EDITORIAL

Research in understudied populations offers local and global insights into the genetics of hypertrophic cardiomyopathy

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by Lipari et al, see p. 89

Research into the genetic basis of hypertrophic cardiomyopathy (HCM) has now entered its fourth decade. Following the seminal discoveries in the 1990s that rare variants in sarcomeric genes segregated with disease in large family pedigrees, our knowledge of HCM genetics and the catalogue of associated variants have rapidly expanded. Clinical genetic testing for HCM patients is now recommended and regularly pursued, with the primary purpose to enable cascade genetic screening in family members, in order to distinguish between relatives at risk and those free from the risk of developing HCM. However, there remain substantial gaps in our knowledge of HCM genetic architecture that continue to limit the effectiveness of genetic testing in this condition. These include uncertainty about the validity of gene-to-disease associations (now being addressed through initiatives such as ClinGen),[1] the accuracy and consistency in interpreting the clinical effect of variants detected in patients, and the wide variability in penetrance and disease severity observed in individuals with pathogenic HCM variants.

However, one of the major obstacles in our understanding of HCM genetics and the application of clinical genetic testing has been the concentration of research and sequencing in patients from North America and Western Europe. This is a general issue across genetics research, with the potential to lead to disparities in the effectiveness of clinical genetics applications between different populations, for example, for the use of polygenic risk scores in common diseases.[2] In cardiomyopathy genetics, it has been demonstrated that non–white patients have a higher rate of variants of uncertain significance (ie, those without sufficient evidence to classify as pathogenic),[3] likely due to the fact that recurrent variants in European ancestry populations have been more thoroughly studied. However, even among different European populations, there is a considerable diversity in the genetic architecture of HCM. Founder mutations that contribute to a substantial proportion of cases have been identified in regions with obvious population bottlenecks (such as Iceland)[4] as well as central continental countries (such as the Netherlands),[5] highlighting the necessity for a more thorough and region-specific investigation of the genetics of HCM.

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Lipari et al[6] explored the genetic basis of HCM in south-eastern Poland, which is the first comprehensive genetic investigation of HCM patients from this region. They sequenced 29 index cases diagnosed with HCM using a broad panel of cardiovascular-associated genes, including the major sarcomeric genes as well as more recently implicated and rarely associated genes. Although the cohort was moderately sized compared with contemporary studies from more established HCM research centers, the findings offer insights not only into HCM genetics in Polish patients but also expand our understanding of rarer variant classes that are associated with this condition.

A recurrent truncating variant in *MYBPC3*, p.Tyr847Ter, was identified in 4 patients (14% of the cohort). This may represent a founder variant for this region and adds to the growing catalogue of founder *MYBPC3* truncating variants in different populations. Although this variant was already able to be classified as pathogenic (based on being a loss-of-function variant in *MYBPC3* in addition to previous reports), the findings in this study have several other insights and implications. The authors found that patients with this variant were diagnosed earlier than those with other sarcomeric variants, although this observation will need to be confirmed with larger

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cohorts given the long history of initial genotype-phenotype correlations in HCM that have not been replicated by subsequent studies. The frequency of the variant in this HCM cohort also suggests, given the reduced penetrance associated with most cardiomyopathy variants, that it may be present at a low but not insignificant frequency in the region's population. The detection of the variant as a secondary finding in future clinical or population studies using exome or genome sequencing will allow for an estimation of the population-level penetrance of this variant as well as a consideration of how such incidental findings should be reported and followed.

It is believed that a range of environmental and non–Mendelian genetic factors may help explain the variable penetrance and expressivity associated with numerous HCM-associated variants. These may include nongenetic factors such as obesity and hypertension, as suggested in a study investigating the carriers of *MYL2*:p.Glu22Lys, a Dutch founder variant with low penetrance in isolation.[7] Genetic variants other than the primary Mendelian variant may also contribute to disease burden and phenotype severity. The presence of additional rare sarcomeric variants that do not meet the evidence threshold for pathogenicity has been shown to be associated with an earlier onset of disease and increased incidence of cardiac events.[8] In the Polish cohort, the one patient with a sarcomeric gene variant of uncertain significance in addition to the putative founder variant also had a more severe phenotype, diagnosed at the age of 7 years, with a QTc>450ms, and requiring a septal myectomy. Rare variants in nonsarcomeric genes may also contribute to the disease phenotype in HCM patients—in this study, the authors propose an intriguing hypothesis about a possible hypomorphic role for variants in genes associated with autosomal recessive syndromes including cardiomyopathy, 4 of which were detected in this cohort in the *PMM2*, *SCO2*, *GUSB* and *GYG1* genes. However, any role for such variants will need further validation by demonstrating enrichment in larger cohorts and assessing their effect in functional assays.

Founder variants such as *MYBPC3*:p.Tyr847Ter may prove to be particularly valuable in research to identify these genetic and nongenetic modifying factors. By studying HCM patients with the same founder variant, any variability associated with the primary sarcomeric variant can be controlled for, enabling an accurate assessment of the effect of other factors that may contribute to the phenotype and disease severity. In addition to the rare variant classes described above, the cumulative effect of common variants with small effect sizes, identified in case-control genome-wide association studies (GWAS) or using endophenotypes (such as left ventricular wall thickness) in population studies, may also plausibly modify the disease phenotype.[9] Large cohorts of HCM cases with founder variants offer the opportunity to comprehensively identify and validate such modifying factors. In future, clinical genetic testing for HCM could assess the overall genetic susceptibility of patients and their relatives, potentially enabling improved prediction of disease risk.

Lipari et al[6] also identified a homozygous truncating variant in *CSRP3*, p.Arg122Ter, in 1 patient with HCM. This is only the second report, and third case, of a "human knockout" in *CSRP3* associated with HCM, following the earlier description of 2 cases from a French cohort.[10] *CSRP3*, the gene encoding the muscle LIM protein, was classified as having moderate evidence for association with HCM by the ClinGen gene curation effort,[1] with an autosomal dominant mode of inheritance. Both missense and truncating heterozygous *CSRP3* variants have been reported, although convincing evidence for pathogenicity only exists for 2 missense variants—p.C58G (segregation with a maximum logarithm of the odds (LOD) score of 5.9)[11] and p.L44P (enrichment in cases over population controls).[12] The reports of biallelic truncating variants suggest that autosomal recessive inheritance in this gene may be a rare cause of HCM. This is supported by population genetic data (no homozygous truncating variants are present in the gnomAD population databases of almost 200 000 individuals) and functional studies, as cardiomyopathy phenotypes are observed when *CSRP3* is knocked out in embryonic stem cell–derived cardiomyocytes[13] and mice (although the mice developed dilated cardiomyopathy with hypertrophy).[14]

This finding further highlights the advantages of diversifying genetic sequencing to include understudied populations, in order to discover novel genetic factors underlying diseases such as HCM as well as to provide additional evidence for genes that are rarely causative. Autosomal recessive inheritance like that observed in the *CSRP3* knockout patient may be particularly relevant for genetic screening in regions with high rates of consanguinity such as North Africa and the Middle East, where rare *CSRP3* truncating variants are more likely to occur in homozygosity through joint inheritance from related parents. These regions have also been characterized by a paucity of both population genetics data and research into cardiomyopathy genetics. The advantages of expanding genetic research in cardiomyopathies to non–European populations was also demonstrated by the identification of a nonrare *MYBPC3* intronic deletion in South Asian populations, present in about 4% of the population but enriched in patients with cardiomyopathy.[15] The identification of such population-specific variants is essential for understanding the genetics of HCM in different populations, as well as for offering broader insights into the diversity of variant classes that contribute to the disease, in this case low frequency variants with effect sizes between rare Mendelian variants and common variants identified through GWAS.

Although the genetic etiology of HCM has been widely studied over the last 30 years, we still have much to learn about the complex interplay between genetic variation and disease phenotype. In particular, expanding genetic research to previously understudied populations is essential to enable effective application of clinical genetic testing for HCM patients and their families worldwide. The findings from such studies are also likely to offer broader insights into the increasingly complex genetics of what was previously considered a relatively simple Mendelian disease.

ARTICLE INFORMATION

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