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# GENETIC INSIGHTS INTO CONGENITAL HEART DISEASE

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**ABSTRACT**

Congenital heart diseases (CHD) are the most common type of birth defect and result in significant mortality worldwide. The etiology for the majority of these anomalies remains unknown but genetic factors are being recognized as playing an increasingly important role. There has been remarkable progress in understanding the genetic basis of cardiovascular malformations.Chromosome microarray analysis has provided a new tool to understand the genetic basis of syndromic cardiovascular malformations.Remarkable improvements in sequencing technology have led to easy testing for cardiomyopathy, single gene syndromic disorders, and Mendelian-inherited congenital heart disease. Understanding the genetic basis for these disorders has improved their clinical recognition and management and led to new guidelines for treatment and family-based diagnosis. The aim of this review is to provide the clinician with a summary of what is currently known about the contribution of genetics to the origin of congenital heart disease. It is expected that this summary will update a wide range of medical personnel, including pediatric cardiologists and pediatricians, adult cardiologists, obstetricians, and surgeons about the genetic aspects of congenital heart disease.

**KEYWORDS** : Congenital heart diseases, ASD, VSD, PDA, TOF, Gene mutations.

## INTRODUCTION

Congenital heart disease (CHD) is the leading cause of birth defects, and accounts for more deaths in the first year of life than any other condition when infectious etiologies are excluded [1]. With an incidence rate of 8/1000 live births, nearly180,000 children are born with CHD each year in india. Of these, nearly 60,000 to 90,000 suffer from critical CHD requiring early intervention. Approximately 10% of present infant mortality in india may be accounted to CHD alone. Despite advances in medical and surgical care, the etiology of CHD is still not completely understood; and with more children with CHD surviving to adulthood and starting families, it becomes even more critical to understand the origins of CHD. Classic studies including the Baltimore-Washington Infant Study have found that CHD is multifactorial, due to both genetic predisposition and environmental influences[2]. Sequencing of the human genome and advances in molecular techniques has led to increasing evidence implicating a stronger role for genetic factors.

Adults who previously underwent corrective procedures for CHDs also need to be monitored, as they are at risk for late complications such as arrhythmias, endocarditis, and heart failure, leading to the need for additional surgery. For the clinician caring for a child with CHD, it is very important to determine whether there is an underlying genetic pattern (eg, deletions, duplications, or mutations), for the following reasons: (1) there may be other important organs involvement; (2) there may be prognostic information (3) there may be important genetic reproductive risks the family should know about; and (4) there may be other family members for whom genetic testing is needed.

The genetics of CHDs is highly heterogeneous. CHD mutations could be familial or sporadic in nature. Familial CHD mutations may occur as autosomal dominant, autosomal recessive, or X-linked traits. These mutations are highly penetrant and result in a variety of clinical manifestations. Nowadays there are a number of genetic tests that can assist the clinician in diagnosing genetic alterations in the child with CHD. These include cytogenetic techniques, fluorescence in situ hybridization (FISH), and DNA mutation analysis.

### Chromosome Analysis

Before the availability of advanced cytogenetic techniques such as FISH, standard chromosome analysis revealed chromosomal aberration in 8% to 13% of neonates with CHD.[3]. With improved resolution in cytogenetic analysis and the availability of molecular techniques, the prevalence of chromosomal abnormalities in selected congenital heart defects is now estimated to be much higher.[4].

### FISH Technology

FISH is a method by which biotinylated test and control DNA probes are hybridized with metaphase chromosomes to determine whether 1 (deletion), 2 (normal), or 3 (duplication) copies of the test region are present.[5]. Specific DNA probes can be located by fluorescence microscopy and will identify well-known deletion syndromes such as del 5p (cri-du-chat). Other fluorescent DNA probes are useful in determining microdeletion syndromes that cannot be detected visually.

### DNA mutation analysis

Mutation analysis identifies changes in the coding sequence of the gene, including small deletions, insertions, or substitutions of nucleotides that alter the encoded amino acid and consequently protein structure. Most methods employ polymerase chain reaction– based assays. Indirect screening methods, such as denaturing high-performance liquid chromatography[6]

or single-strand conformation polymorphism,[7] have been used extensively.

## REVIEW LITERATURE

### CHD ASSOCIATED WITH ANEUPLOIDY AND MICRODELETIONS

While most children born with CHD do not have other birth defects, CHD occurs in association with other anomalies or as part of an identified syndrome in 25 to 40% cases [8]. In addition, approximately 30% of children with a chromosomal abnormality will have CHD [9]. Aneuploidy, or abnormal chromosomal number, accounts for a significant proportion of CHD (Table 1).

**Table 1. Common Syndromes Resulting from Anueploidy and Microdeletions**

| SYNDROME | CARDIAC ANOMALIES | OTHER ASSOCIATED CLINICAL FEATURES |
|---|---|---|
| Trisomy 13 | ASD, VSD, PDA, HLHS | Microcephaly, holoprosencephaly, scalp defects, severe mental retardation, polydactyly, cleft lip or palate, genitourinary abnormalities, omphalocele |
| Trisomy 18 | ASD, VSD, PDA, TOF, DORV, CoA, BAV | Polyhydramnios, rocker-bottom feet, hypertonia, biliary atresia, severe mental retardation, diaphragmatic hernia |

| | | |
|---|---|---|
| Trisomy 21 (Down syndrome) | ASD, VSD, AVSD, TOF | Hypotonia, developmental delay, palmar crease, epicanthal folds |
| 47, XXY (Klinefelter Syndrome) | PDA, ASD | Tall stature, hypoplastic testes, delayed puberty, variable developmental delay |
| Monosomy X (Turner Syndrome) | CoA, BAV, AS, HLHS | Short stature, shield chest with widely spaced nipples, webbed neck, primary amenorrhea |

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; CoA, coarctation of aorta; BAV, bicuspid aortic valve; AVSD, atrioventricular septal defect; IAA, interrupted aortic arch; AS, aortic stenosis; PPS, peripheral pulmonic stenosis.

## SINGLE GENE MUTATIONS

With advances in genetic technology, single gene defects leading to syndromes associated with congenital heart disease have been identified and they are summarized in Table 2. Some of the earliest work was the discovery that mutation of Fibrillin 1 (FBN1) was the cause of Marfan syndrome, which is characterized by progressive aortic root dilation with a predisposition to dissection, lens dislocation, and skeletal anomalies [10]. Holt-Oram syndrome, characterized by atrial and ventricular septal defects, progressive atrioventricular conduction system disease, and radial limb and thumb anomalies, is associated with mutations in the transcription factor, TBX5 [11].

**Table 2. Syndromes Associated with CHD Resulting from Single Gene Defects**

| Syndrome | Causative Gene(s) | Cardiac malformations | Other Clinical Features |
|---|---|---|---|
| Marfan Syndrome | FBLN, TGFBR1, TGFBR2 | Aortic root dilatation and dissection, mitral valve prolapse | Tall stature, arachnodactyly, pectus abnormality, scoliosis, ectopia lentis, spontaneous pneumothorax, |
| Holt-Oram Syndrome | TBX5 | ASD, VSD, AVSD | Preaxial radial ray malformations (thumb abnormalities, radial dysplasia) |
| Noonan Syndrome | PTPN11, KRAS, RAF1 | PS , AVSD, HCM, CoA | Short stature, webbed neck, shield chest, developmental delay, cryptorchidism, |
| Alagille Syndrome | JAG1, NOTCH2 | PS, TOF, ASD, peripheral pulmonary stenosis | cholestasis, typical facies, butterfly vertebrae, ocular anomalies, growth delay, hearing loss, horseshoe kidney |
| Costello Syndrome | HRAS | PS, HCM, cardiac conduction abnormalities | Short stature, developmental delay, coarse facies, nasolabial papillomata |

PS, pulmonic valve stenosis; AVSD, atrioventricular septal defect; HCM, hypertrophic cardiomyopathy; CoA, coarctation of aorta; TOF, tetralogy of Fallot; ASD, atrial septal defect; VSD, ventricular septal defect; AV, atrioventricular; DILV, double inlet left ventricle; DORV, double outlet right ventricle; TGA, transposition of the great arteries; PDA, patent ductus arteriosus.

## SINGLE GENE CARDIAC DEFECTS NOT ASSOCIATED WITH OTHER SYNDROMES

Recently, single gene defects associated with isolated congenital heart disease have been discovered (Table 3). Studies revealed that mutations in NKX2.5 lead to isolated atrial septal defects with atrioventricular conduction delay [12].

**Table 3. Isolated CHD Resulting from Single Gene Defects**

| GENE(S) | CARDIAC DEFECTS |
|---|---|
| BMPR2 | Cardiac septation defects associated with PHTN |
| GATA4 | ASD, VSD |
| CRELD1 | Endocardial cushion defects |
| NKX2.5 | ASD, atrioventricular conduction delay, TOF |
| MYH6 | ASD, hypertrophic cardiomyopathy |

ASD, atrial septal defect; TOF, tetralogy of Fallot; VSD, ventricular septal defect; PHTN, pulmonary hypertension

## FUTURE DIRECTIONS

As the technology for evaluation of the human genome continues to advance, there is an increasing need for professionals to apply and interpret genetic testing in a thoughtful and clinically meaningful way. Pediatric cardiologists and geneticists need cross discipline training in order to provide the best care to patients with congenital heart disease. The increased availability of genetic testing provides an opportunity to improve diagnostic yield and precision and to deliver more sophisticated recurrence risk information.

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