



Genetics of Congenital Heart Disease: A Narrative Review of Recent Advances & Clinical Implications

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Abstract

Congenital heart disease (CHD) is the most common human birth defect and remains a leading cause of mortality in childhood. The advances in clinical management have improved the survival of children with CHD; adult survivors commonly experience cardiac and non-cardiac comorbidities, which affect quality of life and prognosis. Therefore, the elucidation of genetic etiologies of CHD not only has important clinical implications for genetic counselling of patients and families but may also impact clinical outcomes by identifying at-risk patients. Recent advancements in genetic technologies including massively parallel sequencing, have allowed for the discovery of new genetic etiologies for CHD. They are variant prioritization and interpretation of pathogenicity remain challenges in the field of CHD genomics, advances in single-cell genomics and functional genomics using cellular and animal models of CHD have the potential to provide novel insights into the underlying mechanisms of CHD and its associated morbidities. In this review, we provide an updated summary of the established genetic contributors to CHD and discuss recent advances in our understanding of the genetic architecture of CHD along with current challenges with the interpretation of genetic variation. Furthermore, we highlight the clinical implications of genetic findings to predict and potentially improve clinical outcomes in patients with CHD.

Keywords: Congenital heart disease (CHD), genetics, genetic testing, clinical outcomes

Introduction

Congenital heart disease (CHD) is the most common birth defect, affecting nearly 1% of all live births ¹. CHD encompasses a wide spectrum of defects from simple malformations with a favorable prognosis to more complex and severe lesions that require multiple catheter-based or surgical interventions with uncertain long-term outcomes. Although CHD remains a leading cause of morbidity and mortality in childhood, the population of adults with CHD is dramatically expanding. Now, more than 90% of children with CHD survive into adulthood due to significant advances in disease recognition and improved medical and surgical management across the lifespan²⁻⁵. Therefore, understanding the genomic architecture of CHD is increasingly clinically important ⁶. While there have been significant advances in the elucidation of the genetic etiologies for other forms of inherited cardiac disease such as cardiomyopathy and arrhythmias, it has only been with the increased understanding of the molecular pathways regulating cardiovascular development over the past couple of decades that the genetic basis of CHD has become more defined⁷⁻¹⁰. However, the detailed genetic architecture of CHD and how disruption of these underlying regulatory mechanisms results in the spectrum of CHD phenotypes is actively being investigated.

This narrative review was compiled through study, analysis, and discussion of previously published literature. PubMed was searched without time limitations and language restrictions, including articles related to the etiology and genetic contributors of CHD, NGS studies in large CHD cohorts, challenges with interpretation of NGS findings, functional genomics of CHD, and clinical implications of genetic testing and genetic prediction of clinical outcomes in patients with CHD. Search terms included congenital heart defects in combination with genetics, etiology, pathogenesis, mutations/genetic variation, environmental factors, NGS, exome sequencing, whole genome sequencing (WGS), variant prioritization, scRNA-seq, functional genomics, genetic animal models, human induced pluripotent stem cells (iPSCs), noncoding variants or genetic testing and a combination of congenital heart disease, genetics and clinical outcomes.

Established etiologic contributors to CHD

The etiology of CHD is multifactorial as both genetic and environmental factors have been implicated in its etiology ¹². Specific genetic causes can be detected in an estimated 40% of CHD cases (*Figure 1*). Genetic causes of CHD are extremely heterogeneous, including chromosomal anomalies or aneuploidies (estimated 13%, range from 9% to 18%) ¹³ copy number variants (CNVs) (estimated 10–15%: range from 3% to 25% in syndromic CHD and 3% to 10% in non-syndromic CHD) ¹⁴⁻¹⁶ and single gene disorders (12%) ^{11,15-17}. The genetic basis of CHD can be divided into syndromic CHD and non-syndromic CHD, where congenital abnormalities are isolated to the heart.

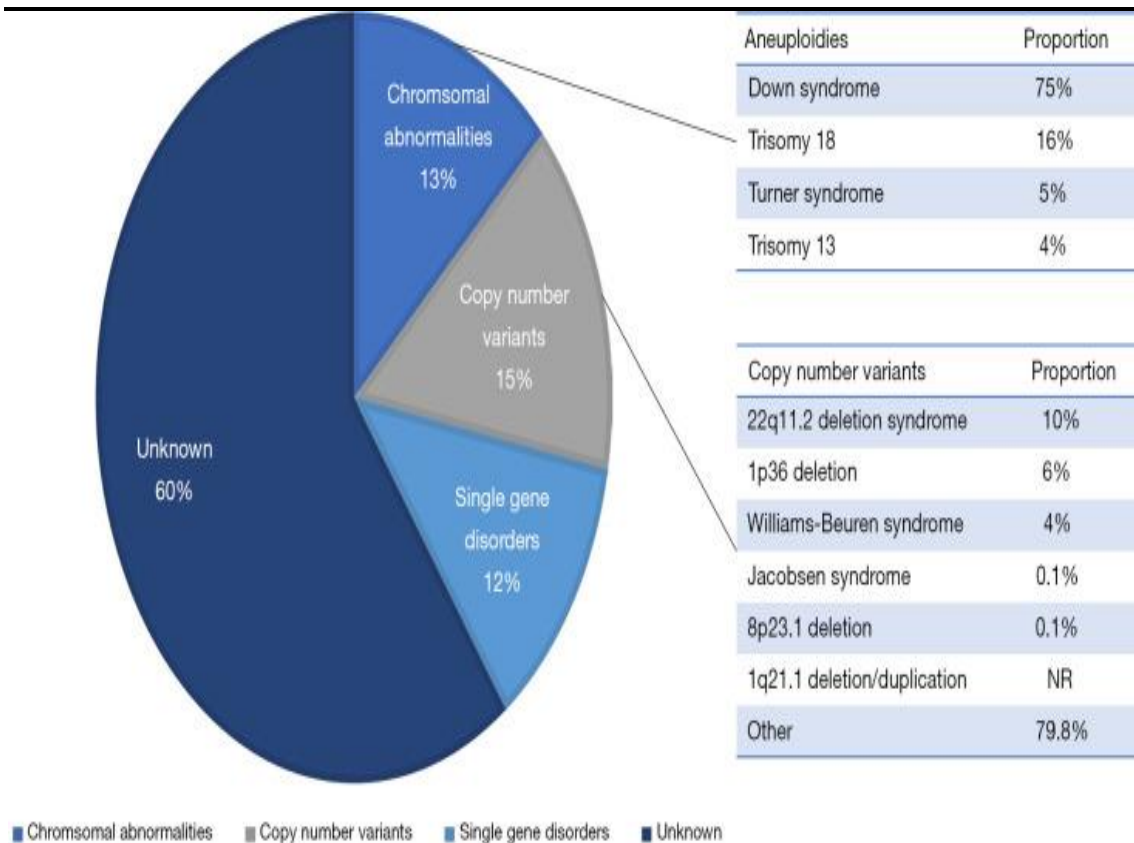


Figure 1

They are established genetic causes of congenital heart disease. Chromosomal abnormalities, copy number variation and single gene variants are associated with ~40% of congenital heart disease cases but the majority (60%) of congenital heart disease remains unknown. All percentages are approximate based on recent publications [11,15-17](#). NR, not reported.

Transcription factors

Transcription factors involved in cardiac development have been identified by genetic studies with multiple animal model systems [32,34](#). NKX, GATA and T-box family members constitute the core regulatory network that is responsible for normal cardiogenesis and are causative genes in CHD [34](#).

Mutations in the homeobox transcription factor *NKX2-5* were first reported as the cause of non-syndromic CHD by studying four kindreds with autosomal dominant disease [28](#). The common phenotype associated with *NKX2-5* mutations is atrial septal defect (ASD) along with atrioventricular conduction abnormalities [29](#). *NKX2-5* mutations have since been reported in a wide spectrum of CHD, including ventricular septal defect (VSD), tetralogy of Fallot (TOF), subvalvar aortic stenosis (AS), pulmonary atresia and hypoplastic left heart syndrome (HLHS), as well as atrioventricular conduction abnormalities, leading to complete heart block and sudden cardiac death [30-33](#). Previous studies demonstrated that mutations in the homeodomain of *NKX2-5* are a case of ASD, while mutations outside the homeodomain may result in TOF [35](#). In addition, mice harboring *NKX2-5* mutations have been reported to recapitulate cardiac phenotypes found in humans [36-38](#).

Identification of *NKX2-5* mutations is clinically beneficial in terms of detecting patients with the increased risk of progressive conduction system disease, sudden cardiac death or asymptomatic ASD.

Challenges with interpretation of NGS results

Although NGS technologies in CHD cohorts have contributed to identifying variants associated with CHD risk, NGS techniques have some challenges that have limited translation to the clinical setting. First, there are difficulties in variant prioritization and interpretation. Second, establishing the pathogenicity of identified variants is still challenging even with advances in *in vitro* and *in vivo* genetic modelling of CHD. Third, with the increased availability and use of WGS, the role of noncoding variation in the genetic architecture of CHD is not clear.

Clinical implications of recent genetic advances

Genetic testing

Over the past 20 years, the advanced genetic testing methodologies (e.g., CMA and exome sequencing) are increasingly being incorporated into the genetic evaluation of patients with CHD, and the results of this testing has important clinical implications. The clinical benefits of genetic testing for patients with CHD include establishing a genetic diagnosis, anticipatory management of CHD and associated extra-cardiac conditions, and clinical screening of at-risk family members ⁴⁰. In addition, genetic testing can provide the information about the genetic causes and the recurrence risk of CHD to support reproductive decisions and to guide perinatal management. While CMA and single-gene testing for specific syndromes are currently utilized as standard genetic testing for patients with CHD and extra-cardiac abnormalities, diagnostic use of NGS technology is allowing the interrogation of large datasets of genetic variants. The overall diagnostic yield of genetic testing varies from the low single digits to close to 40% which depends on the tests available the anatomical lesions, and the presence of extra-cardiac or other relevant clinical features ^{13,27}. Despite the potential utility variant interpretation is challenging as genotype-phenotype correlations remain elusive and phenotypic heterogeneity or incomplete penetrance is present. Communicating complex genetic findings to potentially unsuspecting patients is also challenging. Given the potential psychosocial impact of genetic testing in asymptomatic, phenotype-negative individuals, it is therefore critical that genetic testing should be offered within the context of appropriate genetic counselling so that families are given the opportunity to discuss insurance and other risks well in advance ⁶.

Genetic prediction of clinical outcomes

Despite advances in our understanding of genetics underlying CHD, prediction of clinical outcomes by using genetic findings remains challenging. Initial successful examples of linking common genetic variants for clinical care were limited to areas of prediction of disease risk, disease classification, and drug response ⁴¹. Apolipoprotein E genotypes were associated with adverse neurodevelopmental outcomes after cardiac surgery in patients with CHD ^{42,43}. Additionally, in patients with single ventricle, adrenergic receptor genotypes were associated with poor postoperative outcomes, and renin-angiotensin-aldosterone receptor genotypes were linked to failure of ventricular remodeling after surgery, impaired renal function and somatic growth ⁴⁴.

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