Genetic and Developmental Basis of Cardiovascular Malformations

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KEYWORDS

• Congenital heart defects • Congenital heart disease • Development • Gene dosage

KEY POINTS

- Phenotypic heterogeneity (different phenotypes/same genetic cause) and locus heterogeneity (different genetic cause/same phenotype) are common in CVM.
- Genes important for syndromic CVM may also cause nonsyndromic CVM.
- An understanding of the genes and pathways required for critical stages of heart formation informs the approach to genetic testing and diagnosis.
- The same gene or genetic locus may cause different types of CVMs (phenotypic heterogeneity).
- Mouse models are important tools to investigate the complex genetics of CVMs.

INTRODUCTION

The underlying causes of cardiovascular malformations (CVMs) can include cytogenetic abnormalities, single-gene disorders, environmental causes, or (most commonly) the causes can be multifactorial (**Table 1**). Chromosomal abnormalities account for 12% to 14% of all live-born cases and 20% to 33% of fetal cases of congenital CVMs, indicating that the proper genetic control of cardiac development is

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Table 1
Causes of CVMs

Cause	Example	Characteristic CVMs
Environmental/teratogenic	Lithium chloride	Ebstein anomaly
Genetic		
Chromosomal	Trisomy 21	Atrioventricular canal defect
Contiguous gene/CNV	22q11.2 deletion syndrome	Conotruncal malformations
Single gene	Noonan syndrome	Pulmonary valve stenosis
Epigenetic		
DNA methylation	De novo SMAD2 mutations	Conotruncal malformations LV obstructions Heterotaxy

Abbreviation: CNV, copy number variant.

essential.[1–4] CVMs can occur as isolated findings, as part of a well-defined syndrome, or in conjunction with additional extracardiac anomalies not formally recognized as a syndrome.[5] The designation of CVMs as isolated can be problematic because many important distinguishing features of syndromic conditions, such as developmental delay or dysmorphic features, may not be apparent at initial evaluation. As a result, syndromic cases of CVM may be underestimated. In addition, the traditionally cited incidence for CVMs of ~1% of live births likely also underestimates the scope and impact of disease. Taking into account high rates of CVMs in spontaneous abortuses, common malformations such as bicuspid aortic valve (BAV) (present in 1.2% of the population), and latent cardiac diseases such as aortic dilatation, which are not included in the birth incidence of CVMs, genetically mediated CVMs are likely much more common than was previously thought. When considering the cause of CVMs, as opposed to the proportion of CVM cases that manifest as disease at birth, the incidence increases to approximately 5%.

Recently, we summarized the overall progress in the molecular genetic analyses of CVMs and current recommendations for clinical application of genetic testing. In particular, we reviewed the utility and limitations of chromosomal microarray analyses (CMAs) and the emerging clinical roles for whole-exome sequencing and other next-generation sequencing (NGS) technologies.[6] Readers with an interest in the current clinical testing approaches for CVMs are referred there. This article focuses on common genetic and developmental themes across the wide variety of CVMs and the ability of animal models and knowledge of cardiac developmental biology to affect the understanding of, and approach to, CVMs.

THE GENETIC BASIS OF CARDIOVASCULAR MALFORMATIONS

Epidemiologic studies suggest that a syndromic form of CVM is identifiable in approximately 20% to 30% of cases.[4] Known genetic causes are extremely heterogeneous, encompassing not only mutations in cardiac relevant genes but also more complex chromosomal abnormalities, submicroscopic duplications/deletions, and whole-chromosome aneuploidies (see **Table 1**). As noted earlier, CVMs can be isolated or can occur as part of a well-recognized genetic syndrome, and this distinction may be subtle.

Inheritance patterns for many CVM-associated genetic conditions are well characterized (reviewed in Ref.[6]) (**Table 2**). Genetic syndromic conditions associated with