A heritable basis for congenital heart disease was probably first suggested more than a century ago by a report of 3 cyanotic siblings. In the early 1960s, Zetterqvist in Sweden and Pitt in Australia convincingly demonstrated autosomal dominant inheritance in 2 large, extended families who had atrial septal defects (ASDs) and tetralogy of Fallot, respectively. Of note, Pitt ascertained the diagnosis in 215 of 275 descendants of one man spanning 6 generations, many of whom he personally examined! In contrast, it took at least 2 dozen people to identify a missense mutation of α-cardiac actin (ACTC1) as the cause of ASDs in the Swedish family. Their work, published in 2008, used linkage analysis, positional cloning, and Sanger DNA sequencing to diagnose one mutation in 3 families who had either ASDs or patent ductus arteriosus. Their stated goal was to demonstrate the clinical utility of WES in familial congenital heart disease. More broadly, their results highlight how far the field has come and how far it has to go in bringing genetics to pediatric cardiology.

WES evaluates the ≈1% of the genome that encodes proteins. If a person’s disease is caused by a mutation in the exome, the sequence variant should be present in the WES output file of ≈5×10^7 nucleotides. A well-considered experimental design and bioinformatic pipeline are needed to filter the most plausible candidates from thousands of irrelevant variants. The investigators began by selecting families that demonstrate Mendelian patterns of a specific congenital heart defect, such as tetralogy of Fallot. Whether requiring the same defect in every affected family member increases the chance of finding a mutation is uncertain. Mutations of the same gene defect, such as tetralogy of Fallot, whether requiring the same defect in every affected family member increases the chance of finding a mutation is uncertain. Mutations of the same gene in humans, ≈560 per million live births, assuming a largely monogenic basis for the defects, complete penetrance, and most practical clinical question. Mutations that cause a deleterious effect on protein function. The establishment of pathogenicity is arguably the most challenging scientific problem and most practical clinical question. Mutations that cause premature termination of the protein sequence, a frameshift, or disruption of a splice site are likely to be deleterious. The effect of a mutation that alters one amino acid in a protein is more difficult to judge. To predict the pathogenicity of a mutation, algorithms typically rely on bioinformatic variables, such as the degree of conservation of the sequence across species and the frequency of polymorphisms in humans. Because no algorithm is perfectly sensitive and specific, investigators typically prioritize variants based on the consensus of several methods. Following this general strategy, the authors identified suspect variants in 3 of the 9 families. Two of the families who had ASDs had missense mutations of GATA4 and TLL1. The third family who had patent ductus arteriosus had a single nucleotide deletion in MYH11 predicted to disrupt splicing.

The real challenge is the independent validation of candidate variants. Validation strategies come in 2 flavors. Statistical or dry-lab approaches can broadly implicate variants that affect genes in a common pathway. For example,
a recent, large WES study implicated de novo mutations of histone-modifying genes in the pathogenesis of sporadic, isolated congenital heart disease. In contrast, wet-lab approaches assess the functional effect of a specific mutation in a biological assay. Here, the authors tailored experiments to the gene and its known functions. For example, GATA4 is a transcription factor, so they compared the ability of wild-type and the mutant GATA4 to transactivate a heterologous promoter construct.

The definitive biological assay would be recapitulation of the cardiac phenotype in an animal model that carries the suspect variant. Zebrafish and mouse are the usual model species. Fish do not have a 4-chambered heart, but mutants can be generated relatively efficiently and inexpensively. Mutations affecting cardiac developmental pathways that are shared across species commonly cause an analogous phenotype in the 2-chambered fish heart. Mice do have a 4-chambered heart, but mutants cost much more time and money to engineer and study. In this regard, the recently developed CRISPR-Cas9 genome engineering method significantly lowers the barrier to validation. We suggest that the analysis in engineered mice of a relatively large number of variants discovered by WES may be worthwhile to test the underlying bioinformatic assumptions. Knockout mouse models, which can implicate the function of a gene in cardiac development, do not properly address the effect of missense mutations that can cause a gain or loss of function or affect one of several functions of a gene.

The genetics of congenital heart disease has come a long way since Zetterqvist, Pitt, and others established a heritable basis >50 years ago. Where can we go from here? One may first ask what the genetic basis is in the other 6 families for whom WES yielded no candidate genes. Inherited chromosomal microdeletions or duplications or copy number variants occur in roughly 10% of isolated congenital heart disease. Mutations of regulatory DNA have not been explored; this would require whole-genome sequencing and the development of methods to estimate the pathogenicity of noncoding variants. Less often considered is an oligogenic basis: multiple mutations may contribute to the development of a heart defect. In fact, 2 of the families in the present article suggest this mechanism. The family that carried the GATA4 mutation also carried a mutation of EVC2, mutations of which cause Ellis van Creveld syndrome. Although the family did not have the syndrome, it is clear that mutations of syndromic genes can cause isolated congenital heart disease. Another family that had tetralogy of Fallot carried mutations of MYBPC3 and SOS1; mutations of the latter gene cause Noonan syndrome. Two recent genomic analyses provide compelling evidence for an oligogenic basis of tetralogy of Fallot and atrioventricular septal defects in humans.

Finally, one can ask how we can make genetics relevant to the practice of pediatric cardiology. Specific counseling regarding the risk for future offspring is an obvious application, but there may be even more meaningful emotional benefits for parents and patients. A genetic diagnosis may alleviate the parents’ worry that they did something to cause their child’s heart defect, and a certain diagnosis can in general help individuals cope with their disease. Of course, the nature of pediatric cardiologists and congenital heart surgeons is to intervene. For them, genetics will only be relevant if the information can guide the management of their patients. Recent evidence suggests a common genetic basis for congenital heart disease and neurodevelopmental disability. Children who carry such mutations may, hence, benefit from early intervention and individualized education programs. Certain genetic mutations may affect cardiac outcomes. High-risk patients might, thus, benefit from early and aggressive medical management. Personalized medicine—now that would be a laudable goal for the field in the next 50 years.

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References


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