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'Genetic Basis Of Congenital Heart Disease': A Review

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Abstract:

Congenital heart disease (CHD) has multifactorial etiology. The complex morphologic events and tissue remodeling take place during heart formation and is accompanied by equally complex mode of gene expression. Recent findings of genes responsible for Congenital heart disease have provided new insights into the genetic basis of heart malformation. Several cardiac Transcription Factors (TFs) involved in heart formation have been identified; but the molecular mechanisms underlying spatiotemporal regulation of transcription within the heart remain unclear. In this review an effort is made to collect data of all Transcription Factors involved in formation of various parts of heart also the association of Congenital heart disease with various chromosomal anomalies is presented. This review helps to provides information about genetic basis of cardiac defects. Many types of genetic testing are currently available; other testing is still in the research phase. Awareness of this rapidly advancing field is important which will help the clinicians to understand, identify, prevent and treat individuals who might be at risk of cardiac pathology at an early stage.

Introduction:

Congenital heart disease (CHD) is a leading cause of death in the first year of life. There has been a long-standing clinical view that most CHD occurs as isolated cases. On the basis of studies of recurrence and transmission risks, a hypothesis of multifactorial etiology was proposed.[1] In this type of inheritance, the genetic predisposition of the individual interacts with the environment to cause the congenital heart defect. Recent findings of genes responsible for CHDs have provided new insights into the genetic basis of heart malformation. In this study, attempt is made to review the understandings of different types of heart lesions associated with syndromes for which genetic etiologies are apparent, as well as the recent developments involving the transcription factors for the development of different parts of heart and mutation of gens leading to different CHDs in case of human beings.

This review helps to provides information on the genetic basis for cardiac defects which helps to understand, identify, prevent and treat individuals who might be at risk of cardiac pathology at an early stage. There is a need to find a mutation leading heart defects as early as possible so that they can be treated while the heart is still developing.

Normal development of heart: [2, 3, 4]

The origins of the heart tube are clusters of angiogenic cells which are located in the cardiogenic plate. The cardiogenic plate, which is derived from splanchnoplueric mesoderm, is located cranial and lateral to the neural plate. These angiogenic cell clusters coalesce to form right and left endocardial tubes. Each tube is continuous cranially with a dorsal aorta, its outflow tract, and caudally with a vitelloumbilical vein, its inflow tract. Lateral and cranial folding of the embryo forces the tubes into the thoracic cavity. As a result, these tubes come to lie closer to each other and begin to fuse in a cranial to caudal direction. At approximately day 21 they are completely fused.

Newly formed heart tube bulges into the pericardial cavity and is attached to the dorsal wall by a fold of tissue, the dorsal mesoderm. This is a derivative of foregut splanchnoplueric mesoderm. Eventually this will rupture leaving the heart tube suspended in the pericardial cavity anchored cranially by the dorsal aortae and caudally by the vitelloumbilical veins. As it bulges into the cavity it becomes invested in a layer of myocardium. A layer of acellular matrix, the cardiac jelly, separates the myocardium and the endothelial heart tube.

The newly formed heart tube may be divided into regions. Starting caudally:

- Sinus venosus - consisting of right and left horns.
- Paired primitive atria. These structures will later fuse together to form common atrium.
- Atrioventricular sulcus divides the atria and the primitive ventricle.
- Primitive ventricle expands to become the left ventricle.
- Interventricular sulcus divides the primitive ventricle and the bulbus cordis.
- Bulbus cordis which may be divided as follows:
    1. bulbus cordis - the proximal portion forms the right ventricle
    2. conus cordis
    3. truncus arteriosus
- Aortic sac

By the time the heart tube has formed the bulboventricular loop, the two primitive right and left atria have fused to form a common atrium. It now lies cranial to the primitive ventricle and dorsal to the bulbus cordis. The truncus arteriosus lies on the roof of the common atium causing a depression and indicates where septation of the atrium will occur.

The partitioning of the atrium begins with the appearance of septum primum at about the 28th day. This is a crest of tissue that grows from the dorsal wall of the atrium towards the endocardial cushions- the ostium (opening) formed by the free edge of septum primum is the ostium primum. Before the septum primum fuses with the endocardial cushions, perforations appear in the upper portion of the septum primum. These perforations will coelasce to form the ostium secundum. Unlike the septum primum, septum secundum does not fuse with the endocardial cushions. Its free edge forms the foramen ovale. The left venous valve and the septum spurium, located on the dorsal wall of the right atrium, fuse with the septum secundum as it grows. At the end of the seventh week the human heart has reached its final stage of development. Because the fetus does not use its lungs, most of the blood is diverted to the systemic circulation. This is accomplished by a right to left shunting of blood that occurs between the two atria. The foramen ovale and the septum primum control this right and left communication. The septum primum acts as a valve over the foramen ovale. At birth the child will use its lungs for the first time and consequently more blood will flow into the pulmonary circulation. The pressure increase in the left atrium (where the pulmonary veins empty) will force septum primum to be pushed up against septum secundum. Shortly thereafter the two septa fuse to form a common atrial septum.

Fate of the Sinus Venosus (Formation of the Right Atrium)

Unlike the atria, the sinus venosus remains a paired structure with right and left horns. Each horn receives venous blood from three vessels: Vitelline vein, Umbilical vein and Commom cardinal vein. Communication between the sinus venosus and the primitive atrium, the sinoatrial orifice is centrally located. Gradually the sinoatrial orifice shifts to the right, due to the shunting of blood to the right, until the sinus venosus communicates with only the right atrium. The fate of each structure is as follows:

- the right sinus horn becomes enlarged
- the right anterior cardinal vein becomes the superior vena cava.
- the right vitelline vein becomes the inferior vena cava
- the right umbilical vein is obliterated

Conversely, the left vein counterparts are obliterated and the left sinus horn diminishes in size and forms the coronary sinus and the oblique vein of the left ventricle. Internally, the sinoatrial orifice is flanked by two valves, the right and left venous valves. Superiorly these two valves meet to form the septum spurium. Note that the left horn opens up underneath the orifice of the right horn (sinoatrial orifice). This is the orifice of the coronary sinus.

Further into development the right sinus horn is incorporated into the expanding right atrium. As the atrium expands the smooth tissue of the sinus venosus displaces the trabeculated tissue of the primitive right atrium anteriorly and laterally where it becomes the adult right auricle. The smooth tissue forms part of the atrium called the sinus venarum. Crista terminalis, a ridge of tissue located to the right of the sinoatrial orifice forms the boundary between the auricle and the sinus venarum.

Partitioning of outflow tract:

The final morphological change in the heart is the partitioning of the outflow tract; the truncus arteriosus and the conus cordis into the aorta and the pulmonary trunk. This is accomplished by the development of a septum that forms in the outflow tract and the emergence of the two great vessels. The septum forms from two pairs of swellings which grow from the walls of the outflow tract. These are the truncus swellings and the conus swellings.

Truncal swellings: Right superior this grows distally and to the left. Left inferior this grows distally and to the right. Both develop at the proximal part of the truncus and proceed to grow in two directions; 1) distally towards the aortic sac and 2) into the lumen of the outflow tract where they will eventually fuse together.

Conus swellings: Right dorsal which is continuous with the right superior Left ventral which is continuous with the left inferior like the truncal swellings, the conal swellings grow distally and towards each other, however they appear after the first pair. These conus swellings eventually fuse with the truncal swellings.

Transcription of heart:

The complex morphologic events and tissue remodeling that take place during heart formation are accompanied by equally complex changes of gene expression that produce dynamically regulated chamber as well as left–right specific patterns. Despite important efforts devoted to the study of chamber-specific gene expression and the identification of several cardiac Transcription Factors (TFs) involved in heart formation, the molecular mechanisms underlying spatiotemporal regulation of transcription within the heart remain unclear. A few promoters have been shown to target transgenes to the heart, often in a spatially restricted manner, but the regulatory elements there in hence the pathways responsible for temporal and regional specificity have yet to be defined. The complexity of gene expression during heart development would necessitate a very large number of regulators that

need to be finely regulated themselves. Even then, since few cardiac genes are coordinately regulated at any given developmental time, it would be virtually impossible to achieve this complex regulation except through different combinations of TFs. It is now well accepted that combinatorial interactions govern heart development [5]. They are briefly reviewed below.

The GATA family

The GATA family belongs to the zinc finger superfamily of TFs that bind the DNA sequence A/G GATA A/T. Six members are present in mammals.

Three of which are expressed within the heart, GATA-4, GATA-5 and GATA-6, where they show cellular and/or regional specificity and are differentially regulated throughout development, with GATA-4 being the predominant transcript in cardiomyocytes at all stages.[6]

GATA-4 is detected in all cardiac progenitors. The number of cardiac promoters regulated directly by GATA-4 is more than 30. [7] At the molecular level, GATA-4 interacts with several other TFs to control diverse genetic programs and cardiac cell fates (discussed below). At present, GATA-4 is arguably the most studied cardiac TF and the one that comes closest to the definition of a "master" regulator.

GATA-6 is also found in myocardial as well as vascular smooth muscle cells.

GATA-5 transcripts are largely restricted to endocardial cells.

The MEF2

FamilyMEF2 proteins were originally isolated by virtue of their binding to A/T-rich regulatory sequences present on several skeletal muscle promoters. MEF2 proteins can also be recruited to target genes via interaction with GATA proteins.[8] They are derived from four genes that produce several isoforms through alternative splicing. Gene targeting in drosophila and mice suggests a role for MEF2 in later stages of cardiomyocyte and vascular cell differentiation.[9]

The NK family

As stated earlier, Nkx2.5 was isolated in a screen for mammalian homologues of tinman, an NK-class homeodomain; containing protein required for mesoderm segmentation and heart formation in drosophila.[10] Nkx2.5 binds DNA through its homeodomain. At the molecular level, Nkx2.5 is a GATA-4 collaborator and an important interacting partner of Tbx5.[11]

The T-box family

T-box proteins form a newly identified family of important developmental regulators that share a conserved 180 AA region (the T-domain or T-box) responsible for DNA binding. More than 20 members have been identified so far in mammals.[12]

dHAND/eHAND

Human dHAND and eHAND are two related basic helix-loop-helix transcription factors that are expressed in a complementary fashion in the developing right and left ventricles, respectively. They are also expressed in the neural crest-derived cardiac outflow tract and aortic arch arteries

IRX4 (Iroquois Homeobox gene 4)

Human IRX4 which is present in the developing central nervous system, skin, and vibrissae, but are predominantly expressed in the cardiac ventricles. This Homeobox gene is likely to be an important mediator of ventricular differentiation during cardiac development, which is downstream of NKX2.5 and dHAND.[13]

JAGGED

It is a Notch Ligand, expressed in the developing right heart. Missense mutation (G274D) in JAGGED-1 causes defect in all forms of TOF.

Mutation in JAGGED-1 has been identified in patients with Alagille syndrome.[14]

Elastin

A mutation of Elastin causes supravalvular aortic stenosis and peripheral pulmonary artery stenosis. This mutation is also associated with William syndrome.[15]

TFAP2B

It is expressed in the neural crest. This mutation was observed in families with PDA, hand anomalies and facial dysmorphism.[16]

Fibrillin

Mutation in this gene causes cardiac disease that include dilation of ascending aorta, mitral valve prolapse and dilation of pulmonary artery.[17]

Classification of congenital heart disease:

The CHDs could take place in any side of the heart; atrial, ventricular or vascular. The common defects are classified according to: a) side of the affected heart, b) communication or short circuit between both hearts chambers and c) Presence or absence of cyanosis.[18] According to the Merck manual of Diagnosis[19] the first eight CHDs are the common lesions, which account for 85% of all cases and the remaining (15%) account for variety of rare and complex CHDs.

(1) Atrial Septal Defect (ASD): A septal defect is a hole in different part of the atrial septum which lets some amount of blood from the left atrium to right atrium instead of flowing into left ventricle. It may be single or multiple and can be located anywhere in the atrial septum.

ASDs are classified into 3 major types depending on the different part of the septum: Ostium secundum (Fossa ovalis), Ostium primum and Sinus venosum defect.

(2) Ventricular Septal Defect (VSD): A septal defect is a hole, existing between the lower chambers of the heart. Oxygen rich blood from the lungs is pumped into the aorta from the left ventricle. During this process with VSD some amount of blood is passed into the right ventricle and into the pulmonary artery back to the lungs. As the heart has to pump extra blood and is overworked it might transform the septum into a honey combed Swiss cheese structure with sieve like fenestrations. It is classified into 2 main types according to their location relative to the components of the septum. The common types are perimembranous and trabecular types.

(3) Patent Ductus Arteriosus (PDA): Ductus arteriosus, the temporary duct connecting the left pulmonary artery to the aorta in the fetal heart, fails to close after birth. This allows blood to mix between the pulmonary artery and the aorta, which results in too much blood traveling to the lungs.

(4) Pulmonary Stenosis (PS): Narrowing of the pulmonary valve between right ventricle and the pulmonary artery is called pulmonary stenosis. This results in the right ventricle pumping harder than normal to overcome the obstruction.

(5) Aortic Stenosis (AS): Narrowing of the aortic valve between the left ventricle and the aorta is called aortic stenosis. Normally there are 3 leaflets or cups in a valve, but in a stenotic valve there is one (unicuspid) or two (bicuspid). Obstruction may be valvular, subvalvular (sub aortic) or supra valvular. This makes it hard for the heart to pump blood to the body.

(6) Coarctation of the aorta (COA): It is a constricted segment of the aorta that obstructs blood flow to the lower part of the body and increases blood pressure above the constriction. It usually occurs as isolated disease, but may occur with a VSD, subaortic stenosis or complex CHDs.

(7) Tetralogy of Fallot (TOF): TOF is made up of 4 separate components:

a) VSD, that lets blood pass from the right to the left ventricle without going through the lungs.

b) A narrowing (stenosis) at or just beneath the pulmonary valve. This narrowing partially blocks the blood flow from the right side of the heart to the lungs.

c) The right ventricle is more muscular than normal.

d) The aorta lies directly over the VSD.

Collectively, this results in cyanosis or blue baby, which may appear soon after birth, in infancy or later in childhood.

(8) Transposition of the great arteries (TOA): The great arteries are pulmonary artery and the aorta. The normal positions of the arteries are reversed in this type of defect. The aorta is connected to the right ventricle, while the pulmonary artery is connected to the left ventricle. This results in the right ventricle pumping oxygen poor blood to different parts of the body and the left ventricle pumping oxygen rich blood to the lungs. This defect is commonly associated with VSD, PS, heart block and an Ebstein like malformation of the tricuspid valve, which helps in communicating the oxygen rich blood to different parts of the body.

(9) Atrioventricular Septal Defect (AVSD): A large hole in the centre of the heart exists where the wall between the upper chambers joins the wall between the lower chambers. This is called as a complete AVSD. In case of partial AVSD, either the upper or the lower part of the septum is affected. In addition, the tricuspid and mitral valves that normally separate the hearts upper and lower chambers are not formed as individual valves; instead, a single large valve is formed. This large opening in the centre of the heart lets blood to flow in all direction inside the heart.

(10) Persistent truncus arteriosus: It is a complex malformation where only one artery arises from the heart and forms the aorta and pulmonary artery. That means the pulmonary arteries then branch off this common artery. This defect is found in association with VSD.

(11) Tricuspid Artesia (TA): The valve between the right atrium and the right ventricle is missing. As a result, oxygen-poor blood is pumped into the body along with the oxygen-rich blood. This results in cyanosis or blue baby. This defect is found in association with ASD, VSD and PDA.

(12) Pulmonary Artesia (PA): In this case no pulmonary valve exists; therefore blood cannot flow from the right ventricle into the pulmonary artery and on to the lungs. The only way for the blood to reach the lungs is the ductus arteriosus which is found during the fetal condition which closes after birth. The mixing of oxygen rich blood and oxygen poor blood results in cyanosis.

(13) Total anomalous pulmonary venous connection (TAPVC): In this case, all the pulmonary veins drain into the right atrium instead of left atrium, which brings the mixing of the blood. In addition to this, there is also presence of ASD and VSD, which results in cyanosis. There are three main types of TAPVC, depending on where the pulmonary veins drain. They are referred to as supracardiac, intracardiac, and infracardiac.

(14) Hypoplastic left heart syndrome (HLHS): In this condition the left ventricle and the aorta are small and underdeveloped. Therefore, the mitral and aortic valves are usually tiny or absent. It is one of the top three heart abnormalities to cause problems in the newborn.

(15) Double outlet right ventricle (DORV): It is a most uncommon defect in which both the pulmonary artery and aorta arises from the right ventricle, each with its own outflow tract and valve.

(16) Single ventricle / univentricular heart: It refers to a congenital malformation in which two atria are related to one ventricle that qualifies as

left, right or indeterminate ventricle on purely morphologic ground.

(17) Ebstein′s anomaly (EA): In this case there is a downward displacement of the tricuspid valve into the right ventricle. It is usually associated with an ASD.

(18) Dextrocardia (heart on the right): If the developing heart tube bends to the left instead of the right, then the heart is displaced to the right and develops in a mirror image of its normal state. This is a condition called situs inversus. In many a cases Dextrocardia heart functions normally unless there are no associated vascular abnormalities. In cases where the heart is the only organ, which is transposed, known as isolated Dextrocardia, there are usually other severe cardiac abnormalities associated with it.

Association of congenital heart disease's with chromosomal anomalies:

The association of CHDs with chromosomal anomalies varies between 4-12%.[20] The following are some of them:

(a) Trisomy 21 (Down syndrome): This chromosomal defect has the highest association with major heart abnormalities. At least 40% of Trisomy 21 children will have heart disease; furthermore, 50% of those children with heart abnormalities will specifically be affected with AVS.[21]

(b) Trisomy 18 (Edwards Syndrome): This is the second most common autosomal aneuploidy after Down syndrome. Common CHDs include VSD, AVSD, double outlet right ventricle, and hypoplastic left heart.[22]

(c) Trisomy 13 (Patau Syndrome): Many die in the neonatal period with this syndrome. Common CHDs include ASD, VSD, PDA and cardiac malpositions especially Dextrocardia (6%).[23]

(d) 45 X (Turner Syndrome): About 10% of girls with this syndrome have a clinically evident heart defect and a further 10% will display cardiac disease on echocardiography.[24] Common CHDs include VSD, COA, bicuspid aortic valve, hypoplastic left heart, mitral valve prolapse, and idiopathic aortic root dilatation.[25]

(e) Tetrasomy 22q (cat eye syndrome): The important features of this syndrome are iris colobomata, ear tags and imperforate anus. The CHDs association is found to be 30% of the patients with total anomalous pulmonary venous drainage as major problem.[26]

(f) Tetrasomy 12q (pallister killian syndrome): This is associated with mosaicism of chromosome. The CHDs association is found to be 25% of the patients that includes VSD, COA, PDA, ASD, and AS.[27]

(g) Fragile -X Syndrome: It is caused by a trinucleotide repeat expansion (CGG) in the fragile X mental retardation gene (FMR1) at Xq27.3.[28] Cardiac disease include mitral valve prolapse, which can be seen in up to 50% of adult patients with Fragile X syndrome. There are also incidences of mild dilation of aortic root in adults.[28]

(h) Chromosome Deletion and duplication Syndromes: Congenital heart lesions are common in most of the macro deletion syndromes and the cardiac anomalies vary widely even in those with apparently identical deletion breakpoints. It includes 3q, 4q, 5p, 8p, 9p, 11q, 13q, 18p, and 18q deletion syndromes.[29]

There are an equal number of duplication syndromes that also can be present with multiple congenital malformation and cardiac lesions such as 1p, 2p, 2q, 2p, 5p, 8p, 13q and 16q duplication syndromes.[29] Many affected children have a combination of deletions and duplications involving the respective chromosome segments that were involved in the rearrangement. Some of them are,

(i) Deletion 22Q11.2 syndrome: It comprises of 3 major syndromes: DiGeorge Syndrome (DGS), Velo cardio Facial syndrome (VCFS) and Conotruncal anomaly face syndrome (CTAFS).

Clinically these syndromes have overlapping phenotypes. The land marking features of Digeorge syndromes are heart abnormalities, trouble with calcium level, immune system problems due to the small size or absence of the thymus and or parathyroid.

The important features of velocardiofacial syndrome are cleft palate, heart disease, learning disabilities and a characteristic facial appearance. CATCH 22 is the medical acronym of 22q11 deletion syndrome (which stands for Cardiac defect, Abnormal face, Thymic hypoplasia, Cleft palate and Hypocalcemia 22q11.2 deletion). Individuals with this syndrome have a range of findings, including CHDs particularly conotruncal malformations (TOF, IAA, and TA); palatal abnormalities (velopharyngeal incompetence), sub mucosal cleft palate as well as cleft palate; and learning difficulties. The incidence of this syndrome is 1 in 4500 live births. It is sporadic in ~ 90% of the cases. This deletion is ~ 3Mb long in 90% of the patients and 1.5 Mb in 10% of cases. It is estimated to encompass ~30 genes. It has also been reported that UFD1L gene is not the only target in chromosome 22q11 syndromes for CHDs.[30] Since the recent mouse studies of TBX1 haploinsufficiency have established TBX1 contribution to conotruncal development, it has been hypothesized that human TBX1 haploinsufficiency via chromosome 22q11 deletion plays a major role in human DGS/ VCFS conotruncal disease.[31] Less than 1% of patients with clinical findings of the 22q11.2 deletion syndrome have a translocation between chromosome 22 and 11.[32,33] Standard karyotypic analysis, even with high-resolution banding techniques will only detect 10-20% of 22q11 deletions. Currently, FISH is the method of choice for microdeletion detection.[34]

(ii) Wolf-hirschhorn syndrome: This syndrome is due to deletion of terminal segment of chromosome 4p.[35] There is increased incidence of cleft lip, palate, seizures and heart disease (30%).[36]

(iii) 1q21 Microdeletions: Microdeletion on chromosome 1q21.1 spanning between 1.5 to 3Mb has been reported to be associated with CHDs, particularly anomalies of aortic arch.[37]

Other Major Syndromes:

(a) Noonan syndrome: Children with this syndrome have specific features such as valvular pulmonary stenosis, short stature, mild learning difficulties, and dysmorphic appearance. The cardiac disease seen in this syndrome includes PS[38], ASD, PDA, VSD and asymmetric septal hypertrophy.[39]

(b) Kabuki syndrome: It is characterized by distinct facial anomalies, variable degrees of mental retardation, CHDs and skeletal malformation. The CHDs include ASD, VSD, TOF, PDA, TGA, aortic Coarctation, single ventricle with common atrium and right bundle branch block.[40]

(c) Ellis- van Creveld: It shows skeletal dysphasia characterized by short limbs, short ribs, postaxial polydactyly, dysplastic nails and teeth.[41] CHDs occur in 60% of affected individuals that are disease in primary atrial septation; single atrium and hypoplastic left heart syndrome.[4]

TF mutations/deletions and heart development [43]

TF	Phenotype
GATA-4	Cardia bifida
GATA-5	Cardia bifida
Nkx2.5	Septation and differentiation defects
MEF2C	Right ventricle hypoplasia, septal defects

Tbx5	Atrial hypoplasia, septal defects
dHand	Right ventricle hypoplasia
TEF-1	Myocardial thinning
N-myc	Myocardial thinning
COUP	TFII Atrial hypoplasia
RXR/RAR	Septal defects
Fog2	Outflow tract defects
Tbx1	Septation defects
Pax-3	Septation defects
NFATc	Defective valve development
Hrt2	Aortic coarctation
Smad6	Valve thickening
Irx4	Postnatal cardiomyopathy

Summary:

Ongoing research is now demonstrating that variations or alterations in genes contribute to the origin of CHD to a greater degree than previously suspected. This review has summarized the current knowledge of the genetics of CHD**.** Many types of genetic testing are currently clinically available; other testing is still in the research phase. Awareness of this rapidly advancing field is important for all clinicians, and a multidisciplinary team approach to the child with CHD is necessary for comprehensive care. In addition to physicians and surgeons with expertise in CHD, a geneticist is a highly important member of this team.

Abbreviations: CHD-Congenital heart disease; TF-Transcription factor

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