Letter by Iascone et al Regarding Article, “Population-Based Variation in Cardiomyopathy Genes”

To the Editor:

We read with interest the recent article by Golbus et al in Circulation: Cardiovascular Genetics in which they gained further insights into variants of 3 sarcomere genes associated with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy: MYH7 (cardiac β-myosin heavy chain), MYBPC3 (cardiac myosin-binding protein C), and TTN (titin). They queried the 1000 Genomes Project (1KGP) database to collect protein-altering variations and identified known and predicted pathogenic variation at a higher frequency than what would be expected based on the known prevalence of cardiomyopathies. In the abstract, the authors conclude that this higher frequency of predicted pathogenic protein-altering variations suggests that many of these variants may be insufficient to cause disease on their own but may act as phenotype modifiers and that broad-based genetic testing should be used to characterize HCM and patients with dilated cardiomyopathy. As recognized by the authors, we would further underline that 1KGP represents a fundamental window on genetic variations in humans, but the absence of phenotypic information, functional validation, and the low accuracy of data (90% accuracy at heterozygous sites for novel and rare variants) suggest that the 1KGP data have to be cautiously used, especially for variants with a potential clinical impact.

Furthermore, we would like to point out that human genetic variants are typically referred to as either common or rare to denote the frequency of the minor allele (MAF) in the human population. Golbus et al define the variants with MAF <0.5% as rare, but how much rare has to be a variant to be really rare? The rarity of a variant or the absence in a healthy control population is classically one of the criteria for evaluating the pathogenicity both in research and in clinical settings. In the most rigid definition, an MAF of 1% was used as cutoff. Although an MAF 2% implies that the variant is sufficiently common in the population to be not tremendously deleterious, the opposite is not generally true. Rare variants have arisen recently in the population or have been subject to negative selective pressure because of harmfulness and reduced reproductive fitness. Consequently, the threshold of rarity of a variant depends on disease characteristics, such as the age of onset and mortality, which in turn determine the prevalence of a disease. HCM and dilated cardiomyopathy are relatively frequent diseases characterized by age-dependent penetrance and variable expressivity. The vast majority of patients are asymptomatic or mildly symptomatic, implying a normal reproductive fitness that is further confirmed by the observation that de novo mutations are usually rare. Furthermore, mutations causing HCM and dilated cardiomyopathy are generally private mutations. For these reasons, we believe that an appropriate and specific cutoff has to be set for rarity for any particular disease.

Golbus et al nicely highlight the challenges to classify the great amount of variations detectable now by next-generation sequencing. The authors used as hallmarks of pathogenicity the presence of a variant in Human Genome Mutation Database or the prediction by in silico tools. The presence of a particular variant in the Human Genome Mutation Database merely implies that it was linked with a disease in the literature, although not necessarily causative because of the false reporting rate among disease-causing variants (absence of an appropriate number of tested healthy controls, segregation analysis, or functional validation). Indeed several variants reported by Golbus et al are well-known benign polymorphism although reported in the Human Genome Mutation Database (eg, Ser1491Cys in MYH7, dbSNP entry rs3729823), whereas others, such as Arg869His in MYH7, have been detected in only 1 1KGP sample (NA20513, MAF=0.0005). Interestingly, this sample belongs to the Tuscany 1KGP subgroup, and we detected the same variant in several patients from apparently unrelated families, all coming from Tuscany, suggesting that Arg869His may have a founder effect, as previously reported for other HCM mutations.

Furthermore, the use of in silico prediction tools as independent determinants of pathogenicity, although widely used, is generally questionable as recently demonstrated by Giudicessi et al, considering also that what is valid for a gene does not necessarily apply to another one. Indeed it is essential to consider the pathogenic mechanism associated with mutations of that particular gene in the evaluation of the deleteriousness of a variant because in silico prediction tools are not able to estimate the disease-causing potential of loss-of-function variation, as is the case of MYBPC3.

As underscored by the authors, the only reliable determinants to define a variation as pathogenic essentially are familial segregation analysis and functional validation that are impracticable with the amount of data generated by next-generation sequencing, taking into account that a crucial aspect of the clinical setting is to diagnose a single affected individual with no family history of the disease or with a very small family. From this point of view, the work of Golbus et al is fundamental because it highlights the limits of what we have done so far for evaluating disease potential of genetic variants, emphasizing the importance of creating new tools, criteria, and databases designed and shared by scientific community, allowing the translation of genetic findings from research to clinical practice.

Disclosures

None.

References


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