The 25-Year Genetic Era in Hypertrophic Cardiomyopathy: Revisited
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Genomics in hypertrophic cardiomyopathy (HCM) are now 25 years old. The article of Li et al in this issue of the journal provides an opportunity to revisit and place into perspective several important principles related to the clinical application of genetic testing to the HCM patient population, thereby assessing progress in understanding this heterogeneous condition, the most common of the inherited heart diseases.

Genetic Testing
Perhaps, most important is recognizing the current role achieved by genetic testing in contemporary HCM patient management and family screening. This technology has been available commercially in the United States since 2003, now with 4 fee-for-service companies that have brought advances in genomics for HCM and other genetic diseases out of the research laboratory, and widely available to clinicians.

As a result, the landscape of HCM has changed in several ways. Notable in this regard is the emergence of a new patient subgroup known as gene positive-phenotype negative (ie, genetically affected family members without left ventricular hypertrophy). Recognition of relatives who are gene carriers and, therefore, at risk for developing clinical disease demonstrates the power of HCM mutational analysis not otherwise possible. However, the precise likelihood of incurring clinical disease, or the age at which phenotype conversion could occur, remain uncertain with the possibility that some patients will achieve advanced age without developing left ventricular hypertrophy.

The most clinically impactful outcome of predictive family screening is the possibility of excluding those relatives without the family mutation from the risk of developing HCM and further clinical consideration. However, for such an initiative to be actionable, a pathogenic (disease-causing) mutation must be identified in a family member with clinically expressed HCM (ie, with left ventricular hypertrophy).

Of note, the relatively low yield of genetic testing for probands in predictive cascade family screening is perhaps not widely appreciated within the clinical cardiovascular community (Figure 1). About 50% of HCM genetic tests produce a negative result, indicating that the causative gene (or genes) responsible for the disease in those patients are not yet known and consequently do not appear in the testing panel. Alternatively, a variant of unknown significance may be reported in ≈15% to 20% of patients. Either a negative test or variant of unknown significance is an indeterminate result which provides no useful clinical information and precludes predictive testing in other family members (Figure 2).

Important insights in this regard are found in the single institution study of Li et al from Toronto General Hospital, in which 558 probands with clinical expression of HCM were assessed by genetic testing; MYH7 and MYBPC3 were...

Figure 1. Top, Distribution of genetic test results in a population of clinically diagnosed probands with hypertrophic cardiomyopathy. Bottom, Genetic testing interpretations, depicted with respect to probabilistic variant classifications commonly used by testing laboratories to format reports and express the presence or absence of pathogenicity. Benign and likely benign variants are not regarded as responsible for disease (ie, polymorphisms). Variant of unknown significance (VUS) is a variant with its contribution to disease currently unresolved. Absence of a mutation (in a proband) is considered indeterminant and of no relevance for clinical screening. Category assignments are based on expert professional judgment of laboratory geneticists using currently available data, but are also subject to change over time (reclassification).
the most common disease genes. Notably, pathogenic mutations were identified in only 35% of these probands, most frequently in women and the young, or in those with a family history of HCM or sudden death.

These findings are novel and informative by providing a reliable number (ie, 35%) for the true yield and proportion of families that will have access to generational genetic screening should they choose this strategy over (or following) clinical screening with echocardiography and cardiovascular magnetic resonance (CMR) imaging.4,8 This is a particularly important observation because too often the likelihood of successful genetic family screening has been cited as 50% to 70%,1,2 a figure that includes variants of uncertain significance, which are usually sarcomere mutations not yet regarded as disease causing.2

Conversely, the other two thirds of patients will not have this option of cascade generational screening at this time. Therefore, in only a minority of HCM probands can the result of genetic testing be considered actionable for family screening. For these reasons, the new Li et al3 data permit practicing cardiologists and genetic counselors to convey reliable information and expectations about the use of genetic testing to patients with HCM and their families, essential in this era of full transparency.

Prognosis

Sudden Death

A second major issue is the role of genetic testing in predicting prognosis and clinical outcome for individual patients with HCM, including the risk for sudden death (Figure 2). After considerable early enthusiasm and hope that the discipline of molecular genetics with mutational analysis would revolutionize HCM and the prediction of clinical course (that is, it would be possible to reliably distinguish benign from malignant mutations as prognostic markers1,9), it is now apparent that identification of specific single-nucleotide mutations cannot reliably anticipate future clinical events, including sudden death (Figure 2).2,10,11

This principle is substantiated further by the Li et al3 data in which sudden death risk was not increased among HCM patients with a disease-causing mutation. This circumstance can likely be attributed to the substantial (if not extreme) genetic heterogeneity of HCM, now with 11 disease-causing genes and a multitude of >1500 individual mutations, most of which are novel and private (ie, currently confined to a single family). In addition, 2 genes (MYH7 and MYBPC3) are dominant among all identified genes, accounting for 70% of patients, making meaningful clinical correlations difficult.1,2,10,11 This genetic profile was not anticipated when mutational analysis was heavily promoted as a clinical management tool 20 years ago.1

Heart Failure

At present, the most powerful clinical predictor of heart failure progression in HCM is left ventricular outflow obstruction present either at rest15 or with physiologic (exercise) provocation.13 Nevertheless, additional predictive markers for heart failure specifically in patients without LV outflow obstruction14 would be an important contribution to patient management.15 In this regard, Li et al13 have assembled data to clarify this issue by demonstrating an interesting relationship.
between pathogenic sarcomere mutations (largely MYH7 or MYBPC3 genes) and the likelihood of heart failure events. A multivariate analysis reports that pathogenic sarcomeric mutations as a group represent an independent risk marker for the combined end point of adverse HCM-related heart failure events, including development of progressive heart failure symptoms and death, systolic dysfunction, and transplant, all in the absence of LV outflow obstruction.

However, the gene positive versus gene negative study design and strategy used in Li et al's does not provide information that can be easily translated to the bedside to anticipate heart failure progression in order to impact clinical decision making for individual patients with HCM. A major limitation to this approach is the difficulty in distinguishing true pathogenic mutations from ambiguous variants of unknown significance, a dilemma that often constitutes the Achilles heel of diagnostic genetic testing.

Also, not necessarily fully appreciated by the practicing cardiovascular community is that the assignment of pathogenicity to sarcomere mutations does not rely on a standardized and uniform approach to mutation interpretation and is expressed on a probabilistic rather than a binary (ie, definitive yes or no) scale. Hence, the pathological significance of sarcomere variants is subject to variability in interpretation, and over time also to the possibility of reclassification by which mutations regarded as pathogenic can be reassigned to variant of unknown significance and vice versa when new relevant information becomes available. This has contributed to the current circumstance in which it is not possible to use individual sarcomere mutations in HCM risk stratification to predict arrhythmic events. In addition, it would have been of interest to know whether, in the Toronto cohort, late gadolinium enhancement progression (compared with reliance on sarcomere gene-positivity) because extensive late gadolinium enhancement can predict progression to end-stage heart failure.

In addition, the Li et al's data raise an unfortunate clinical limitation—that is, earlier recognition of a susceptibility to heart failure in nonobstructive HCM would not necessarily offer actionable prophylactic measures to alter natural history of the disease, in contrast to the practice in HCM of risk stratification and sudden death prevention with implantable defibrillators. However, the observation that gene-positive patients may be at greater risk for heart failure events underscores the need for future investigations defining undoubtedly complex pathophysiologic mechanisms by which disease progression develops in HCM, which may or may not prominently involve mutations in genes of the cardiac sarcomere. Finally, Li et al's raise the intriguing but unresolved issue of multiple sarcomere mutations and risk (ie, double hits as predictors of HCM-related heart failure progression [or sudden death]). Notably, 6% of their patients with advanced heart failure had 2 sarcomere mutations. These findings are consistent with and add to a literature suggesting an association between multiple sarcomere mutations and adverse outcome in HCM. Unfortunately, considering the low event rate characteristic of HCM, resolving the role of multiple mutations in the natural history of this disease will continue to be challenging in the absence of large and prospectively studied populations.

Conclusions

This is an opportune time for a realistic appraisal of genetic testing in HCM, including its strengths and limitations. Now, after a quarter century, such methodology is widely available to the practicing sector, with potentially powerful predictive cascade family screening possible, although a viable option for only a minority of families. Several limitations continue to impact the power of genetic testing with respect to directing clinical management strategies, including prevention of heart failure progression and sudden death.

Disclosures

Dr Barry J. Maron is a consultant for GeneDx. The other author reports no conflicts.

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