Genetics and Genetic Testing in Congenital Heart Disease

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KEYWORDS

• Congenital anomaly • Cardiovascular malformation • Development • Genetics
• Genetic counseling • Genetic testing

KEY POINTS

- Congenital heart defects (CHDs) are the largest contributor to worldwide infant morbidity and mortality.
- Known genetic causes encompass single-gene mutations, complex chromosomal abnormalities, submicroscopic rearrangements, and whole-chromosome aneuploidies.
- Significant proportions of CHDs are associated with extracardiac malformations and/or occur as components of a genetic syndrome.
- Advancements in genetic testing technologies have facilitated improved diagnostics and identification of novel genetic causes of CHD.
- Genetic consultation and counseling are integral components of risk assessment and clinical care. Evaluation by a geneticist is essential when a possible syndrome is suspected.

INTRODUCTION

The impact of congenital heart defects (CHDs) is profound. With a traditionally cited incidence of 8 per 1000 live births (~1%), and a need for expert cardiologic intervention in 3 of every 1000 newborns,[1] CHDs are both the single largest cause of infant morbidity and mortality worldwide and a significant source of global economic burden.[2,3] Taking into account very high rates of CHDs in spontaneous abortuses[4] and subtle or subclinical abnormalities in another 1% to 2% of patients[5] the true overall incidence of CHDs is undoubtedly much greater. Although these figures effectively convey the large global clinical impact of CHDs, they fail to communicate both the

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enormous diversity of phenotypes among affected individuals and the emerging understanding of the complexity of genetic and developmental causes.

Research into the mechanisms that regulate heart development has advanced significantly in the last 20 years. Studies using a diverse array of model organisms, including mice, frogs, and zebrafish, have facilitated major insights into normal and abnormal cardiogenesis. Furthermore, systems biology approaches designed to assess functional convergence of causative CHD genes and associated transcriptional responders (genes with altered cardiac expression) have suggested that multiple CHD risk factors are more likely to act on different components of a common functional network than to directly converge on a common genetic or molecular target.[6,7] These findings, coupled with an ever-expanding list of CHD-associated gene mutations,[8] chromosomal abnormalities,[9] environmental causes,[10,11] and epigenetic insults,[12,13] hint at a significant complexity to both normal heart development and CHD pathogenesis. This article describes current understanding of the major embryologic events that shape the developing heart. It then provides a brief overview of key signaling and molecular concepts relevant to these developmental processes. Readers desiring additional details are directed to recent comprehensive reviews.[14–21]

Overview of Heart Development

Cell lineage is an important concept for heart development because distinct lineages support the development of specific cardiac compartments such that structural anomalies may result from dysregulation of a single cell lineage, multiple lineages, or specific inductive interactions between lineages. During the second and third weeks of human development, 2 mesodermal subpopulations, the first heart field (FHF) and second heart field (SHF) contribute cells to the developing heart. Although the FHF will ultimately contribute to the left ventricle and portions of the atria and right ventricle, the SHF supports development of the future outflow tract (OFT), ventricular septum, and the remainder of the atria and right ventricle.[22] Cells of the FHF originate in splanchnic mesoderm of the anterior lateral plate and in response to inductive signals from adjacent endoderm become the first cardiac precursors to differentiate.[23] Gastrulation movements help to position the cardiogenic mesoderm as bilateral folds alongside the prechordal plate. By 17 to 19 days, the cardiogenic folds coalesce anteriorly to form the cardiac crescent, a transient structure that fuses and detaches from the dorsal pericardial wall as a linear, bilaminar heart tube. Subsequent establishment of axial left-right asymmetries directs asymmetric growth and rightward looping of the heart tube, properly positioning the heart for future chamber and valve development. While these movements are occurring cells from the SHF have already begun migrating from positions dorsal and posterior to the heart tube to support elongation of the arterial and venous poles. During weeks 6 and 7 an epithelial to mesenchymal transition populates the common atrioventricular canal and OFT with loose mesenchymal cell populations called endocardial cushions. Mature valves arise through extensive cushion remodeling and become highly stratified into distinct layers. Meanwhile, neural crest cells delaminate from the dorsal neural tube and migrate into the developing OFT to support septation of the great vessels, as well as maturation of the aortic and pulmonary valves.[24] Significant cardiac contributions are also made by cells of the proepicardium, which originate from venous coelomic mesothelium and support development of the future epicardium and coronary vasculature.[25] As development nears completion the heart is refined into a muscular, 4-chambered organ capable of regulating incoming and outgoing blood