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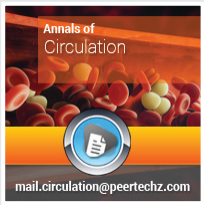

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Review Article

The genetic etiology of critical congenital heart disease

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Abstract

Congenital Heart Disease (CHD) is the most common kind of birth defect. Congenital heart disease is the most common birth defect and the leading cause of death in newborns. The causes of CHD are complicated and involve both genes and the environment. Congenital heart disease includes problems with the septum, the valves, and the outflow tract. Correctional heart surgery and new strategies for managing CHD have massively enhanced life expectancy. 490 percent of CHD newborns who live through their first year will become adults. Studies of the molecular genetics of humans and animal models of development are enhancing our understanding of normal heart development and cardiac diseases. A recent study demonstrates that microRNAs are implicated in congenital heart diseases. Epigenetic variables were eventually revealed to influence heart development. Several genes are responsible for congenital cardiac abnormalities as well as genetic disorders. This paper describes the categorization, environmental, and genetic causes of Coronary Heart Disease (CHD), the role of key CHD-causing genes, and potential options for preventing CHD.

Introduction

Cardiac anatomical irregularities known as Congenital Heart Defects (CHDs) affect embryos and newborns. Congenital Heart Disease (CHD) is the most common birth abnormality, with estimates of its frequency ranging from 2-3 per 1000 live births for clinically acute defects to 6 per 1000 for moderately severe CHD. These heart wall defects might have an impact on internal valves, the septum between the atria and ventricles, and significant arteries and veins [1]. Congenital heart abnormalities (CHDs) account for about 30% of cardiac illnesses and, depending on their severity, have a significant infant mortality rate [2]. Depending on the type of cardiac lesion, these defects might have mild to fatal symptoms. Poor weight gain, breathing problems, fainting, cyanosis, problems with limb development, respiratory infections, and other symptoms can occur [3]. The symptoms of CHDs can vary. These are collectively referred to as the "VACTERL" alliance. (V for vertebral malformations, A for anal atresia, C for cardiovascular problems, T for tracheoesophageal fistula, E for esophageal atresia, R for renal (kidney) and/or radial anomalies, and L for limb deformities) [4].

The causes of CHD are complicated and include both hereditary and environmental factors. Several of the molecular networks that drive normal heart development and the morphogenetic events that are disrupted during cardiogenesis and lead to CHD are also being unraveled [5,6]. Infectious disorders and CHD were the leading causes of newborn and infant deaths before surgical intervention. In the United States, around 1%, i.e., 40,000 babies per year, are affected by congenital heart defects. 25% (1 in 4) of CHD babies suffer catastrophic CHD. 4.2% of newborn fatalities were caused by CHD. The predicted survival rate for infants with a non-critical CHD is approximately 95% until age 18. Hence, the number of individuals with CHDs is rising. Globally, about 2% - 10% of live births are believed to be affected by CHD [7].

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The late 1950s advent of corrective heart surgery and breakthroughs in CHD long-term management have greatly enhanced life expectancy. Since more than 90% of infants with CHD who survive the first year of life continue into adulthood, clinical care has become more complicated because many patients now have late problems [8]. It has become clear that long-term clinical outcomes (including heart failure, arrhythmia, and aneurysm) vary across patients with the same type of CHD and between patients with different types of CHD [9-11]. Some have a simple clinical conclusion, whereas others are adversely affected by many late complications [12]. Based on medical records, it has been hard to figure out which patients are most likely to experience the most severe delayed complications. Since so many CHD patients have reached reproductive age, their offspring are also at risk [13].

Classification of CHD's

CHDs are typically categorized into two types: Isolated CHDs and complex CHDs, which are accompanied by other cardiac issues. They can be divided into cyanotic and acyanotic categories based on whether or not the affected infant turns blue. The 2002 "International Congenital Heart Surgery Nomenclature" divides CHDs into hypoplasia, obstruction, septal, and cyanotic defects [14]. Hypoplasia occurs when one side of the heart develops abnormally, preventing it from pumping blood. Depending on the affected side, it is called hypoplastic left or right heart syndrome. Hypoplasia symptoms include cyanosis. This rare CHD is the most dangerous. CHDs result from narrow or blocked heart valves, veins, or arteries. Aortic stenosis, aortic coarctation, and pulmonic stenosis are common, although subaortic and bicuspid aortic valve (BAV) stenoses are uncommon. Most blockages produce hypertension or heart hypertrophy [15]. In septal defects, the septum fails to develop between the atria (atrial septal defects [ASDs]) and the ventricles (ventricular septal defects [VSDs]). The most common CHDs are VSDs and ASDs [16]. Inadequate delivery of oxygen to the body's tissues results in cyanosis, which is a bluish discoloration of the skin. Cyanotic defects include total atypical pulmonary venous connection, tricuspid atresia, chronic truncus arteriosus, tetralogy of Fallot (TOF), and transposition of the major arteries [17].

Environmental factors causing CHD

CHD can be genetic or nongenetic. CHD is associated with environmental teratogens including PCBs, dioxins, and pesticides; maternal risk factors like alcohol consumption; febrile disorders in the first trimester; and antibiotic usage during pregnancy, in addition to infectious agents [18,19]. Nongenetic causes continue to rise despite global attempts to fight them. CHD is also connected with an increase in obesity, diabetes, hypercholesterolemia, and antiviral medication [20]. CHD can be caused by gene mutations, single nucleotide polymorphisms, altered RNA, epigenetics, chromosomal abnormalities (such as duplication or deletion), and other reasons.

CHD and its genetic causes

CHD is a disease that can be caused by different genes. Different types of CHD have been linked to specific chromosomal problems, such as the trisomy of chromosome 21 and the deletion of chromosome 22q11. CHD has been linked to 50 human disease genes, but most CHD-related mutations happen in just a few developmental genes [21], like NKX2–5, GATA4, and NOTCH1 [22-24]. Targeted gene deletion in mice found that more than 500 genes cause problems with the heart [25] About the same number of CHD genes are found in all humans. Recognize that most people with CHD have never had a mutation or chromosomal defect that could have caused it. CHD genes have been found, but their genetic causes are not identified [26,27]. Molecular genetics and developmental biology have found many genes for heart development. Gene mutations are linked to a number of birth defects of the heart and genetic diseases. Because the mutations were exclusively found in affected individuals and were absent from control samples, it was determined that they changed the structure or function of proteins [28].

Functions of the CHD-causing genes

- **NKX2-5, NK2 transcription factor-related, locus 5:** Genes that include homeoboxes have important roles in the regulation of tissue-specific gene expression, which is essential for the differentiation of tissues and for establishing temporal and spatial developmental patterns. Because mutations in NKX2-5 disrupt the development of the heart in the embryo, it is clear that NKX2-5 plays a crucial role in this process [29].

- **CFC1, cripto, FRL-1, cryptic family 1:** This gene makes a member of the CFC family, which is part of the EGF-Cripto, Frl-1, and Cryptic (CFC) families. These proteins participate in crucial aspects of the intercellular signaling pathways that are active during embryogenesis. This gene has the potential to become mutated, which would result in autosomal visceral heterotopia. This protein is involved in left-right asymmetric morphogenesis, which occurs during the process of organ formation [30].

- **PROSIT240, MED13L, mediator complex subunit 13-like:** The evolutionarily conserved THRAP genes encode a family of proteins that regulate embryonic development. These genes are also referred to as THRAP2. THRAP2 has a vital role in the early development of both the heart and the brain [31].

- **ZFPM2, zinc finger protein, multitype 2:** This gene is responsible for the encoding of a zinc finger protein that is broadly expressed among members of the FOG family of transcription factors. GATA family proteins, which play a crucial regulatory role in mammalian hematopoiesis and cardiogenesis, are able to influence the activity of other family members [32].

- **Jagged 1, jagged 1 (Alagille syndrome):** The jagged-1 protein that is present in humans is the homolog of the jagged protein that is found in Drosophila. The JAG1 gene is responsible for encoding this protein. Alagille syndrome is caused by mutations in the Jagged 1 protein, which is the ligand for the receptor notch 1 [33].

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- **CRELD1, cysteine-rich with EGF-like domains 1:** The class of cysteine-rich domains known as epidermal growth factor-like repeats is responsible for mediating interactions between proteins that have a wide variety of functions. CRELD1 is the first member of a family of proteins that are found in matricellular tissue [34].

- **GATA4: GATA binding protein 4:** This gene's product is a zinc finger transcription factor that belongs to the GATA family and is a member of the GATA family. It is assumed that this protein can regulate genes that play a role in the differentiation and function of embryonic and myocardial cells. This gene mutation has been linked to septal defects in the heart [35].

- **ZIC3, Zic family member 3; heterotaxy 1:** This gene produces a member of the C2H2-type ZIC family, which is a zinc finger protein. Mutations in this gene induce X-linked visceral heterotaxy [36].

- **Activin A receptor, type 2, beta:** The TGF superfamily is comprised of structurally related signaling proteins, and activins are members of this family. Activins are dimeric growth and differentiation factors. These receptors are a family of transmembrane proteins.

- **LEFTYA, left-right determination factor 2:** The product of this gene is a member of the TGF-family protein. During development, the encoded protein is generated, and its production contributes to the determination of the left-right asymmetry of organ systems. This gene mutation has been linked to abnormalities in the left-right axis, most notably in the heart and lungs [37].

- **ELN, elastin:** The protein produced by this gene is one of the two portions of elastic fibers. These gene deletions and mutations were indeed associated with autosomal dominant cutis laxa and autosomal dominant cutis laxa, as well as supra-valvular aortic stenosis [38].

- **TBX5, T-Box 5:** This gene is a member of a phylogenetic family of genes known as the T-box genes, as all of them share a similar DNA-binding domain. It is possible that the encoded protein plays a role in the development of the heart as well as the specification of limb identity. There has been a connection established between genetic variations in this gene and Holt-Oram syndrome [39].

- **TFAP2B, transcription factor AP-2 beta:** The protein that is produced by this gene belongs to the AP-2 family of transcription factors. In addition to its role as a transcriptional repressor, this protein also plays the role of a transcriptional activator. The mutations in this gene are the cause of autosomal dominant Char syndrome, and we can deduce that it plays a role in the development of neural crest cells [40].

- **PTPN11, protein tyrosine phosphatase, non-receptor type 11:** This gene codes for a member of the protein tyrosine phosphatase (PTP) family. Signaling molecules called PTPs control processes as diverse as cell division, differentiation, and mitosis, as well as malignant transformation. Mutations in this gene account for Noonan syndrome and acute myeloid leukemia [41].

- **SOS1, son of sevenless homolog 1:** The guanine nucleotide exchange factor is the protein encoded by this gene. RAS proteins are membrane proteins that interact with guanine nucleotides and engage in signaling cascades. Gingival fibromatosis type 1 and Noonan syndrome type 4 are related to mutations in this gene [42]. There is a correlation between mutations in this gene and gingival fibromatosis 1 as well as Noonan syndrome type 4.

- **CHD7, chromodomain helicase DNA binding protein 7:** The protein encoded by this gene belongs to the helicase family and contains several different helicase domains. Certain people with CHARGE syndrome have been found to have genetic variations in this gene [43].

- **EVC, Ellis van Creveld syndrome:** The protein encoded by this gene possesses a transmembrane region and a leucine zipper. Ellis-van Creveld syndrome and Weyers acrodental dysostosis have been confirmed to be associated with this gene [44].

- **FBN1, fibrillin 1:** A member of the fibrillin family is produced by this gene. Marfan syndrome, isolated ectopia lentis, Weill-Marchesani syndrome, MASS syndrome, and Shprintzen-Goldberg craniosynostosis have all been linked to genetic variations in this gene [45].

- **KRAS and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog:** The protein encoded by this gene is a member of the small GTPase family. This transforming protein has been linked to several types of cancer, which include lung adenocarcinoma, mucinous adenoma, pancreatic ductal carcinoma, and colorectal cancer [46].

- **BRAF, v-raf murine sarcoma viral oncogene homolog B1:** This gene's product is a serine/threonine protein kinase, and it's a member of the Raf/Mil family. This protein controls the cell cycle, differentiation, and secretion-related MAP kinase/ERK signaling pathways. Variations in this gene have been related to cardiofaciocutaneous syndrome [47].

- **MEK1, MAP2K1, mitogen-activated protein kinase 1:** The protein encoded by this gene is a mitogen-activated protein (MAP) kinase and a member of the dual-specificity protein kinase family. Numerous cellular processes, such as proliferation, differentiation, transcription regulation, and development, involve this kinase [47].

- **MEK2, MAP2K2, mitogen-activated protein kinase 2:** The protein kinase encoded by this gene is a member of the mitogen-activated protein (MAP) kinase family with dual specificity. The importance of this kinase in

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the transmission of signals involving mitogen-induced growth factors is well established. Mutations in this gene result in the cardiofacial-cutaneous syndrome [48].

- **HRAS, v-Ha-ras Harvey rat sarcoma viral oncogene homolog:** It belongs to the family of Ras oncogenes. These gene products are essential components of signal transduction cascades. These gene mutations lead to the development of Costello syndrome. Several types of cancer have been linked to genetic variations in this gene [49].

- **TGFBR2, transforming growth factor receptor 2:** The protein encoded by this gene belongs to the TGFB receptor subfamily of Ser/Thr protein kinases. Marfan syndrome, Loeys-Deitz aortic aneurysm syndrome, and a variety of cancers have all been linked to a mutation in this gene [50].

The genetic structure of CHD

- **Chromosomal and mendelian syndromes:** Malformations of the aortic arch (Patent Ductus Arteriosus [PDA] and Aortic Coarctation), the outflow tract (Tetralogy of Fallot [TOF], the Common Arterial Trunk [CAT], and Transposition of the Great Arteries [TGA]), and the heart's ventricles (atrial septal defects [ASD], Ventricular Septal Defects [VSD], and Atrioventricular Septal Defects [AVSD]) are all defining traits of CHD [51]. An estimated 20% of CHD is caused by chromosomal and Mendelian abnormalities (11.9% and 7.4%, respectively) [52].

- **Non-Mendelian/non-chromosomal congenital heart disease:** It is obvious that our knowledge of the genetic pathways that lead to non-Mendelian, non-chromosomal (sporadic) CHD is confined. Epidemiological studies have shown that there is a 2% - 5% higher incidence of CHD recurrence in siblings and progeny, which implies a role for shared genes and/or environment [53].

Future perspectives and strategies

- **Bioinformatics:** The completion of the human genome project marks the beginning of the postgenomic period. In spite of the fact that the human genome contains between 30,000 and 40,000 genes, not much is known about their roles, interactions, and regulation. In order to discover the underlying molecular mechanisms of CHD, bioinformatics is an invaluable and indispensable resource. Discovering the molecular basis of coronary artery disease is an exciting and rapidly growing field of study. More research into the molecular mechanisms of cardiac development will lead to a better understanding of the genetic basis of CHD and, ideally, improved genetic counseling and treatment for affected individuals and their families [54].

- **Epigenetics:** Carcinoma, congenital malformations, developmental disabilities, and psychiatric disorders are just some of the diseases for which there is mounting evidence that epigenetic alterations, caused by DNA methylation and histone modifications, play an important role as genetic factors. DNA methylation is an epigenetic trigger that regulates gene expression. It is primarily established during gestation. Establishing and maintaining differentiated cell lines is possible because these expression states can be carried over to subsequent generations [55].

- **Animal models:** Studies in animals have greatly improved our knowledge of heart formation and uncovered new genes that may play a role in human disease. The remarkable homology between mammalian genomes, as well as the many similarities in anatomical structures, cell biology, and physiology, make mammalian analogues such as the mouse and rat suitable for modeling different diseases in human beings [56]. Modern transgenic techniques have allowed the creation of murine models that accurately represent the symptoms of human diseases. Consomic rat strains, in which an entire chromosome has been introgressed into the isogenic background of another strain, offer a rapid approach to mapping a trait to a chromosome [57].

- **MicroRNA:** MicroRNAs (miRNAs) are highly conserved, small (22-mer) RNA molecules that control the gene's expression by binding to the 3' untranslated locations of specific mRNAs. The scope and diversity of this class of tiny regulatory RNAs have only recently been acknowledged. A majority of grown consomic rats have a patent ductus arteriosus. An adult consomic rat's mediastinal dissection and aortic injection exhibit the passage of contrast from the aorta to the major pulmonary artery through a patent ductus arteriosus. The study groups of M.E. Mitchell et al. have presented evidence that miRNAs may operate as essential regulatory agencies in the early stages of development. There is speculation that the role of miRNAs in controlling gene expression in higher eukaryotes may be as essential as that of transcription factors. Each miRNA is expected to have a vast array of targets, and each mRNA may be influenced by many miRNAs. There are currently over 460 human miRNAs recognized [58]. In recent times, it was shown that targeted elimination of the muscle-specific miRNA, miR-1 to 2, demonstrated a variety of activities for miR-1 to 2 in the heart, comprising regulation of cardiac morphogenesis, electrical conduction, and cell-cycle regulation. MiRNA dysregulation may result in congenital heart disorders in human beings [59].

- **Gene expression (microarrays):** Accurate gene expression data for CHD can be obtained using microarray analysis. More than 60 percent of human genes have been identified as having several isoforms, according to recent studies. Conversely, proteins

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synthesized from alternatively spliced isoforms of the same gene can have distinct properties and functions. A better understanding of the roles played by the various splicing variants of genes is necessary for proper development [60].

- **Genome-wide studies:** The ability to conduct genome-wide genetic association studies to find susceptibility genes for common diseases has been made possible by recent improvements in genotyping techniques as well as our knowledge about human genetic variation. Large sample sizes (several hundred cases and controls) and multistage designs involving a large number of coding sequence variants (300,000) are required to accurately identify alleles with significant effect sizes (a twofold increase in relative risk). Another strategy for discovering low-frequency variants that influence disease susceptibility is the direct sequencing of key genes in cases and controls [61,62].

Conclusion

Cardiovascular disease molecular biology is fascinating and developing. Despite advances in heart development, most human CHD cases remain undiagnosed. The best hope for resolving these significant clinical issues lies in the application of methods designed to deal with genetically complex diseases, as well as technologies that can investigate the role played by molecular pathways. New discoveries and technologies can improve our understanding of CHD genetic variables. From single-gene mutation studies to genome-wide investigations, the number of clinically available genetic tests increased sharply. In conclusion, CHD suspects should consider genetic consultations and testing. Genetic causes of isolated, non-syndromic CHD have been revealed.

Genetic therapy for CHD families will benefit from identifying disease genes and loci in familial cases. The ultimate goal is to provide realistic therapeutic opportunities. Mutations in the regulatory regions of critical (heart) developmental genes may also lead to disease by affecting target gene expression. This will affect developmental networks at specific times and places. Therefore, before developing treatment alternatives, CHD's molecular genetics and pathology must be understood.

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