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Review Article

Advancement in research on genes associated with fetal congenital heart disease (CHD) and diagnostic testing methods

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ABSTRACT

Introduction: Congenital heart disease (CHD) is one of the most common congenital malformations, and is a polygenic disease related to some major genes and involved in environmental factors. With the progress of science and technology, the progress was both in the studies of genetic patterns and testing methods. Understanding how each gene participates in normal and pathological anatomy is an important goal of CHD research. We reviewed the development of testing methods and CHD-related genes, to provide some enlightenment for the CHD prenatal diagnosis and hope to realize the intervention and treatment on the gene level of CHD in the future.

Congenital heart disease (CHD) is a kind of cardiovascular malformation caused by abnormal development of the heart and blood vessels during human embryonic development. CHD is one of the most common congenital malformations [1], and its incidence rate is 4 ‰ ~5% [2]. The internationally recognized birth rate of children with CHD is about 8 ‰. Recent studies in Shanghai, China show that the live birth rate of newborns with CHD has reached about 26.6 ‰ [1]. It is one of the common causes of death in neonatal defects [3].

With the development of ultrasound and pediatric cardiac surgery, it can be diagnosed during pregnancy and treated surgically after delivery. However, it is necessary to determine whether there are serious chromosomal or genetic abnormalities. At present, it is recognized that CHD is a polygenic disease related to some major genes and involved in environmental factors. Therefore, it is particularly important to clarify the genetic factors of CHD for pregnant women and the prognosis of children.

With the progress of science and technology, there has been progress in the location of CHD that may lead to cardiac abnormalities. The progress was both in the studies of genetic patterns and testing methods. Understanding how the normal heart develops and how each cell participates in normal and pathological anatomy is an important goal of CHD research. Therefore, this article makes a summary to provide some enlightenment for the CHD prenatal diagnosis and treatment of it.

1. Methods for testing CHD genes

1.1. Traditional testing methods

At present, it is believed that the heritability of CHD is 55%~65%, in which single gene inheritance accounts for 15% and multi-gene inheritance accounts for 85%, while CHD caused by the joint action of heredity and pregnancy risk factors accounts for 75%~90% of the total.[4] At present, we can use chromosome karyotype analysis to diagnose CHD caused by chromosome abnormalities, such as CHD caused by Down syndrome. In addition, with the development of science and technology, single nucleotide polymorphism (SNP) arrays and other technologies are also used to diagnose CHD caused by abnormal gene fragments. At the same time, whole-exome sequencing, whole-genome sequencing, circulating cell-free DNA screening, and other technologies can also be used to diagnose CHD caused by a single gene.[5]

1.2. Single cell RNA sequencing

Personalized medicine is the ultimate aim of medical research and

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development. Currently, single-cell RNA sequencing(scRNA-seq) represents a promising avenue for gaining insights into heart development and diseases. The development of this technology has already yielded valuable insights into the key regulators of cardiogenesis and the pathophysiological mechanisms underlying CHD.[6]

Goodyer et al.[7] leveraged scRNA-seq technology to investigate the transcriptome characteristics of cells in the heart's conduction system and identified specific genes associated with each component. These findings hold great promise for improving the diagnosis, treatment, and intervention of arrhythmias and heart block. By combining scRNA-seq data from both mice and adult human heart tissues,[8] researchers can pinpoint which cells and tissues express genes of interest related to heart disease in genome-wide association studies.[9,10] Cardiac maturation is a complex process that involves the coordination of multiple cell types and their respective environments. With scRNA-seq, researchers can gain insights into the interactions between cells. For instance, Wang et al.[11] integrated scRNA-seq data from multiple stages of mouse heart development to construct a cell interaction network and regulatory signal network. Beyond cellular interactions, spatial information is also crucial in understanding heart development. Asp et al.[12] combined scRNA-seq data from human embryonic heart cells, RNA sequencing data from spatial transcriptomics, and in situ sequencing data to create a 3D gene expression map of the developing heart. This approach can be used to identify cells that contribute to normal development and those involved in pathological conditions.

Therefore, scRNA-seq technology can accurately locate the gene expression of a single cell and identify the causes of a different kind of CHD.

1.3. Long-read genome sequencing

Third-generation sequencing (TGS) methods further complete the knowledge about these processes based on long reads and the ability to analyze DNA or RNA at a single molecule level. Long-read sequencing provides additional possibilities to study genome architecture and the composition of highly complex regions and to determine epigenetic modifications of nucleotide bases at a genome-wide level.[13] This technique can also be used to study the etiology of CHD, but there are few population-based experiments at present.

1.4. Methylation pattern

Previous reports have shown that CHD incidence can be influenced by genetic etiology and environmental risk factors. And the gene-environmental interaction can affect the development and differentiation of myocardium through epigenetic regulation of using DNA methylation, histone, RNA modification, etc. DNA methylation is the most widely studied epigenetic mechanism. The maladjustment of DNA methylation at different stages of embryonic development can lead to abnormal silencing of tissue-specific genes, thus increasing the risk of heart malformation. There is the correlation among specific CpG island methylation sites in different tissues. By analyzing the correlation between methylation changes in peripheral blood cells and methylation changes in heart tissues, also some possible biomarkers can be found to establish a prediction model for CHD incidence.[14]

1.5. Proteomics

With the advent of the post-genome era, proteomics as a large-scale, high-flux, systematic emerging discipline, researches a particular type of all proteins in cells, tissues, or body fluids through a variety of technologies, aims to analyze dynamic changes of protein expression in cells and modification status, understand the interaction between proteins in cells, and thus reveal protein function and cell life activities. Proteomics specializes in the study of biological and pathophysiological issues from the perspective of proteins. Proteomics can map all proteins expressed in the heart at any time and under any conditions, and determine the protein changes related to the etiology, progression, outcome and treatment response of CHD through analysis of differentially expressed proteins. The identification of these CHD-related specific proteins and to study of their expression patterns, post-translational modification status and functional characteristics are the basis and key to the etiology and pathophysiology of various types of CHD.[15]

2. Congenital heart disease-related genes

2.1. GATA family

The *GATA* transcription factor family (*GATA* binding factor) has six subtypes, of which *GATA1, GATA2,* and *GATA3* mainly affect the development of hematopoietic tissue, while *GATA4, GATA5,* and *GATA6* play an important role in regulating the expression of a large number of cardiac-related genes. When the gene mutation occurs, it is closely related to the occurrence of CHD.[2]

2.1.1. GATA4

GATA4 is highly conserved in the process of evolution. It is one of the early signs of heart cells in the process of embryonic development and begins to express in the early stage of heart development. *GATA4* is located on chromosome 8p23.1 and has 7 exons.[16] *GATA4* plays a key role in the differentiation of cardiac precursor cells, cyclization of the heart, compartmentalization of atrioventricular, and maintenance of the conduction system. In autosomal dominant inheritance, *GATA4* mutation is related to most atrial septal defects (ASD). Some patients are complicated with ventricular septal defect (VSD), pulmonary stenosis (PS), severe diastolic dysfunction, and atrioventricular reflux, but not with systolic function, cardiac conduction system, or coronary system diseases. Studies have shown that *GATA4* must play its role with NK2 homeobox 5 (*NKX2.5)*. The mutation of *NKX2.5* cannot normally bind to *GATA4*, and *GATA4* cannot play its role.[17] At the same time, some studies believe that *GATA4*, *NKX2.5,* and T-box gene 5 *(TBX5)* work together to regulate the expression of multiple downstream target genes, thus affecting the differentiation and maturation of cardiac structures at various stages. Studies have shown that *GATA4* defects can lead to a variety of CHD, such as tetralogy of Fallot (TOF), PS, ASD, VSD, atrioventricular septal defects (AVSD), patent ductus arteriosus (PDA), etc.[18] Posch et al. believed that the defect of the *GATA4* gene may be related to simple atrial fibrillation. Similarly, fetal arrhythmia may also be caused by the defect of *GATA4*.[19] Liu et al. believed that *GATA4* mutation is of great significance for VSD.[18] Xiong et al.[20] studied 224 patients with CHD in southern China and believed that *GATA4* has more important significance for CHD than *NKX2.5* in the Chinese population. In conclusion, *GATA4* acts in combination with other genes to regulate gene expression, which is related to the occurrence of a variety of heart defects, and has certain significance in the Chinese population.

2.1.2. GATA5

Published literature has confirmed the correlation between different *GATA5* sequence variations and different forms of CHD, including atrial fibrillation, TOF, VSD, etc. In addition, two new variants of *GATA5* (c.943T > A, p.S315T and c.274G > T, p.A92S) were also found in sporadic CHD patients. The variation frequency was about 1% and was distributed at the N and C ends of *GATA5*.[21]

2.1.3. GATA6

GATA6 is located on 18q11.2, containing 7 exons. Current studies have found that abnormal expression of the *GATA6* in vascular smooth muscle cells and neural crest can lead to cardiovascular defects, including interrupted aortic arch (IAA) and persistent truncus arteriosus (PTA).[22] Therefore, the main function of the GATA6 is to regulate the morphology of the cardiac outflow tract and aortic arch, which may lead to CHD. Maitra et al. studied 310 children with CHD and believed that *GATA6*

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may lead to TOF and AVSD.[23] At the same time, some studies believed that *GATA6*, similar to *GATA4*, regulated the expression of downstream genes. Its mutations and defects may lead to cardiac outflow tract abnormalities, especially having an important impact on the occurrence of the outflow tract (OFT) and PTA.[24] Lin et al. found that mutations in *GATA6* may lead to TOF and ASD in 270 Chinese children with CHD.[25] In conclusion, *GATA6* is highly expressed in the cardiac outflow tract, large blood vessels, pancreas, and ovary. Its defect may lead to abnormal development of the above organs. In CHD, often leads to abnormalities of TOF, AVSD, aorta, and pulmonary artery.

2.2. T-box family

2.2.1. TBX1

TBX1 plays an important role in the development of the cardiac outflow tract, and also participates in and affects the migration and differentiation of neural crest cells.[26] Human *TBX1* is located on chromosome 22q11.2 and has three subtypes A, B, and C. There were 8 exons in the coding region of these three subtypes. Yagi et al.[27] reported that *TBX1* mutation was associated with sporadic conotruncal anomaly face syndrome (CAFS) and DiGeorge syndrome. In addition, *TBX1* is located in 22q11.2, and 22q11.2 microdeletion syndrome (22q11DS) is the most common in humans, including DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome (CAFS), Opitz GBBB syndrome. Such syndromes are mainly manifested in cardiac malformation, craniofacial malformation, pharyngeal palate cleft, thymic dysplasia, hypocalcemia, and cognitive and mental abnormalities.[28] Among them, cardiac malformation is the main cause of death and has a high incidence.

2.2.2. TBX5

TBX5 is located on 12q24.1 and has 8 exons.[29] This gene is the most widely studied in heart development, has obvious functions in many heart lineages and structures, and plays an important role in embryonic development.[30] *TBX5* has been identified as the pathogenic gene of Holt-Oram syndrome (HOS).[31] In addition, some studies believe that the mutation of *TBX5* also plays a role in the occurrence of ASD and AVSD.[32] Homsy et al. believed that the expression mode of *TBX5* during early cardiac development was dynamic. This dynamic expression mode was very critical for the initial differentiation of the atrioventricular cavity and the correct formation of the septum, so it may lead to ASD or AVSD.[33] In conclusion, *TBX5* plays an important role in the pathogenesis of atrioventricular septal defect and HOS and is one of the important pathogenic genes of heart defects in the Chinese population. The expression level of *TBX5* is very important for maintaining the stability of the cardiac gene network. The decrease in the *TBX5* dose leads to poor differentiation and function impairment of human cardiomyocytes. The type of susceptible cardiomyocytes can be changed by reducing the *TBX5* dose. *TBX5* and myocyte enhancer factor 2C(*MEF2C)* can synergistically treat ventricular septal defects in vivo. *TBX5* sensitiveness is related to congenital heart disease and cardiac function.[34]

2.2.3. TBX20

TBX20 is located on chromosome 7p14.2 and has 8 exons. The gene regulatory element of *TBX20* is located in the 100bp (629–527bp) fragment before the translation starts codon ATG. It is found that this fragment is the core promoter region of *TBX20*, and it is confirmed that there is a functional site binding to transcription factors in this region.[35] In the mouse model, *TBX20* was expressed in developing cardiac primordial cells, cardiomyocytes, endocardial cushion, cardiac outflow tract, atrioventricular canal, and atrial septal marginal tissue. Kirk et al. believed that the missense mutation of *TBX20* was related to the onset of CHD in white people.[36] Liu et al. found in the study of 203 Chinese CHD patients that *TBX20* mutation may be related to the pathogenesis of ASD, total anomalous pulmonary venous return (TAPVR), and TOF.[37] Therefore, *TBX20* as a member of the *T-box* family plays an important role in the development of the heart and has a certain impact on the incidence of CHD. Especially, it plays an important role in the pathogenesis of AVSD, TOF, dilated cardiomyopathy, double-outlet right ventricle (DORV), and other valvular diseases.[38]

2.3. NKX2.5

NKX2.5 belongs to the Hombox gene family, located in 5q3511, and contains two exons. It is one of the earliest markers of cardiac precursor cell differentiation. It is highly conservative in the process of evolution and is necessary for the normal development of the heart of drosophila, mice, and human beings.[39] About 1%~4% of congenital heart abnormalities are caused by this gene.[40] It was found that *NKX2.5* mutations were related to familial ASD, and then it was found that *NKX2.5* mutations were also related to other phenotypes of CHD, such as VSD, TOF, endocardial cushion defect (ECD), left ventricular hypoplasia syndrome, DORV, transposition of the great arteries(TGA), tricuspid stenosis, etc.[41]

2.4. MYH6

Myosin heavy chain 6 (*MYH6)* is mainly expressed in the rapid ATPase of atrial tissue.[42] This gene is located on 14q11.2 and consists of 39 exons, 37 of which contain coding information. Van Rooij et al.[43] found that the intron of *MYH6* encodes cardiac-specific microRNA, which affects cardiomyocyte hypertrophy and fibrosis, and affects the expression of *MYH7* on stress and thyroid function. According to the research of Hang et al., *MYH6* affected the growth and differentiation of the heart, especially the composition of myocardial tissue, and played a certain role in the occurrence of cardiac diseases such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and sick sinus syndrome.[44]

2.5. TFAP2B

Transcription factor AP-2 beta (*TFAP2B*) belongs to the *TFAP* family, located on human chromosome 6q12.3, and contains 7 exons, which are mainly responsible for the synthesis of neural crest-related transcription proteins. It participates in the growth and development of the mammalian heart, kidney, neural tube, and other tissues and organs, and regulates the proliferation and apoptosis of related cells.[45] Satoda et al. found in the study of two families with Char syndrome that *TFAP2B* was likely to be associated with PDA occurrence in this syndrome.[46] Zhao et al. also found that *TFAP2B* abnormality was likely to lead to Char syndrome, which is related to PDA and may even lead to more serious VSD, resulting in congenital heart malformation.[47] Therefore, *TFAP2B* is one of the important genes leading to CHD, which is closely related to the occurrence of PDA and Char syndrome.

2.6. GLI1

GLI family zinc finger 1(*GLI1*) is located at 12q13.2–12q13.3, containing 14 exons. Qiu et al. studied 180 patients with simple CHD and believed that *GLI1* was likely to be associated with simple CHD in the northeast population of China.[48] Therefore, *GLI1* affects the expression of downstream *GATA4*, *NKX2.5,* and other genes, leading to CHD, which may lead to simple heart disease.[49]

2.7. MTHFR

The methylenetetrahydrofolate reductase (*MTHFR*) is located on 1p36.22 and contains 11 exons. The abnormality of this gene affects the absorption and metabolism of folic acid, leading to congenital neural tube dysplasia and CHD. Yanamandra et al. found that the *MTHFR* 677C > T mutation in Down syndrome children was significantly higher than that in the control group among the white race. Therefore, it may be the cause of Down syndrome and related cardiac abnormalities.[50]

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2.8. NOTCH1

Notch homolog 1(*NOTCH1)* is a member of the *NOTCH* gene family, located at 9q34.3, and contains 4 exons, which play an important role in the development of early embryonic nerve and muscle cells.[51] This gene defect is associated with a variety of diseases, such as aortic valve dysplasia, aortic valve calcification, VSD, and TOF.[52] According to the research of Grag et al., the mutation of *NOTCH1* 3322C > T was related to the occurrence of CHD such as aortic valve calcification and AS.[51] Wang et al. studied 297 patients with CHD in China and believed that the *NOTCH1* defect was related to the occurrence of TOF and VSD.[53] It can be seen that this gene mainly affects the development of the aorta, plays a certain role in the occurrence of TOF and VSD, and is one of the important genes leading to CHD.

2.9. JAG1

Jagged 1(*JAG1)* is located on 20p12.2 and contains 26 exons, which is highly conserved in the process of evolution. *JAG1* is associated with the *NOTCH1* receptor, and their binding triggers a cascade reaction leading to proteolysis, which eventually leads to the release of intracellular media of receptors in the membrane, activates key transcription factors in the nucleus and plays an important role in cell differentiation and morphology.[54] *JAG1* defect often leads to Alagille syndrome, while 95% of patients with Alagille syndrome have congenital cardiac abnormalities, and their cardiac defects range from mild peripheral pulmonary artery stenosis to severe TOF.[55] Eldadah et al. found that the mutation of *JAG1* G274D could lead to CHD, including TOF, VSD, aortic right shift, and PS.[56] Therefore, *JAG1* plays an important role in the angiogenesis of CHD, which can lead to the occurrence of heart and macrovascular malformations such as TOF.

2.10. CRELD1

The cysteine-rich with EGF-like domain 1 (*CRELD1)* is the first gene found to be related to the pathogenesis of AVSD.[57] This gene is located on 3p25.3 and contains 11 exons, which is highly conserved among species. *CRELD1* is expressed in the atrioventricular endocardial pad of embryonic development, which has aroused the interest of researchers.[58] The results showed that overexpression of *CRELD1* could down-regulate the protein expression of Aggrecan, which was one of the main extracellular matrix components of the atrioventricular valve and septum formed the endocardial cushion, suggesting that *CRELD1* may participate in the pathogenesis of AVSD. Therefore, *CRELD1* is highly related to the occurrence of AVSD and is one of the important factors leading to CHD.

2.11. VEGFA

Vascular endothelial growth factor A (*VEGFA*) is located on 6p21.1 and contains 8 exons. This gene mainly induces mitosis of vascular endothelial cells. In the study of the mouse model, Stallmans et al. found that it could lead to 22q11 microdeletion syndrome, thus causing birth defects. *VEGFA* defect can interact with *TBX1*, resulting in 22q11 deletion syndrome and birth defects such as cardiovascular abnormalities.[59] Therefore, *VEGFA* defect can lead to TOF and DiGeorge syndrome and may be related to 22q11 microdeletion syndrome, increasing the incidence of CHD and other birth defects.

2.12. CITED2

Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2(*CITED2*) gene is located on 6q24.1, including 3 exons. Yin2 et al. found through the mouse model that the *CITED2* defect would lead to the death of mice due to heart malformation in utero. Cardiac defects include ASV, VSD, aortic straddle, DORV, PTA, and right aortic arch. The study also found that the *CITED2* defect may interact with *TFAP2*, resulting in abnormal development of the embryonic neural tube, neural crest, and heart.[60] Sperling et al. found in the study of 392 patients with CHD that 7 mutation sites of *CITED2* were not found in the normal control population, and 3 of them caused the change of amino acid sequence. Therefore, the mutation of this gene is likely to lead to CHD, especially congenital ASD, and VSD.[61] In conclusion, *CITED2* may cause severe heart defects and large blood vessels and neural tube defects in embryos, and its mutation may also be related to the occurrence of AVSD.

Table 1
Genes and related CHD.

Gene		Related CHD
GATA family	*GATA4*	TOF, PS, ASD, VSD, AVSD, PDA, simple atrial fibrillation, arrhythmia
	GATA5	atrial fibrillation, TOF, VSD
	GATA6	IAA, PTA, TOF, AVSD,OFT, ASD
T-box family	*TBX1*	sporadic CAFS, 22q11DS, DGS, VCFS, CAFS, Opitz GBBB syndrome
	TBX5	HOS, ASD, AVSD
	TBX20	ASD, TAPVR,TOF, DORV
NKX2.5		ASD, VSD, TOF, ECD, left ventricular hypoplasia syndrome, DORV, TGA, tricuspid stenosis
MYH6		hypertrophic cardiomyopathy, dilated cardiomyopathy, and sick sinus syndrome
TFAP2B		Char syndrome, PDA, VSD
GLI1		simple heart disease
MTHFR		Down syndrome
NOTCH1		aortic valve dysplasia, aortic valve calcification, VSD and TOF, AS
JAG1		TOF, VSD, aortic right shift, PS
CRELD1		AVSD
CITED2		ASV, VSD, aortic straddle, DORV, PTA and right aortic arch, AVSD
HAND2		malformation of the endocardial pad and great arteries

CHD: congenital heart disease;*CITED2*: Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2; *CRELD1*: cysteine-rich with EGF-like domain 1; *GLI1*: GLI family zinc finger 1; *HAND2*: heart and neural crest derivatives-expressed 2; *MTHFR*: methylenetetmhydrofolate reductase; *MYH6*: Myosin heacy chain 6; *NKX2.5*: NK2 homeobox 5; *NOTCH1*: Notch homolog 1; *TFAP2B*: transcription factor AP-2 beta; *VEGFA*: vascular endothelial growth factor A; *TOF*: tetralogy of Fallot; PS: pulmonary stenosis; ASD: atrial septal defect; VSD: ventricular septal defect; AVSD: atrioventricular septal defects; PDA: patent ductus arteriosus; IAA: interrupted aortic arch; PTA: persistent truncus arteriosus; OFT: outflow tract; CAFS: conotruncal anomaly face syndrome; 22q11DS: 22q11.2 microdeletion syndrome; DGS: DiGeorge syndrome; VCFS: velocardiofacial syndrome; HOS: Holt-Oram syndrome; TAPVR: total anomalous pulmonary venous return; DORV: double-outlet right ventricle; ECD: endocardial cushion defect; TGA: transposition of the great arteries; AS: aortic stenosis.

2.13. HAND2

Heart and neural crest derivatives-expressed 2(*HAND2*) is located on 4q34.1 and is closely related to the development of the heart, especially the great arteries. Srivastava et al. found that *HAND2* was expressed during the formation of the aortic arch and right ventricle in mice.[62] Zeisberg et al. found that in the *GATA4* deficient mouse model, the expression of *HAND2* in the experimental group was significantly lower than that in the normal control group. Therefore, it was concluded that the normal expression of *HAND2* requires the participation of *GATA4*.[63] They interact with each other and affect the development of the embryonic heart. Lei et al. studied 131 CHD patients and found that the mutation of *HAND2* has an impact on the formation of the right ventricle and cardiac outflow tract in China.[64] It can be seen that *HAND2* affects the growth and development of myocardial and arterial cells, resulting in the malformation of the endocardial pad and great arteries, leading to serious CHD. Its correct expression is related to *GATA4*, which is one of the important factors leading to CHD.

Also, we know the expression and influence of genes vary among different races and regions. More genes may be related to CHD, but we selected the above genes for review because these genes selected in the

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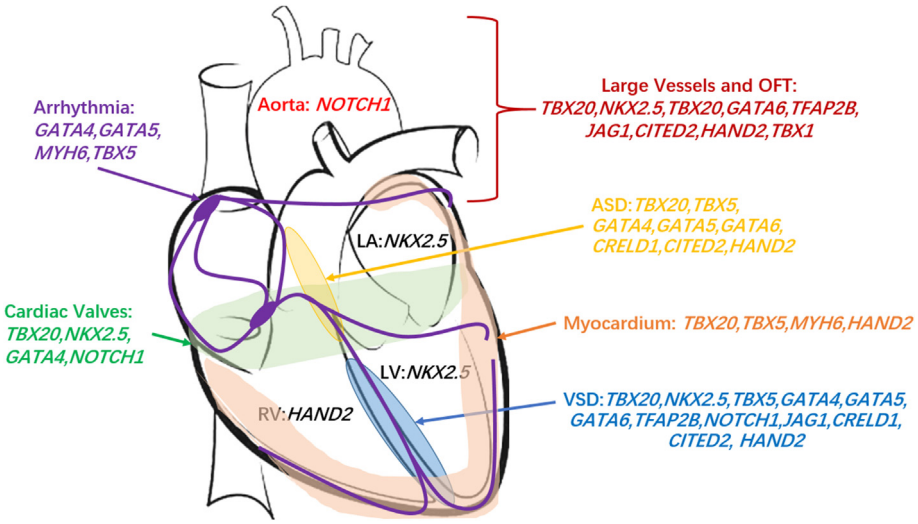

Fig. 1. Mapping of various genes in CHD.

article are more widely expressed in the Chinese population, and studies have shown a close relationship between these genes and CHD. Table 1 displays the CHD types that are associated with the aforementioned genes. Fig. 1 depicts the distribution and mapping of various genes in CHD.

In summary, there are many genes related to CHD, and there are network effects between each gene. Different genes have certain localization effects on the pathogenesis of CHD. At the same time, with the development of testing technology, the joint testing methods and expression evaluation of multiple genes can further clarify the pathogenesis of CHD. It was found that there were network effects and location effects among different genes, and the incidence of CHD was correlated with the amount of gene expression. Therefore, through the research on the gene of CHD and the test of animal experiments, it is possible to realize the intervention and treatment of the gene level of CHD in the future.

Consent for publication

All authors agreed that this article would be published in the Gynecology and Obstetrics Clinical Medicine.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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