Congenital heart defects are present in 1% of all live births and are a significant burden on the parents and family, healthcare system, and overall community. Congenital heart defects (CHD) are also identified in 10% of still births and are presumed to be a substantial cause of early fetal demise. With advances in prenatal diagnosis, corrective strategies, and longitudinal care, infant mortality has substantially declined. Today >75% of CHD children who survive the first year of life will enter into adulthood. Elucidating the cause of an offspring’s CHD is greatly valued by parents, providing comfort that the defect was because of genetic randomness beyond their control and that certain problems arise from the same underlying genetic issue and not from preventable errors.1 As Helen Taussig stated 50 years ago “Our next great step forward will come in the field of cause and prevention of malformations.”2 Causes of CHD are often divided into genetic and nongenetic influences. The advantage of contemporary genomic technologies including single-nucleotide polymorphism (SNP) arrays, next-generation sequencing, and copy-number variant platforms are accelerating the discovery of genetic causes of CHD. Importantly, these tools enable the study of sporadic cases, the most common presentation of CHD. A review article summarizing this field entitled the “Genetics of Congenital Heart Disease: The Glass Half-Empty” previously highlighted the limitations of genetic technologies for assigning causality.3 Articles such as the present one in this journal entitled “Genome-Wide Association Studies and Meta-analysis for Congenital Heart Defects”4 are important studies performed using distinct patient cohorts from multiple sites. We are now looking for the complex multigenetic explanations for CHD in a multifactorial scheme, including epigenetic and environmental factors. There is renewed optimism in the field such that today we would see the genetics of CHD but hopefully now with the glass half-full.

See Article by Agopian et al

This current article from the University of Texas School of Public Health and the Children’s Hospital of Philadelphia, along with the National Heart Lung and Blood Institute’s Pediatric Cardiac Genomics Consortium (PCGC), hypothesizes that common individual variants contribute to architecture of congenital heart disease risk. Genome-wide association studies (GWAS) were conducted in 5 cohorts from clinical populations, including 3 cohorts from Children’s Hospital of Philadelphia and 2 using the multiple clinical centers in the PCGC. This is a relatively large sample size compared with other GWAS of CHD and evaluated both inherited and maternal genetic effects, but in the overall scheme of genetic evaluation is still a small sample size. In conotruncal heart defects (CTD), case–parent trios and left ventricular outflow tract defect (LVOTD) case–parent trios and a cohort with conotruncal defects and pediatric controls were compared. The GWAS assessed the inherited (case) genotype in all cohorts and the maternal trios. The authors also conducted meta-analysis using GWAS results in CTD cohorts, the LVOTD cohorts, and from combined CTD and LVOTD cohorts. The genetic variants were denoted with Combined Annotation Dependent Depletion scores to predict the potential deleterious-ness of individual variants and other scores for regions that focus on predicting the functional impact of noncoding variants.

In the individual GWAS, significant associations were only identified in Children’s Hospital of Philadelphia conotruncal defect case–control GWAS. In this analysis, 52 CTD-associated inherited genotypes were found, with 49 of these SNPs in introns of MGA74C, which is involved in the biosynthesis of an N-glycan precursor. Two of the SNPs in the MGA74C had Combined Annotation Dependent Depletion scores >10, thus predicted to be highly deleterious. But because these variants were not significantly related to CTD in the meta-analysis, it may be that associations identified in the Children’s Hospital of Philadelphia case–control represent false-positive findings and cannot be extrapolated to have predictive use. Additionally, there was no SNP overlap or evidence of replication for any of the associations identified in the individual cohorts.

In the authors’ meta-analysis, only one GWAS was detected in an intragenetic SNP associated with LVOTD. This one novel candidate region associated with LVOTD was in inherited (case) genotype for rs72820264 on chromosome 6p24.3. According to the authors, the nearest downstream gene OFCC1 has been associated with oral facial clefts, and the region has been linked to a rare autosomal dominant syndrome that includes CHD and ventricular noncompaction.5 However, the scale Combined Annotation Dependent Depletion score was 1.5, suggesting that this variant is not likely to be highly deleterious. Top suggestive associations from the authors’ meta-analysis included the maternal variant of interest SLC38A3, which was predicted to be within the most 10% of deleterious variants in the genome with Combined Annotation Dependent Depletion score of 14.85 and projected in the third quartile of the externally replicated GWAS SNPs. This gene may play a key role in fetal development as a primary supplier of glutamine, necessary for early gestation fetal growth.
It is important to understand the genetic causes and influences on the development of congenital heart defects for us to advance the fields of pediatric cardiology and adult congenital heart disease. This undertaking is not an easy task. The accompanying article performed a GWAS using large genetic cohorts from a single center and the PCGC that was much needed in these areas of medicine. However, this investigation does not answer what are the genetic causes of congenital heart defects but may give us a glimpse into what could be the complex multigenetics of CHD. This study presents potential candidate regions for the most common cyanotic CHD, tetralogy of Fallot, and the most severe LVOTD, hypoplastic left heart syndrome. This study suggests that a few of the single SNPs confer relatively large risks of nonsyndromic conotruncal defects and LVOTDs. As this article states, these results can help suggest pathway-based studies to better identify genes that influence the risk of CHD via common variants. Future work needs to focus on candidate loci defining functional or developmental pathways. Using the same PCGC cohort, a landmark article described the de novo mutations in histone-modifying genes and congenital heart disease. Whole-exome sequencing of 362 sporadic CHD trios identifying a likely causative, de novo variants in HOMC. The next year, Warburton et al.3 wrote that de novo and rare inherited copy-number variant contribute to CHD in an unselected sample of children with CTD or hypoplastic left heart syndrome. We then showed in a global genetic analysis of mice using a forward genetics screen and mouse embryonic imaging a broad spectrum of CHD mutant lines. This study had a predominance of left–right laterality defects such that 30% had heterotaxy and revealed a central role for ciliary function in CHD.4 Subsequently, it was proposed that because of the complex multigenetic nature of CHD, it took multiplicity hits for hypoplastic left heart syndrome to occur in mice.5 Also in 2015, Thorsson et al.6 described chromosomal imbalances in patients with CHD with a meta-analysis revealing potentially critical regions involved in heart development, with varying levels of importance. Clearly, early transcription factor mutations can lead to both structural and functional congenital heart disease in mice and man.7 However, genetics are clearly only part of the picture.

Half a century ago, mentors of one of this editorial’s authors (L.L.) William Strong and Dorothy Thompkins stated in an audiovisual program and book, “the etiology of congenital heart disease is due to multifactorial inheritance.” Multifactorial inheritance implies that a predisposed infant, genetically determined by many genes and exposed to an environmental trigger during the critical phase in cardiac development results in congenital heart defects.12 To this day, this concept stands and a recent review “Genetics of Congenital Heart Disease” proposes that multifactorial inheritance persists with a strong link between CHD incidence and the extrauterine environment.13 It is becoming better recognized that patients with complex CHD deal with neurodevelopmental delay and learning deficits, which can also burden on families with congenital heart defects. Again using the PCGC consortium of 1 to 20 nonsyndromic complex CHD trios, Homsy et al14 have identified genetic commonality between heart and brain development as a significant contributor to the clinical overlap between CHD and neurodevelopmental delay. The GWAS study published today adds to the past 5 years of major papers looking for the causes of CHD.

In summary, we still only know what causes one third of congenital heart defects, with genetic, epigenetic, and environmental influences on cardiac development. This article by Agopian et al.15 has significantly furthered the research that must be done to incrementally elucidate developmental pathways that can explain multiple genetic hits that cause CHD. Our precise understanding of the biology and genetics of CHD still have the glass only halfway—but with all of the recent work, perhaps the glass can more optimistically now be said to be half-full instead of half-empty. Future work in the field should be aimed at filling the knowledge glass to the rim.

Disclosures
None.

References

Key Words: Editorials ■ child ■ genome-wide association study ■ genotype ■ infant ■ tetralogy of Fallot
Genetics of Congenital Heart Disease: Is the Glass Now Half-Full?
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