Molecular Diagnostics of Cardiomyopathies
The Future Is Here

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Major advances have been made in defining the genetic basis of inherited cardiac diseases. There are now >40 cardiovascular diseases in which a genetic cause has been identified, ranging from the inherited cardiomyopathies, such as hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), to primary arrhythmogenic disorders, such as familial long QT syndrome.\(^1\)\(^-\)\(^3\) The successful identification of causative genes in these diseases has resulted from a combination of dedicated efforts by researchers around the world as well as from rapidly emerging genetic technologies to analyze DNA. Genetic analysis, which previously took months or years to undertake, can now be performed in days or weeks. These exciting developments are now facilitating a surge in genetic information related to a range of human diseases and enhancing our understanding of how genetic differences influence health and disease.

In this issue of Circulation: Cardiovascular Genetics, Meder et al\(^4\) present an exciting insight into the future of how the latest genetic technologies may be used to improve the effectiveness and efficiency of comprehensive genetic screening of patients with HCM and DCM. The authors devised a rapid, high-throughput mutation screening strategy using a microarray-based target enrichment covering the coding regions of 29 known and 18 novel potential cardiomyopathy genes followed by next-generation sequencing (NGS). NGS represents a collection of newer technologies that use a combination of new strategies related to how genetic samples are prepared, advanced methods of DNA sequencing and imaging, and novel approaches to genome alignment and assembly.\(^5\) Although essentially a proof-of-principle study looking at a small selection of 10 patients (5 HCM, 5 DCM), the authors successfully show that such a targeted, comprehensive approach of screening the coding region of 47 candidate genes is successful in the identification of a number of potentially key DNA variants that may act as either disease-causing mutations or modifiers of phenotype expression.

The study by Meder et al\(^4\) raises a number of important issues, which are considerations not only for genetic testing in HCM and DCM, but in the evaluation of all medical genetic diseases. Specifically in HCM, efforts over 2 decades have identified at least 13 causative genes, with the most comprehensive genetic screening strategies resulting in a mutation pick-up rate of \(\approx 60\%\).\(^6\) The mystery that surrounds HCM, and what has eluded genetic researchers to date, is what accounts for the remaining 40% of cases where no genetic mutations are currently identified. Many possibilities have been considered, including nonexonic genetic changes (eg, intronic variants), large deletions or duplications, promoter mutations, epigenetic factors, copy number variants, non-Mendelian traits, and possibly causative genes that have yet to be identified.\(^7\)\(^-\)\(^9\) In contrast to HCM, the current mutation detection rate in families with DCM is significantly lower, with most 15- to 20-gene DCM panels having a pick-up rate of no more than 30% overall.\(^10\) This low pick-up rate largely has been due to the presence of rare, “private” mutations in isolated families,\(^11\) and as such, has significantly impeded the clinical utility of routine commercial genetic testing in patients with DCM.

To this end, NGS approaches, of which Meder et al\(^4\) propose 1 iteration, may be the genetic platform required to systematically and comprehensively analyze many genes and to identify the missing links in the genetic basis of both HCM and DCM, thereby providing a more clinically useful and accurate genetic testing strategy. The major current limitations in genetic testing for both HCM and DCM relate to the high cost of testing as well as the limitations on the number of genes to be tested. More recently, panels of genes, rather than single gene tests, have been developed for most inherited cardiac diseases. Genetic testing strategies incorporating NGS platforms, as demonstrated by Meder et al, have the capability to allow larger numbers of genes to be studied simultaneously and to detect a greater variety of mutation types, which will inevitably increase the pick-up rates for genetic testing and substantially reduce the cost of testing. These advances have major implications for practicing clinicians, who will need to integrate these genetic findings into the clinical management of their patients, as a diagnostic tool, and in the future, to potentially inform treatment and prognosis.

Although these amazing advances in genetic technologies and approaches will no doubt improve our understanding and identification of genetic causes of cardiomyopathies, the incomprehensible amount of genetic information generated is a significant challenge for analysis and interpretation and, ultimately, the application of these complex genetic findings in the diagnosis and management of patients and families. The current study detected 57,548 known or novel DNA variants and 21,663 small insertions or deletions in 10 patients.\(^4\) This scale of genetic data...
will require a combination of bioinformatic, genetic, and functional interpretation in order to sort the wheat from the chaff and thereby identify the key DNA changes relevant to the individual patient. Many factors will need to be considered in determining the biological significance and pathogenicity of the variants identified. These factors include the absence of the variant in normal populations; the type of change in the amino acid that the DNA variation encodes; the conservation of the amino acid residue among species and isofoms; and where possible, the coinheritance of the DNA variant in other family members. Although determining pathogenicity has been a major challenge when using traditional candidate gene approaches where 1 or 2 variants may need to be considered at any one time, the use of NGS platforms to study many genes concurrently means that the challenge of determining the clinical relevance of DNA variations is amplified exponentially.

Specifically, many clinically relevant issues will arise, including variants of uncertain significance; individuals who may have 2 or more disease-causing mutations; and individuals who may carry particular genetic variants but do not yet express clinical disease, so-called genotype-positive-phenotype negative individuals.7,12–16 Although these issues may appear separate, they are indeed very closely interrelated. A DNA variant of uncertain significance can alter the interpretation of whether the variant is the cause of disease, can affect whether a patient is a single or multiple mutation gene carrier, and can influence whether an individual is classified as genotype positive-phenotype negative. Therefore, determining disease pathogenicity of DNA variants identified by newer genetic approaches remains a crucial step in successfully translating these genetic discoveries to utility in clinical practice. The challenges of integrating masses of genetic information, interpreting the biological implications, and applying these findings in the setting of complex clinical phenotypes will require a multidisciplinary approach to the evaluation and management of families with inherited cardiac diseases.17,18 In particular, the role of cardiac genetic counselors who are the interface between these genetic technologies and the patient will need to evolve in order to help patients to understand and make informed decisions about the array of complex results likely to be generated. Furthermore, genetic counselors will be essential in coordinating family practice. The challenges of integrating masses of genetic information, interpreting the biological implications, and applying these findings in the setting of complex clinical phenotypes will require a multidisciplinary approach to the evaluation and management of families with inherited cardiac diseases.17,18 In particular, the role of cardiac genetic counselors who are the interface between these genetic technologies and the patient will need to evolve in order to help patients to understand and make informed decisions about the array of complex results likely to be generated. Furthermore, genetic counselors will be essential in coordinating family studies to determine pathogenicity of variants.

These are exciting times in what could only be described as a genetic revolution. Technologies such as NGS now have the capability to deliver rapid, relatively inexpensive, comprehensive, and accurate genetic information. NGS platforms are now able to interrogate millions of base pairs of DNA faster and cheaper than current genetic testing approaches. The application of such technologies is far reaching, and includes direct application in clinical genetic testing as well as in research efforts to facilitate our understanding of the genetic causes of human disease.19,20 As technologies continue to advance and readily available human genome testing among individual patients becomes a reality, personalized medicine will emerge at the forefront of clinical management strategies, and the face of medicine will have changed forever. The future is here.

Disclosures
None.

References

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