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GENETICS AND NON GENETIC RISK FACTORS ASSOCIATED TO CONGENITAL HEART DISEASES

Anatomy

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ABSTRACT

Congenital heart diseases (CHDs) are the most common congenital anomalies with an estimated Prevalence of 9 in 1000 live births. Congenital Heart Diseases (CHD) are structural anomalies of the heart arising from abnormal development of the heart and major blood vessels. It is the significant reason for mortality and morbidity among children's. The aim of this review is to conduct searches for peer reviewed research papers published since 2000, with keywords "congenital heart defects," "incidences," "Genetics and non inherited risk factors associated to congenital heart diseases." The study of genes, non-coding RNAs and subtle chromosomal changes, elucidating their implications to the etiology of congenital heart diseases. Studies have also implicated non-hereditary risk factors such as rubella infection, advanced maternal age, pre gestational diabetes mellitus, and obesity, drugs usage during pregnancy and smoking and drinking alcohol during pregnancy in causing CHDs. This review provides an overview of the etiology, prevalence, genetic and non genetic risk factors, and advances in the treatment of congenital heart defect. Consequently, we plan to solidify our insight on multifactorial reasons for CHDs in order to clear a path for additional exploration in regards to CHDs.

KEYWORDS

Congenital heart diseases, Cardiac transcription factor genes, Non Genetic risk factors

INTRODUCTION:

Congenital Heart Diseases (CHD) are defined as an abnormality in 'Cardio circulatory' structure or function that is present since birth, even though it discovered later. CHD among all birth defects is the main cause of death in infancy. At least 18 distinct types of congenital heart defects are recognized, with many additional anatomic variations. These structural defects are the result of abnormal embryonic heart development and can be anatomically classified into abnormalities of the septa, the heart valves, and inflow or outflow tract of the heart. These structural defects most often have functional consequences, but of varying degree and significance. Some structural defects do not have important functional significance in early life such as the aortic valve with two leaflets, the prolapsing mitral valve, a small persistent patency of the arterial duct, small septal defects and patency of the oval foramen. 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.

The birth prevalence of CHD is reported to be 8-12/1000 live births. Considering a rate of 9/1000, about 1.35 million babies are born with CHD each year globally. The congenital heart defects can be life threatening during early childhood, and infants born with this disorder are at much higher risk (~ 12) of mortality especially in the 1st year of life. The genetic basis for many of these defects remains elusive, mutations in genes encoding core cardiac transcription factors have emerged as major contributors to many forms of congenital heart disease. Many of the genes associated with CHD, including NKX2-5, GATA4, TBX5, NOTCH1, and TBX20, were identified using early genetic techniques. In this review, we highlight transcription factor pathways known to be important for normal heart development and discuss how abnormalities in these pathways have been linked to morphological and functional forms of congenital heart defects.

The non genetic risk factors like rubella during pregnancy, pregestational diabetes, Certain medications taken during pregnancy like(thalidomide, angiotensin-converting enzyme (ACE) inhibitors, statins, the acne medication isotretinoin and lithium),smoking, drinking alcohol during pregnancy, and heredity. Consequently, we aim to reducing the burden of disease and consolidate our knowledge on multifactorial causes of CHDs and pave a way for further research regarding CHDs.

Genetic study in CHD

Most CHD occurs sporadically and in a non-syndromic fashion. In a subgroup of CHD a genetic origin can be demonstrated, which include chromosomal abnormalities, copy number variations (CNVs) and single gene defects. The majority of non-syndromic CHD is historically believed to be multifactorial in origin, i.e. multiple (unknown) genetic and environmental factors contributing to the CHD. A genetic cause can be demonstrated in only a small subset of individuals and families with non-syndromic CHD. In some patients, high-penetrance mutations in one of several genes that are known to be involved in heart development can be identified. In addition, more recently de novo CNVs have been shown to contribute to several types of non-syndromic CHD, including tetralogy of Fallot (TOF), left-sided heart defects (bicuspid aortic valve (BAV), aortic coarctation) and several other types of CHD.

Single gene defects and CNVs are found in only a minority of non-syndromic CHD, however. The majority of non-syndromic CHD is historically thought to be due to multifactorial inheritance. These genetic susceptibility factors interact with each other as well as with environmental risk factors, which, if a certain threshold is reached together lead to CHD. Environmental factors that have been implied in CHD include maternal disease (e.g. diabetes mellitus, hypercholesterolemia, hyperphenylalaninemia), infectious agents (maternal Rubella), several medications (ACE inhibitors, retinoids) and substance abuse (alcohol, cocaine). Use of folic acid during pregnancy has been hypothesized to be protective against CHD in the child, and folate deficiency is suspected to be a CHD risk factor.

The first reported single-gene mutation in humans with non-syndromic CHD was in the NKX2-5 gene, encoding a homeobox transcription factor. Its role as a transcription regulator during early embryonic heart developmental has been known for many years. Mice haplo-insufficient for NKX2-5 show abnormalities of the (atrial) septum and valve development as well as hypoplasia of the cardiac conduction system, especially the AV-node. Analogue to these abnormalities in animal studies, in humans most NKX2-5 mutations have been reported in patients with familial atrial septal defects (ASD) and conduction disorders, mainly atrio-ventricular block. Although NKX2-5 mutations can also lead to

Table I

Transcription factors with mutations found in human patients with congenital heart disease and reported Interaction partners.

Transcription Factor	Associated CHD Phenotype	References
1) NKX2-5	ASD, VSD, AVSD, TOF, SVAS, LVNC, PA, PS, PDA, MV anomalies, conduction defects, DORV, PAPVR, TAPVR, heterotaxy, TGA	McElhinney DB, Geiger E, Blinder J, Benson DW, Goldmuntz E (2003) NKX2.5 mutations in patients with congenital heart disease. J Am Coll Cardiol 42(9): 1650–1655., 2003

2) GATA4	ASD, AVSD, VSD, PS, AR, VPS, PDA, TOF, AF	Granados-Riveron JT, Pope M, Bu'lock FA et al. Combined mutation screening of NKX2-5, GATA4,and TBX5 in congenital heart disease: multiple heterozygosity and novel mutations. Congenit Heart Dis 2012;7:151-9
3) TBX5	ASD, VSD, AVSD	Smemo S, Campos LC, Moskowitz IP, Krieger JE, Pereira AC, Nobrega MA. Regulatory variation in a TBX5 enhancer leads to isolated congenital heart disease. Hum Mol Genet 2012;21:3255-63
4) TBX20	ASD, VSD,COA,PDA, MS	Posch MG, Gramlich M, Sunde M et al. A gain-of-function TBX20 mutation causes congenital atrial septal defects, patent foramen ovale and cardiac valve defects. J Med Genet 2010;47:230-5

Other types of CHD, the proportion of patients carrying such a mutation is lower in these groups. The overall mutation detection rate in sporadic CHD is reported to be 2%. The mutations that have been identified are spread among the entire coding region of the gene, without genotype-phenotype correlation.

There are numerous syndromes in which CHD may occur, and many of these are associated with specific CHD types. These syndromes can be caused by chromosomal abnormalities, including aneuploidies and structural aberrations. Moreover, mutations in genes involved in pathways that are important in the development of multiple organ systems can lead to syndromic CHD.

Non Genetic Risk Factors in CHD

Pre-gestational diabetes has been associated with multiple types of CHD including ASD, atrioventricular septal defect, CoA, double-outlet right ventricle, pulmonary atresia, total anomalous pulmonary venous return, TGA, tetralogy of Fallot, truncus arteriosus, and VSD. Although the mechanisms underlying the association between diabetes and CHD are not well understood, it appears that hyperglycemia plays a critical role. A positive association exists between hyperglycemia during embryogenesis and the risk for congenital malformations among infants of diabetic mothers.

Advanced maternal age has been implicated to the etiology of congenital heart diseases possibly because age increases the chances of chromosomal aberrations. Advanced maternal age was found to be associated with an increased risk of Ebstein's anomaly and transposition of the great arteries (TGA).

Several recent meta-analyses consistently report a general association between maternal overweight and obesity and risk for congenital heart defects in the offspring. The increased risk associated with maternal obesity includes a wide range of different cardiac defects, including septal defects aortic arch defects, persistent ductus arteriosus, conotruncal defects, left ventricular outflow tract obstruction defects, and right ventricular outflow tract defects. One source of bias could be the fact that body mass index (BMI) estimations in many of these studies were based on retrospective of self-reported data, which are associated with recall bias.

There is a strong correlation between drug exposure, viral infection, and conotruncal defects. Congenital rubella infection is a risk factor for many malformations including the CHDs. Certain medications taken during pregnancy like(thalidomide, angiotensin-converting enzyme (ACE) inhibitors, statins, the acne medication isotretinoin and lithium) are associated to CHD. The toxic chemical agents including pesticides, polychlorinated compounds, phthalates, alkyl phenolic compounds, bisphenol A, heavy metals, hydrocarbons, marijuana, and cocaine are also associated to CHD. After meta‒ analysis, we found that paternal exposure to chemical agents or drugs had a strong association with increased risk of CHDs.

Smoking during pregnancy has been found to increase the risk of congenital heart defects and women who smoke cigarettes have a substantial possibility of having children with atrial septal defects.With all these environmental factors implicated, in causing CHDs, it is therefore reasonable to say both genetic and environmental factors are being associated with congenital heart defects.

CONCLUSION

The multifactorial etiology of congenital heart diseases gives us a challenge to explicitly establishing Specific causative factors and therefore plan intervention strategies. Both Genetic and Non ‒ genetic risk factors are associated to CHDs. Community education programmes should be initiated in the high-risk population to encourage fertility at certain age, building a healthy life habit, beginning with quitting smoking and drinking, and trying to avoid environment exposures. Maternal counseling for periconceptional control of blood glucose, adequate weight maintenance, intake of folic acid tablets, avoidance of stress is needed to prevent CHD.

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