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The genetic landscape of congenital heart disease in pediatrics: From molecular insights to emerging therapies

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Abstract

Aim: This review aims to explore the genetic basis of congenital heart disease (CHD) in pediatric populations by identifying key gene mutations involved in cardiac development and evaluating the current status of genetic screening and emerging gene-targeted therapies. The objective is to bridge the gap between molecular discoveries and clinical applications in pediatric cardiology.

Methodology: A comprehensive literature review was conducted across multiple databases including PubMed, Cochrane Library, Scopus, and ClinicalTrials.gov. Articles published between 2010 and 2024 were selected based on strict inclusion criteria, focusing on pediatric patients with CHD, documented genetic mutations, and studies involving genetic diagnostics or interventions. Data were extracted regarding gene function, mutation effects, intervention types (e.g., genetic screening, CRISPR-Cas9 therapy), and clinical outcomes.

Results: Key genetic mutations such as NKX2-5, GATA4, TBX5, NOTCH1, and CHD7 were identified as major contributors to various forms of CHD, including atrial and ventricular septal defects, valve anomalies, and syndromic heart conditions. These mutations affect transcriptional networks critical for cardiac morphogenesis. Genetic screening has proven valuable in early diagnosis and family counseling, while preclinical studies using CRISPR-Cas9 and other gene-editing technologies show promise in correcting pathogenic mutations. However, gene therapy remains largely experimental and is not yet applied in routine clinical practice.

Conclusion: Genetics plays a central role in the etiology and progression of congenital heart disease in children. The integration of genetic testing into pediatric cardiology is transforming diagnostic and management approaches. Although gene-targeted therapies are still in developmental stages, ongoing research supports their potential as future curative interventions. Large-scale clinical trials and ethical considerations will be essential for translating these innovations into standard care.

Keywords: Pediatric cardiology; Congenital heart disease; Genetic mutations; NKX2-5; GATA4; TBX5; CRISPR-Cas9; Gene therapy; Genetic screening; CHD7

1. Introduction

Congenital heart disease (CHD) remains the most common type of birth defect, affecting approximately 1% of live births worldwide. Despite significant improvements in surgical techniques, medical management, and critical care, CHD continues to represent a major cause of morbidity and mortality in infants and children. Historically, the focus of CHD management has been predominantly structural—centered on anatomical correction through surgery or catheter-based interventions [1]. However, in recent decades, the growing field of cardiovascular genetics has revealed that many

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congenital heart defects are deeply rooted in molecular and genetic abnormalities that arise during early embryogenesis.[2]

The human heart Is a complex organ that forms through a highly coordinated sequence of genetic signaling pathways. Disruption in the expression or function of key developmental genes can result in incomplete or abnormal formation of cardiac structures such as septa, valves, and outflow tracts. Mutations in genes such as NKX2-5, GATA4, and TBX5 have been directly implicated in a range of cardiac malformations, from isolated atrial septal defects to more complex syndromic conditions like Holt-Oram and CHARGE syndromes [3]. These discoveries underscore the importance of a genotype-to-phenotype approach in understanding the variability, severity, and progression of CHD.

In parallel with our expanding knowledge of cardiac genetics, technological advances such as next-generation sequencing (NGS) and CRISPR-Cas9 gene editing have revolutionized both diagnostics and therapeutic possibilities. NGS allows for the rapid and comprehensive identification of pathogenic variants even in neonates and fetuses, enabling earlier diagnosis and family counseling. Meanwhile, preclinical research into gene correction technologies suggests the potential for future curative therapies that target the molecular root of disease rather than merely addressing its anatomical consequences.[4]

Given the critical and evolving role of genetics in pediatric cardiology, this review aims to provide a comprehensive overview of the current knowledge surrounding genetic mutations in CHD, assess the outcomes of recent clinical studies and trials involving gene-targeted interventions, and evaluate the future potential of personalized genomic medicine in this field. In doing so, we hope to bridge the gap between molecular discoveries and clinical applications, and highlight the challenges and opportunities that lie ahead in the era of precision cardiology.[5]

2. Methods

2.1. Study Design and Objective

This study was designed as a comprehensive narrative and systematic review, aiming to synthesize the current scientific literature on the genetic basis of congenital heart disease (CHD) in pediatric populations. The review focused on identifying and analyzing genetic mutations associated with CHD, as well as assessing the clinical outcomes of genetic screening and emerging gene-targeted therapies. The objective was to explore both the biological mechanisms and the clinical applications of genetic findings in pediatric cardiology.

2.2. Search Strategy

A systematic literature search was conducted using major electronic databases including PubMed, Embase, Scopus, Cochrane Library, Google Scholar, and ClinicalTrials.gov. The search was limited to peer-reviewed articles published between January 2010 and March 2024. The following keywords and Boolean operators were used:

"congenital heart disease" AND "genetics" OR "genetic mutations" OR "gene therapy" OR "pediatric cardiology" OR "CRISPR-Cas9" OR "clinical trials" OR "genetic screening."

The search was supplemented by manually reviewing the reference lists of relevant articles and reviews to identify additional eligible studies not captured by the database queries.

2.3. Inclusion and Exclusion Criteria

Studies were selected based on the following inclusion criteria:

- Research involving pediatric patients (0–18 years) diagnosed with congenital heart disease.
- Studies examining the role of specific genetic mutations in cardiac development or disease progression.
- Articles reporting clinical trials, cohort studies, case-control studies, or translational preclinical research related to gene-targeted therapies or genetic screening.
- Publications written in English with accessible full texts.

Exclusion criteria included:

- Studies focused solely on adult-onset heart disease or acquired cardiovascular conditions.
- In vitro studies without in vivo validation.

- Non-peer-reviewed sources, editorials, opinion pieces, or conference abstracts lacking primary data.

2.4. Data Extraction and Analysis

From each selected study, the following data were systematically extracted: study design, sample size, patient age range, specific genetic mutations involved, type and severity of CHD, genetic diagnostic methods, type of intervention (e.g., genetic screening, gene therapy), and clinical outcomes. When applicable, outcome measures such as improvement in cardiac function, reduction in surgical need, or changes in disease progression were recorded.

Data were summarized in thematic categories, and qualitative synthesis was performed to identify trends, gaps, and consistencies across studies. Where multiple studies addressed the same gene or therapy, comparative analysis was conducted to assess the consistency of findings. A meta-analysis was not performed due to the heterogeneity of study designs and outcome measures, but aggregated clinical trends were noted where appropriate.

3. Results

The genetic underpinnings of congenital heart disease (CHD) have become a central focus of pediatric cardiology research in recent years. With advancements in genome sequencing and molecular biology, scientists and clinicians are now able to identify specific mutations that directly contribute to the malformation of cardiac structures during embryonic development. Among the most well-characterized genes involved in pediatric CHD are NKX2-5, GATA4, TBX5, NOTCH1, and CHD7—each playing distinct and sometimes overlapping roles in heart development.[6]

One of the earliest and most frequently studied genes in this context is NKX2-5. This gene encodes a cardiac-specific homeobox transcription factor essential for heart looping, chamber formation, and conduction system development. Mutations in NKX2-5 are commonly linked to atrial septal defects (ASDs) and atrioventricular conduction block. These mutations are often inherited in an autosomal dominant manner with incomplete penetrance, meaning that not all individuals with the mutation show symptoms, yet they can still pass it to their offspring. Functional studies have shown that mutant NKX2-5 proteins lose their ability to bind DNA or interact with cofactors such as GATA4, thereby disrupting transcriptional regulation of downstream genes vital for cardiac morphogenesis. Clinically, patients may present with isolated ASDs, AV block, or both, and in some cases, may progress to complete heart block necessitating pacemaker implantation.[7]

GATA4 is another transcription factor that plays a critical role during cardiac embryogenesis, particularly in the development of the endocardial cushions, septa, and myocardium. GATA4 works synergistically with NKX2-5 and TBX5 to regulate cardiac gene expression. Mutations in GATA4 have been linked to a spectrum of cardiac anomalies, including ventricular septal defects (VSDs), atrial septal defects, and even conotruncal defects in certain cases. GATA4 mutations can either be inherited or occur de novo, and several genotype-phenotype studies have indicated that the nature and location of the mutation significantly affect clinical severity. Loss-of-function mutations tend to be associated with more severe defects and reduced myocardial function, as they impair cardiomyocyte proliferation and differentiation.[8]

Moving forward, TBX5, the gene implicated in Holt-Oram syndrome, is a crucial determinant of cardiac and limb development. Holt-Oram syndrome is an autosomal dominant disorder characterized by upper limb malformations (especially radial ray anomalies) and cardiac defects, most commonly ASDs and VSDs. TBX5 encodes a T-box transcription factor that regulates the expression of structural and signaling proteins in the developing heart. Experimental models in mice have demonstrated that TBX5 haploinsufficiency results in impaired chamber septation and conduction system anomalies. In humans, patients with TBX5 mutations often present early in life, and diagnosis is typically supported by clinical genetic testing combined with echocardiographic evaluation. The condition is also notable for its frequent association with bradycardia and conduction delays, reinforcing the gene's dual role in structural and electrical cardiac development.[9]

Another important gene is NOTCH1, which plays a central role in cell fate determination, particularly during valvulogenesis—the formation of heart valves. Mutations in NOTCH1 have been strongly associated with bicuspid aortic valve (BAV), aortic valve stenosis, and aortic coarctation. These conditions often go undetected until later in life, although evidence now supports the utility of early genetic screening in individuals with family histories of valve defects. NOTCH1 mutations appear to interfere with endothelial-to-mesenchymal transition (EMT), an essential process in valve and outflow tract development. In addition to structural abnormalities, NOTCH1 has been implicated in the calcification of the aortic valve in adulthood, making it a gene of interest not only in congenital conditions but also in age-related cardiovascular disease.[10]

Finally, the CHD7 gene, encoding chromodomain helicase DNA-binding protein 7, is most famously associated with CHARGE syndrome—a complex genetic condition involving coloboma, heart defects, choanal atresia, retarded growth, genital anomalies, and ear abnormalities. In over 70% of CHARGE patients, CHD7 mutations are identified, with cardiac anomalies present in approximately 75–85% of cases. Common cardiac findings include tetralogy of Fallot, atrioventricular septal defects, and aortic arch anomalies. Unlike the more "isolated" cardiac gene mutations, CHD7-related heart disease often appears as part of a broader systemic disorder. This highlights the importance of multidisciplinary care and genetic counseling in managing affected children and their families.

As genetic databases grow and sequencing becomes more affordable and widespread, researchers are uncovering even more candidate genes involved in CHD, such as ZIC3, ELN, JAG1, and TGFβ pathway genes. The future may reveal that CHD results from complex interactions between multiple low-penetrance mutations, epigenetic modifications, and environmental factors such as maternal illness or drug exposure during pregnancy.[11]

4. Discussion

The genetic architecture of congenital heart disease is complex and multifactorial, involving both high-penetrance mutations in developmental genes and more subtle genetic variants that modify disease expression. The five key genes discussed—NKX2-5, GATA4, TBX5, NOTCH1, and CHD7—represent only a subset of the growing catalog of genetic contributors to CHD, yet they illustrate the diversity of cardiac phenotypes and mechanisms affected by genetic disruption.[12]

A major theme emerging from these findings is that many of these genes operate in overlapping transcriptional networks and signaling pathways. Disruption of one gene often leads to a cascade of downstream effects, altering not just the structure of the heart but also its function and electrophysiological integrity. This explains why patients with genetic CHD frequently exhibit comorbid conditions like arrhythmias or progressive heart failure, even after successful surgical correction of structural defects.

From a clinical standpoint, these genetic insights are transformative. Early genetic testing, particularly in syndromic or familial cases, can guide diagnostic decision-making, improve risk stratification, and inform long-term follow-up plans. Furthermore, the identification of disease-causing mutations opens the door for targeted interventions, such as personalized drug therapies, gene correction strategies (e.g., CRISPR-Cas9), and advanced reproductive counseling for at-risk families.[13]

Nevertheless, challenges remain. The variable expressivity and incomplete penetrance of many mutations make it difficult to predict individual outcomes based solely on genetic findings. Ethical concerns also surround the use of gene editing technologies in pediatric populations, and the long-term consequences of such interventions are still unknown.

In conclusion, the integration of genetic analysis into pediatric cardiology is revolutionizing our understanding and management of congenital heart disease. While we are still in the early stages of applying this knowledge therapeutically, the foundation has been laid for a future in which precision medicine plays a central role in the care of children with CHD.

5. Conclusion

The growing body of evidence linking specific genetic mutations to congenital heart disease (CHD) in children has significantly reshaped the landscape of pediatric cardiology. Through the exploration of key genes such as NKX2-5 , GATA4 , TBX5 , NOTCH1, and CHD7 , it has become clear that genetic factors play a central role not only in the structural development of the heart but also in its electrical function and long-term physiological performance. These mutations interfere with highly conserved molecular pathways that are essential for embryonic cardiac morphogenesis, leading to a broad spectrum of clinical manifestations ranging from isolated septal defects to complex syndromic presentations.

Advances in molecular diagnostics—particularly next-generation sequencing—have made it possible to detect these mutations early, often before the onset of clinical symptoms. This early detection allows for proactive monitoring, timely interventions, and personalized treatment plans tailored to the genetic profile of each patient. Furthermore, as research into gene-targeted therapies and genome editing progresses, the potential to directly correct or mitigate the effects of pathogenic mutations is becoming increasingly plausible, although still largely experimental.

Despite these promising developments, several challenges remain. Many of the current findings are based on small sample sizes, and the variability in phenotypic expression even within families makes it difficult to draw universally

applicable conclusions. Moreover, ethical considerations, especially concerning gene editing in pediatric populations, must be addressed carefully before such therapies can be widely adopted.In conclusion, genetics has emerged as a cornerstone in the understanding, diagnosis, and future treatment of congenital heart disease in children. While we are not yet at the point of routine clinical application of gene therapies, the integration of genetic screening and research into routine cardiology practice holds immense promise for improving outcomes and transforming care for pediatric patients with CHD

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

The study was approved by the Ethics Review Committee of the Bashkir State Medical University,

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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