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Review Article

Crucial Genes in Cardiogenesis: Their Role in Congenital Heart Disease

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Abstract

Congenital heart diseases (CHDs) arise from anatomical abnormalities in the heart and major blood vessels during fetal development, significantly impacting morbidity and mortality rates globally. Key genes play crucial roles in cardiogenesis and the pathogenesis of CHD. Notable among these are NKX2-5, GATA4, TBX1, TBX5, and KDM6A. NKX2-5 is essential for cardiac morphogenesis and is linked to various defects, including atrial septal defects. GATA4 acts as a powerful activator of cardiac genes and works in conjunction with NKX2-5 to initiate cardiogenesis; variants in this gene are associated with multiple CHDs. TBX1 and TBX5 are critical for proper cardiovascular development, with mutations resulting in significant phenotypes characteristic of specific syndromes. KDM6A, a histone demethylase, regulates gene expression during embryonic development and is implicated in CHD through its role in essential signaling pathways. Understanding these genes enhances the knowledge of CHD mechanisms, paving the way for personalized treatment strategies and improved clinical outcomes. Continued research into the genetic basis of CHD is vital for developing effective interventions and providing better genetic counseling for affected families.

Keywords: Congenital heart diseases (CHDs); RNA; GATA4

Congenital heart diseases (CHD) can be described as anatomical abnormalities in the heart or major blood vessels that develop during fetal growth [1]. More specifically, they are defined as significant structural defects in the heart or intrathoracic great vessels that have actual or potential functional implications [2]. CHD is the collection of disorders that impact the cardiovascular system. The four main cardiovascular conditions impacting children include acquired heart disease, arrhythmias, systemic hypertension, and congenital heart defects (CHD) [3]. Among these, CHD is the most common. It encompasses various other conditions including angina, stroke, rheumatic heart disease, CHD, peripheral arterial disease, aortic aneurysm and dissection, deep vein thrombosis, as well as other less prevalent cardiovascular ailments [4].

Congenital heart disease is the most common type of congenital cardiovascular malformation linked to birth defects, causing significant morbidity and mortality globally. The classification of CHD remains challenging due to its complex pathogenesis [5]. CHD includes a broad range of defects, from simple malformations with a favorable prognosis to more complex and severe abnormalities requiring multiple catheter-based or surgical interventions, often with uncertain long-term outcomes [6]. CHD is the most common hereditary impairment, with cardiac defects present in roughly 1% of all live births [7]. Approximately 20%–25% of CHD cases, equating to about 1 in 500 births, are classified as critical congenital heart defects (CCHDs) [8]. These critical cases necessitate immediate and extensive medical and surgical intervention for the infant's survival. CHDs pose a substantial challenge to both clinical practice and public health. In lower-income countries, where advanced medical resources are limited, CHDs are linked to exceptionally high mortality rates. In contrast, in high-income countries such as those in North America and Europe, CHDs are associated with lifelong health complications and significantly contribute to pediatric in-hospital care costs, making them one of the leading factors driving these expenses [9].

The inheritance of CHD is intricate. Significant structural abnormalities can arise early in embryonic development, impacting multiple organ systems [10]. The prognosis depends on the specific structural anomalies present, with 13% of newborns exhibiting extracardiac abnormalities or functional defects, potentially resulting in associated neurodevelopmental delays [11]. Genetic variants are the primary cause in 34% of CHD cases, but the extent to which these variants manifest as clinical symptoms varies greatly [12]. Understanding the intricate gene regulatory networks associated with these genes is essential to uncover phenotype diversity [13]. Development in sequencing methods, including gene screening, and whole-genome sequencing (WGS), along with a better understanding of the mechanisms behind CHD, will enable more personalized management based on an individual's risk profile [7]. A genetic diagnosis can enhance confidence in the diagnosis, prompt clinicians to diagnose the related extracardiac abnormalities, and provide valuable information for family planning as more individuals with CHD reach childbearing age [14]. With guidance from expert genetic counselors, individuals can be aware of the risks of passing genetic variants to their offspring.

Etiology of CHD

Despite significant advancements in medical care and detection technology, the underlying causes of most CHD remain poorly understood. Enhancing the understanding of disease mechanisms is crucial to reducing the frequency of CHD occurrences. Over recent decades, there has been a growing consensus that both genetic and environmental factors contribute to the development of CHD [15]. Progress in molecular genetic diagnosis has provided valuable opportunities to explore the genetic underpinnings of CHD. Moreover, numerous animal models have demonstrated the profound impact of genetic factors on CHD etiology. These studies have identified numerous structural genes, transcriptional regulators, and signaling molecules essential for normal cardiac development [16].

The development of CHD is complex, involving both genetic and environmental factors. Approximately 40% of CHD cases can be attributed to specific genetic causes. These genetic causes are highly diverse and include chromosomal anomalies or aneuploidies, which account for about 13% of cases, with a range between 9% and 18% [17]. Copy number variants (CNVs) are responsible for an estimated 10–15% of cases, varying from 3% to 25% in syndromic CHD and 3% to 10% in non-syndromic CHD [18]. Additionally, single-gene disorders contribute to 12% of CHD cases [19]. The genetic basis of CHD can be categorized into syndromic CHD, where congenital abnormalities are present in multiple organs, and non-syndromic CHD, where the abnormalities are confined to the heart.

Genetic abnormalities associated with syndromic CHD

Several well-known syndromes are associated with chromosomal aneuploidies, CNVs, and pathogenic variations in single genes. These syndromes include Down syndrome [20], Turner syndrome [21], 22q11.2 deletion syndrome (DiGeorge syndrome) [22], 1p36 deletion syndrome [23], Williams-Beuren syndrome [24], and Holt-Oram syndrome [25], among other genetic abnormalities.

Monogenic causes of non-syndromic CHD

Non-syndromic CHD can be broadly categorized into three groups:

- **Transcription factors:** This group includes genes such as CITED2 [26], GATA4 [27], TBX5 [28], and NFATC1 [29], along with other types of transcription factors.
- **Cell signaling molecules:** Examples in this category include ACVR1/ALK2 [30], HEY2 [31], NOTCH1 [32], and VEGFA [33] as well as various other cell signaling and adhesion proteins.
- **Cardiac structural proteins:** This category includes ACTC1 [34], DCHS1 [35], ELN [36], and MYH11 [37], in addition to other studied types of cardiac structural proteins.

Genetic alterations induced CHD

While the causes of CHD are multifactorial, recent genetic research has highlighted the significant impact of genomic variations on its development. Aneuploidies, marked by chromosomal abnormalities, and CNVs, including structural genomic disorders, have been confirmed as key factors in the genetic underpinnings of CHD. Furthermore, monogenic genetic patterns, which involve mutations in single genes, have been identified as etiological factors in a subset of CHD cases. Figure 1 documented the mode of action and their respective inheritance mechanisms. Understanding the complex interactions among these genetic changes is crucial for gaining deeper insight into the genetic basis of CHD, which can lead to earlier diagnosis, improved prognostication, and personalized therapeutic strategies [7].

Genetics and pathogenesis of CHD

Various epigenetic factors can influence genes associated with CHD. As a result, both genetic and epigenetic factors are increasingly recognized as significant triggers in the pathogenesis

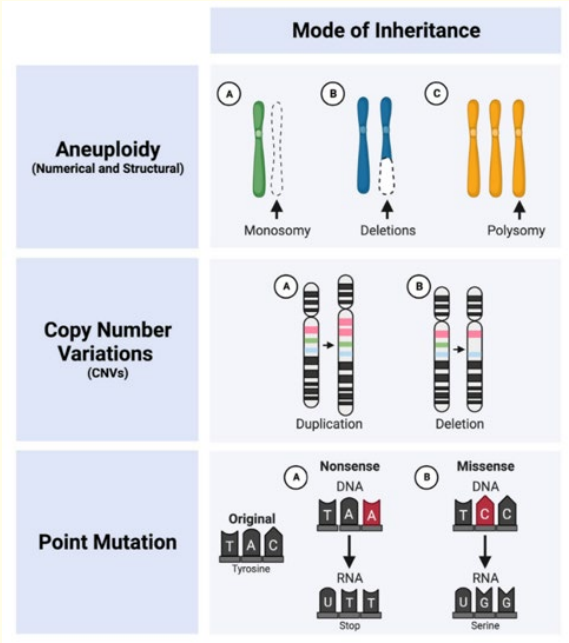

Figure 1: Type of inheritance. Genetic modifications, involving aneuploidy, copy number alterations, and point mutations, lead to the pathogenesis of CHD. This figure has been created using Bio Render [7].

of CHD [5]. Several genes linked to CHD, such as NKX2-5, GATA4, TBX5, NOTCH1, and TBX20, were originally identified through early genetic techniques [38]. While advances in clinical management have enhanced the survival rates of children with CHD, adult survivors often face cardiac and non-cardiac comorbidities that impact their quality of life and prognosis. Therefore, understanding the genetic causes of CHD is crucial, not only for providing effective genetic counseling to patients and their families but also for potentially improving clinical outcomes by identifying patients at risk. Moreover, advancements in genetic technologies, such as massively parallel sequencing, have enabled the identification of new genetic causes for CHD [6].

Due to significant advancements in disease recognition and enhanced medical and surgical management, over 90% of children with CHD now survive into adulthood [39]. Consequently, understanding the genomic architecture of CHD is becoming increasingly important in clinical practice.

While significant progress has been made in understanding the genetic causes of other inherited cardiac diseases, such as cardiomyopathy and arrhythmias, it is only in the past couple of decades that a deeper understanding of the molecular pathways regulating cardiovascular development has clarified the genetic basis of CHD [40]. However, the detailed genetic architecture of CHD and the ways in which disruptions in these regulatory mechanisms lead to various CHD phenotypes are still being actively researched [6].

Remarkable improvements in genetic sequencing technologies, such as massively parallel or next-generation sequencing (NGS), have enabled the identification of rare variants in new candidate genes that are likely to contribute to non-syndromic CHD [41]. Additionally, recent progress in powerful new techniques like single-cell RNA sequencing (scRNA-seq) has revealed the roles of individual cells in cardiac development and the pathogenic mechanisms by which genetic mutations in a small subset of cells lead to cardiac malformations [42].

Essential genes linked to cardiogenesis and congenital heart defects

Cardiac development is a meticulously regulated process orchestrated by cardiac transcription factors (cTFs). The spatiotemporal expression of crucial genes (Figure 2), and regulators that determine cardiac cell lineage drives the development and differentiation of the cardiovascular system [43]. During this critical period, the heart is highly susceptible to errors, and even minor alterations in gene expression or dosage can result in malformations in heart structures, contributing to CHD [44].

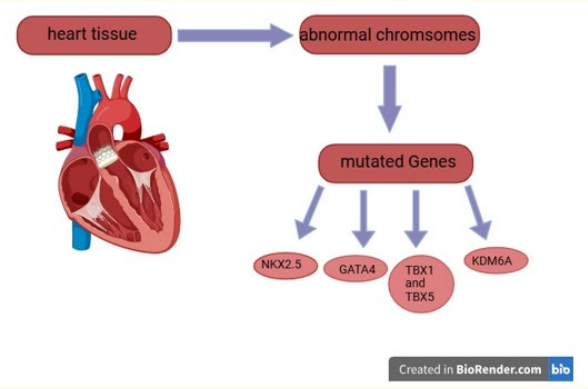

Figure 2: Essential genes implicated in CHD.

It is estimated that around 400 genes may be involved in the development of CHD, many of which have yet to be identified [19]. These include genes encoding (1) critical and interconnected cardiac transcription factors (cTFs) involved in cardiac development, such as NKX2.5, GATA4, and T-box family TBX1 and TBX5; (2) structural proteins like MYH6, ACTC1, and ELN; and (3) signaling factors, including neurogenic locus notch homolog protein 1 and vascular endothelial growth factor [40]. Additionally, advances in bioinformatics tools will facilitate more sophisticated analyses. Coupled with many collaborative efforts, these advancements will provide an opportunity to assess the impact of genetic variations that predispose individuals to complex forms of heart development defects [45].

NKX2.5

NKX2-5 gene is a transcription factor containing a homeobox domain that plays a vital role in early heart development [46]. It is situated on chromosome 5q35.1 and is extensively researched due to its essential function in cardiac morphogenesis, electrical conduction, and chamber formation [47]. This gene is expressed at the early embryonic stage and remains crucial for maintaining cardiac structure and function [46]. Variants in NKX2-5 have been closely linked to congenital heart defects (CHDs), conduction abnormalities, and certain types of cardiomyopathies.

NKX2.5 is a key regulator of cardiac development. In zebrafish, ectopic expression of nkx2.5 expands the cardiogenic field [48]. Although heart development begins, it halts early, suggesting some redundancy within the NK2 gene family in mammals. Mutations in NKX2.5 are frequently linked to atrial septal defects (ASDs) and conduction abnormalities. Additionally, NKX2.5 mutations have been observed in cases of VSD), TOF, aortic stenosis, and hypoplastic left heart syndrome (HLHS), highlighting the multifaceted roles of NKX2.5 in heart development [6].

GATA4

One of the essential genes frequently implicated in CHD and cardiogenesis is GATA4. This gene is a powerful activator of numerous cardiac genes, involving those encoding natriuretic peptides (NPPA and NPPB), cardiac myosin heavy chain (MYH6 and MYH7), and troponin isoforms (TNNI3 and TNNC1), and the cardiac muscarinic m2 acetylcholine receptor (CHRM2). GATA4 functions as a cofactor with NKX2.5; neither gene alone can trigger

cardiogenesis [49]. GATA4, along with the relevant GATA5 and GATA6 genes, is expressed in the developing heart. Variants of GATA genes have been linked to CHD, with GATA4 variants being related to ASD, VSD, and TOF [6].

TBX1 and TBX5

TBX5 is highly expressed in the forelimb buds and the developing heart, while TBX1 is located in the pharyngeal endoderm, mesoderm, and ectoderm. Loss-of-function mutations in TBX1 or TBX5 lead to significant cardiovascular phenotypes, which are characteristic of 22q11.2 deletion syndrome and Holt-Oram syndrome, respectively [50]. Isolated variants in TBX1 result in highly variable phenotypes. In humans, TBX1 variants are often linked to abnormalities in pharyngeal arch development and ventricular septation. The function of TBX1 is evidently complex and dose-dependent, so even small variants, such as single nucleotide polymorphisms (SNPs) or changes in its expression levels, can lead to a range of effects [51].

KDM6A

Lysine demethylase 6A (KDM6A), located on the X chromosome, encodes a histone demethylase that removes repressive methylation markers (H3K27me3), thereby activating gene expression [52]. It plays a critical role in embryonic development, including the regulation of key cardiac genes. Mutations or disruptions in KDM6A have been associated with congenital anomalies, including CHD, due to its role in modulating pathways such as NOTCH, WNT, and BMP, which are essential for heart formation [53].

Previous studies have shown that KDM6A mutations impair chromatin remodeling, leading to defective transcription of genes critical for cardiac development [54]. In mouse models, KDM6A deletion results in defective heart looping and separation, mimicking human CHD phenotypes [55].

KDM6A in mice has demonstrated its essential role in embryonic development [56]. Complete loss of KDM6A results in embryonic lethality, indicating KDM6A is needed for survival [57]. Heterozygous KO mice, which partially mimic Kabuki syndrome phenotypes, show defects in neural development and skeletal formation. In cancer research, KDM6A-deficient mouse models have been used to study its role as a tumor suppressor [58]. Loss of KDM6A has been shown to increase susceptibility to bladder and pancreatic cancer, supporting clinical findings that KDM6A mutations drive tumorigenesis [59]. Conditional knockout models have also been used to investigate its role in immune cell differentiation, cardiac development, and metabolic regulation.

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