strategies to the 2012 data, the resultant data would not support a frequency as high as 1:200. Rather, it would seem to continue to support the 1:500 frequency of the disease more prevalently referenced in the published data. This frequency would take into account reduced penetrance (i.e., gene-positive, phenotype-negative cases), as well as HCM cases with nongenetic causes. With that said, these numbers will likely continue to change as our variant interpretation strategies continue to evolve. More standardized variant classification criteria would be helpful and improvements in that area have been made (3,4). However, the complexities of variant classification will likely continue to leave this field somewhat in flux, and the example with HCM presented here is likely just the tip of the iceberg.

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REPLY: What Is the True Prevalence of Hypertrophic Cardiomyopathy?

We thank Dr. Baudhuin and colleagues for their letter regarding our recent article (1). They raise the very important and topical issue of DNA variant classification in determining whether a genetic finding is pathogenic, benign, or a variant of uncertain significance (VUS). As Dr. Baudhuin and colleagues would be aware, major international initiatives are being established to develop robust and reliable classification criteria to determine the pathogenicity of DNA variants in hypertrophic cardiomyopathy (HCM), and indeed all other cardiovascular genetic diseases. Such classification systems and variant interpretation need to take into account rapidly evolving human genetic databases such as the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, Exome Variant Server (ESV), and most recently, the Genomics England 100,000 Genomes Project, as well as in silico tools (such as polyphen2 and SIFT), functional data, and cosegregation studies in families.

Significantly, the final outcome of the genetic evaluation is "probabilistic," that is, it is not a "yes/no" answer but rather a probability that the variant identified causes disease on the basis of the available supporting evidence (2,3). Dr. Baudhuin and colleagues correctly point out that over time, variant classifications can change due to new information, and this can change the classification from pathogenic to VUS or benign, and alternatively from VUS to pathogenic. We agree that this is a product of the rapid escalation of available genetic information due to newer, faster, and cheaper sequencing technologies, and highlights the importance of periodic re-evaluation of all variants. In HCM, we have previously reported that reclassification is required in up to 10% of families with HCM (4). Furthermore, the issues surrounding variant classification highlight the urgent need to have organized collaborative international efforts to curate all human disease genes and to develop classification systems directly relevant to cardiovascular disease. The recently published American College of Medical Genetics and Genomics guidelines are an important first step in this process, but need significant adaptation and modification for such guidelines to be reliable and accurate in the specific interpretation of variants relevant to cardiovascular disease. To this end, the recently developed National Institutes of Health-funded Clinical Genome Resource (ClinGen) initiative provides the hope of improving genomic interpretation by a coordinated international effort from both clinical and research communities, with the key goals to share data, build knowledge, develop and refine variant classification, and improve care.

Importantly, the revised estimated prevalence of HCM of up to 1 in 200 people is on the basis of several factors in addition to the rate of pathogenic mutations in what are known as highly intolerant sarcomere genes. Advanced imaging techniques with high-resolution cardiovascular magnetic resonance provide more reliable diagnosis by identifying left ventricular hypertrophy not appreciated with echocardiography, expanded recognition of the genotype-positive, phenotype-negative subset, while more comprehensive family-based clinical and genetic surveillance and higher clinical index of suspicion is resulting in more asymptomatic patients being identified with HCM (Central Illustration in Semsarian et al. [1]). Taking together all of these considerations, HCM appears more prevalent than current estimates, promoting greater visibility for the disease, enhancing diagnosis and consideration of contemporary treatment options (5), and ultimately improving care and outcomes in patients and families with HCM worldwide.

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