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REVIEW TOPIC OF THE WEEK

Advances in the Genetics of Congenital Heart Disease

A Clinician's Guide

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JACC JOURNAL CME

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CME Objective for This Article: After reading this article, the reader should be able to: 1) identify patients with congenital heart disease who will benefit from referral to a clinical genetics service; 2) explain the genetic basis of congenital heart disease to affected patients and their families; and 3) compare available genetic technologies and their respective applications.

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ABSTRACT

Our understanding of the genetics of congenital heart disease (CHD) is rapidly expanding; however, many questions, particularly those relating to sporadic forms of disease, remain unanswered. Massively parallel sequencing technology has made significant contributions to the field, both from a diagnostic perspective for patients and, importantly, also from the perspective of disease mechanism. The importance of de novo variation in sporadic disease is a recent highlight, and the genetic link between heart and brain development has been established. Furthermore, evidence of an underlying burden of genetic variation contributing to sporadic and familial forms of CHD has been identified. Although we are still unable to identify the cause of CHD for most patients, recent findings have provided us with a much clearer understanding of the types of variants and their individual contributions and collectively mark an important milestone in our understanding of both familial and sporadic forms of disease. (J Am Coll Cardiol 2017;69:859–70)

CURRENT STATUS OF GENETIC RESEARCH IN CONGENITAL HEART DISEASE

Since the first report specifically addressing the genetics of congenital heart disease (CHD) in the 1950s (1), much research has been devoted to understanding the heritable nature of this condition, including the notable work of James Nora on multifactorial inheritance in the 1960s (2), as well as the landmark Baltimore-Washington Infant Study assessing the epidemiology of CHD in the 1980s (3) (**Figure 1**). Familial forms of CHD have provided most of the genetic information on structural heart disease to date because of their suitability to early research techniques, including linkage analysis and candidate gene approaches. Indeed, many of the genes associated with CHD, including *NKX2-5*, *GATA4*, *TBX5*, *NOTCH1*, and *TBX20*, were identified using these early genetic techniques (4–8); however, a prerequisite to the use of linkage analysis is the existence of large families with multiple affected individuals segregating disease according to Mendelian principles, which is rare in CHD (9).

The development of chromosomal microarray (CMA) technology, including array comparative genome hybridization and single-nucleotide polymorphism (SNP) arrays, in the early 2000s provided a new tool for research in the field (**Figure 1**). Using CMA, a novel candidate gene, *TAB2*, was identified after the identification of an 850-kb deletion on chromosome 6q that was shared among 12 patients with CHD (10). Since then, a number of studies have used CMA to locate novel candidate genes involved in heterotaxy (10), isolated tetralogy of Fallot (TOF) (11), and left-sided CHD (12), as well as novel genomic regions of interest (13). Comparative genome hybridization has largely replaced routine karyotyping in clinical practice as part of the initial assessment of newborns with important CHD. Although CMA has many uses, particularly in the clinical and diagnostic setting, such as excluding diagnoses of trisomy 21, 22q11 deletion syndrome, and other major chromosomal abnormalities, it is fairly limited from a research perspective.

The contribution of somatic mutations as a potential genetic mechanism emerged after the discoveries of the Reamon-Buettner and Borlak research group and the Leipzig heart collection (14,15). This was a highly attractive hypothesis that could explain the clinical presentation of many of the isolated, sporadic forms of CHD. A number of other research teams attempted to replicate these findings using fresh-frozen tissue (as opposed to formalin-fixed hearts) but did not identify any important somatic mutations (16,17). Although subsequent studies suggest that somatic mutations are not a common cause of CHD, there is a possibility that they may play an as yet undetermined role in disease development in a