Pediatric heart disease, aka cardiovascular disease in the young, comprises varied phenotypes, including cardiovascular malformations, cardiomyopathies, vasculopathies (eg, Marfan syndrome), and cardiac arrhythmias. Cardiovascular malformations are a major component of pediatric heart disease and constitute a substantial portion of clinically significant birth defects, with a definition-dependent estimated incidence of 4 to 50 per 1000 live births.1,2 Despite advances in diagnosis and therapy, the morbidity and mortality associated with cardiovascular malformations and other forms of pediatric heart disease make them important clinical problems. Thus, there has been considerable interest in understanding their cause.

Because of early recognition of environmental teratogens such as rubella, thalidomide, and high altitude, considerable attention was focused on environmental factors; however, in the Baltimore-Washington Infant Study,3 common risk factors identified for pediatric heart disease were positive family history and maternal diabetes mellitus. Numerous examples of increased risk of pediatric heart disease in family members of affected individuals have been published.4 The association of cardiovascular malformations and other birth defects with chromosomal abnormalities5 provides further support for a genetic origin. Based on studies of recurrence and transmission risks, a hypothesis of multifactorial origin was proposed.6 In this type of inheritance, an individual’s genetic predisposition interacts with other genes and/or environmental factors to cause heart disease.

However, in the past 2 decades, mendelian inheritance models have been used to exploit molecular genetic and cytogenetic observations in multiplex families.7 The discovery that heterozygous mutation of the transcription factor NKX2.5 causes familial pediatric heart disease exemplifies this progress (reviewed elsewhere8). From these studies, it has been learned that the new genetic taxonomy of pediatric heart disease does not precisely align with the clinical taxonomy used by anatomiasts, cardiologists, and surgeons. For example, there is not a tetralogy of Fallot gene or an atrial septal defect gene. Furthermore, individuals within a family harboring the same mutation may exhibit clinically distinct phenotypes that cross the clinical taxonomy boundaries. Indeed, a recurring theme in genetic studies of pediatric heart disease has been the phenomena of genetic heterogeneity, reduced penetrance, and variable expressivity. Taken together, these findings suggest that what appeared to be simple inheritance is really complex inheritance because genotype does not predict phenotype. These findings validate the concept that pediatric heart disease results from complex inheritance and at the same time help explain the difficulties in identifying genetic causes of pediatric heart disease.

The study by Winston and colleagues9 in this issue of Circulation addresses these issues in a murine model. To study genetic origins of pleiotropic heart defects with incomplete penetrance, they analyzed the cardiac phenotype in mutant mice (Nkx2.5+/−) from a C57Bl/6 background and compared them with progeny of outcrosses (F1) to the strains FVB/N and A/J and to F1×F1 intercrosses or backcrosses to the parent strain (F2). Although their phenotyping modality did not allow analysis of valve abnormalities or conduction defects previously identified in murine heterozygotes,10–12 cardiac phenotypes of atrial, ventricular, and atrioventricular septal defect and double-outlet right ventricle were precisely determined by cardiac histological sections. Analysis of >3000 Nkx2.5+/− hearts from 5 F2 crosses demonstrated the profound influence of genetic modifiers on disease presentation. From the incidences and coincidences, they found that anatomically distinct malformations have shared and unique modifiers. All 3 strains carry susceptibility alleles at different loci for atrial and ventricular septal defects. Relative to the other 2 strains, A/J carries polymorphisms that confer greater susceptibility to atrial septal defect and atrioventricular septal defect and C57Bl/6 to muscular ventricular septal defect. Segregation analyses revealed that ≥2 loci influence membranous ventricular septal defect susceptibility, whereas ≥3 loci and at least 1 epistatic interaction affect muscular ventricular septal defect and atrial septal defect. The authors conclude that alleles of modifier genes can either buffer perturbations on cardiac development or direct the manifestation of a defect, but in a genetically heterogeneous population, the predominant effect of modifier genes is health.

Implications for Future Gene Discovery

Strong heritability and recurrence risk ratio estimates support a genetic basis for pediatric heart disease. Pedigree
analyses have been interpreted as indicating simple mendelian inheritance for a variety of phenotypes, and there are numerous examples of discovery using model-based approaches for cardiovascular malformations, arrhythmias, and cardiomyopathies. However, the genetic cause of pediatric heart disease is still unknown in most situations.

Findings from the Winston et al study emphasize the importance of detailed cardiac phenotyping and provide insight into the challenges of genetic discovery. A model system involving perturbation of a single gene in a relatively simple (compared with human) genetic background would be expected to demonstrate simple mendelian inheritance, but this was not the case. Segregation analysis revealed the presence of phenotype-specific genetic and epistatic modifiers. Although the study was not powered to discover the modifiers, identifying their presence provides an explanation for the pleiotropic phenotypes observed in the mutant mice. Taken together, these findings implicate complex inheritance of the heart malformations. What are the implications for genetic discovery and determination of causality in studies of human pediatric heart disease?

With completion of the Human Genome Project, it is clear that genetic variation is common and occurs on many different scales, ranging from gross karyotype alterations to single nucleotide changes. The discovery of genetic variation has been streamlined and made accessible through the availability of chip platforms. Two general strategies exist for using this genetic variation for gene discovery: linkage and association. Linkage exploits the cosegregation of trait loci with genetic variants within families; thus, family data are a necessity. In contrast, association can be performed in families or in unrelated individuals. Family-based association tests afford protection against elevated type I error rates (resulting from hidden stratification) and improved power for rare traits compared with use of data on unrelated individuals, a decided advantage of family-based designs. However, the objective of such approaches is to find a single genetic variant sufficient to cause disease. This may be unrealistic given the findings of Winston and colleagues, which demonstrate that although Nkx2.5 has an important role in heart development, by itself, Nkx2.5 mutation may not be sufficient to cause disease. That is, the ability of Nkx2.5 to cause disease depends on other genetic or epistatic factors. The implication of these findings is that researchers must move beyond the expectation that a single variant will cause disease. Although analytical methods to evaluate the effects of ≥2 genetic variants are well established, the ability to apply these methods in a high-throughput manner must be developed. Furthermore, researchers must realize that these more complex models require additional power. For example, for an investigator to have power to detect a 40% increase in risk for a trait that occurs in 1% of the population, a sample size of 5000 individuals is required for a 1:1 case-control cohort. For an interaction analysis, an effect yielding a 50% increase in risk would require 9000 individuals.

Despite advances in diagnostic precision and definitive therapies with excellent survival for pediatric heart disease overall, our understanding of its cause is rudimentary. Studies in the past 2 decades have provided insight into the genetic origins of pediatric heart disease but in turn have raised additional questions. Findings reported by Winston et al serve to illuminate results of earlier genetic studies and point a direction for future studies.

Source of Funding

This work was supported by the National Institutes of Health (HL69712).

Disclosures

None.

References


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KEY WORDS: Editorials ■ genetics ■ heart septal defects, atrial ■ heart septal defects, ventricular ■ transcription factor
Complex Story of the Genetic Origins of Pediatric Heart Disease
D. Woodrow Benson and Lisa J. Martin

Circulation. 2010;121:1277-1279; originally published online March 8, 2010;
doi: 10.1161/CIR.0b013e3181d98516
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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