

Epigenetics in Congenital Heart Disease

Subjects: **Genetics & Heredity**

Contributor: Benson Lim

Congenital heart disease (CHD) is the most common birth defect among newborns worldwide and contributes to significant infant morbidity and mortality. Owing to major advances in medical and surgical management, as well as improved prenatal diagnosis, the outcomes for these children with CHD have improved tremendously so much so that there are now more adults living with CHD than children. Advances in genomic technologies have discovered the genetic causes of a significant fraction of CHD, while at the same time pointing to remarkable complexity in CHD genetics.

cardiogenesis

cardiac development

epigenetics

transcriptional regulation

congenital heart disease

1. Introduction

Congenital heart disease (CHD) refers to a heterogeneous collection of structural abnormalities of the heart or the great vessels present at birth. It is the most common birth defect in newborns, affecting >1 million live births per annum globally and causing 10% of stillbirths. The moderate and severe forms of CHD affect approximately 6–20 per thousand live-births ^[1], and is a major cause of infant mortality and morbidity in the developed world ^[2], accounting for ~40% of infant deaths in North America ^[3]. In the most recent era, the survival and outcome of CHD patients, including children with complex cardiac defects, have improved significantly such that more than 75% of CHD children who survive the first year may be expected to reach adulthood in developed countries ^[4]. This increased survival is due to advances in prenatal and postnatal diagnosis, innovation in surgical techniques, as well as improved clinical surveillance and translational research, which have dramatically improved the clinical management of CHD. As a result, there are more adults living with CHD than there are children with CHD ^[5]. Nevertheless, the clinical course of children with complex CHD may be associated with many late sequelae, and affected children sometimes require subsequent invasive procedures and eventual heart transplantation due to heart failure caused by progressive ventricular dysfunction ^[6].

Thus, a greater understanding of the etiology of CHD is fundamental, in our effort to improve diagnosis, clinical management and counselling on risk of recurrence during subsequent pregnancies. With only 20–30% of cases traced to a known cause ^[7], the etiologies of CHD may be divided into genetic and non-genetic categories. While non-genetic etiologies of CHD such as environmental teratogens and infectious agents are widely studied ^[2], there is still a lot yet to be uncovered for the genetics and epigenetics of CHD ^[2]. With advancement of sequencing techniques, there has been greater appreciation of the significant genetic contribution to CHD in the recent 10–15

years, although its genetic basis was first recognized more than 3 decades earlier [8]. Epidemiology points to a strong genetic contribution in a proportion of CHD [9]. A greater concordance of CHD exists for monozygotic than dizygotic twins, and there is increased risk of recurrence among siblings or subsequent pregnancies [9]. Conversely, it is also notable that for a large proportion of CHD, particularly the severe forms, there is no other family history of CHD. This underlies a significant contribution from *de novo* genetic events [9]. Despite this, a specific causal genetic mutation is still only recognized in a minority of cases of sporadic CHD [10]. Currently, approximately 35% of CHD cases, with or without extracardiac malformations, can be attributed to genetic factors (Table 1) including monogenic (3–5%) or chromosomal (8–10%) anomalies, and copy number variants (3–25%). Environmental causes (2%) such as maternal diabetes, smoking or alcohol use, are recognized in ~20–30% of patients [1][11][12][13][14]. The genetics of CHD is also complex; a single candidate gene or genetic variant can produce a spectrum of heart malformations and may even occur in phenotypically-normal humans. Variation in genetic penetrance also occurs in affected families, resulting in a range of CHD phenotypes in the same pedigree [15][16].

Table 1. Genes and loci commonly associated with syndromic congenital heart disease.

Syndrome	Genes	Loci	Cardiac Disease	% CHD
Alagille	<i>JAG 1</i>	20p12.2	PPS, TOF, PA	>90
	<i>NOTCH2</i>	1p12-p11		
CFC	<i>BRAF</i>	7q34	PVS, ASD, HCM	75
	<i>KRAS</i>	12p12.1		
	<i>MAP2K1</i>	15q22.31		
	<i>MAP2K2</i>	19p13.3		
Cantu	<i>ABCC9</i>	12p12.1	PDA, BAV, HCM, CoA, PE, AS	75
Char	<i>TFAP2B</i>	6p12.3	PDA, VSD	58
CHARGE	<i>CHD7</i>	8q12	TOF, PDA, DORV, AVSD, VSD	75–85
Costello	<i>HRAS</i>	11p15.5	PVS, ASD, VSD, HCM, arrhythmias	44–52

Syndrome	Genes	Loci	Cardiac Disease	% CHD
DiGeorge	<i>TBX1</i>	22q11.2 deletion	Conotruncal defects, VSD, IAA, ASD, VR	74–85
Ellis-van Creveld	<i>EVC</i> <i>EVC2</i>	4p16.2 4p16.2	Common atrium	60
Holt-Oram	<i>TBX5</i>	12q24.1	VSD, ASD, AVSD, conduction defects	50
Kabuki	<i>KMT2D</i> <i>KDM6A</i>	12q13 Xp11.3	CoA, BAV, VSD, TOF, TGA, HLHS	50
Noonan	<i>PTPN11</i> <i>SOS1</i> <i>RAF1</i> <i>KRAS</i> <i>NRAS</i> <i>RIT1</i> <i>SHOC2</i> <i>SOS2</i> <i>BRAF</i>	12q24.13 2p22.1 3p25.2 12p12.1 1p13.2 1q22 10q25.2 14q21.3 7q34	Dysplastic PVS, ASD, TOF, AVSD, HCM, VSD, PDA	75
Williams-Beuren	7q11.23 deletion (<i>ELN</i>)	7q11.23	SVAS, PAS, VSD, ASD	80

Syndrome	Genes	Loci	Cardiac Disease	% CHD
Carpenter	<i>RAB23</i>	6p11.2	VSD, ASD, PDA, PS, TOF, TGA	50
Coffin-Siris	<i>ARID1B</i>	6q25	ASD, AVSD, VSD, MR, PDA, PS, DEX, AS	20–44
	<i>SMARCB1</i>	22q11		
	<i>ARID1A</i>	1p36.1		
	<i>SMARCB1</i>	22q11.23		
	<i>SMARCA4</i>	19p13.2		
	<i>SMARCE1</i>	17q21.2		
Cornelia de Lange	<i>NIPBL</i>	5p13	PVS, VSD, ASD, PDA	33
	<i>SMC1L1</i>	Xp11.22		
	<i>SMC3</i>	10q25		
Mowat-Wilson	<i>ZEB2</i>	2q22.3	VSD, CoA, ASD, PDA, PAS	54
Rubinstein-Taybi	<i>CBP</i>	16p13.3	PDA, VSD, ASD, HLHS, BAV	33
	<i>EP300</i>	22q13.2		
Smith-Lemli-Opitz	<i>DHCR7</i>	11q12-13	AVSD, HLHS, ASD, PDA, VSD	50

TGA, transposition of great arteries; TOF, tetralogy of Fallot; VR, vascular ring; and VSD, ventricular septal defect. *Note:* % CHD denotes the proportion of patients with the particular genetic syndrome affected by CHD. Adapted from [7].

There remains much to be learned about the genetic and epigenetic bases of CHD, which we are only now beginning to understand through tissue, animal and computational modelling. Multiple experimental animal models have provided invaluable understanding into the molecular mechanisms of CHD. In humans, the basis of these molecular mechanisms remains poorly understood owing to its complexity. Moreover, most CHDs are not part of any genetic syndrome i.e., sporadic malformations, with neither a family history nor a clear Mendelian inheritance

of the disease [8]. Whole exome and genome sequencing efforts reveal mutations in genes that contribute to CHD [17], but mutations in protein coding genes only account for 35% of CHD [9]. Importantly, many of these protein coding genes are now recognized as those encoding components of the epigenetic molecular pathways (e.g., histone modifying enzymes), underpinning a causality hypothesis for “molecular epigenetics”, or pathways that regulate networks of gene expression [9].

2. Overview of Congenital Heart Disease

As CHD comprises a heterogeneous group of cardiac malformations, the key clinical manifestation is dependent on the type of CHD. Since Maude Abbott developed The Atlas of Congenital Cardiac Disease more than a century ago, the classification of CHD has evolved substantially [18]. Broadly speaking, CHD can be classified, based on morphology and hemodynamics, into cyanotic and acyanotic CHD. Cyanosis is a bluish discoloration of the skin and mucous membrane resulting from reduced oxygen saturation in the circulating blood. Patients with cyanotic CHD have mixing of deoxygenated with oxygenated blood, with overall reduction of circulating oxyhemoglobin.

Common examples of acyanotic CHD include atrial septal defect (ASD) and ventricular septal defect (VSD). In ASD, there is a defect/hole in the septum/wall that divides the left and right atria; in VSD, the defect is in the septum between the left and right ventricles. Notably, VSD is one of the commonest congenital malformation of the heart. Atrioventricular septal defect (AVSD), also known as endocardial cushion or atrioventricular canal defect, comprises of a defect in atrioventricular septum, and malformed atrioventricular valves. In these defects, oxygenated blood shunts from the oxygen-rich (left) chambers to the oxygen-poor (right) chambers; therefore, these lesions are also termed left-to-right shunts. As the mixing is from the oxygenated to the deoxygenated chambers, there is no reduction in the oxygen saturation in the systemic circulation. However, this may result in increased pulmonary blood flow with consequent lung congestion.

Cyanotic CHD encompass defects such as tetralogy of Fallot, pulmonary atresia, transposition of the great arteries, double outlet right ventricle, persistent truncus arteriosus, tricuspid atresia, and total anomalous pulmonary venous drainage, to name a few. [Table 2](#) summarizes the common types of cyanotic CHD.

Table 2. Cyanotic congenital heart diseases.

Cyanotic CHD	Brief Description
Tetralogy of Fallot (TOF)	A common cyanotic CHD; characterized by pulmonary stenosis/right ventricular outflow tract obstruction, VSD, over-riding aorta and hypertrophy of the right ventricle
Transposition of the great arteries (TGA)	Discordant ventriculoarterial connection—the right ventricle is connected to the aorta (instead of pulmonary artery), and left ventricle to pulmonary artery (instead

Cyanotic CHD	Brief Description
	of aorta)
Double outlet right ventricle (DORV)	Both the aorta and pulmonary artery arise predominantly or completely, from the right ventricle
Persistent truncus arteriosus	Failure of septation of the primitive truncus into the aorta and pulmonary artery, resulting in a single, common arterial trunk that overlies a large VSD
Hypoplastic left heart syndrome (HLHS)	Underdevelopment of the left-sided structures of the heart, including the ascending aorta, left ventricle and aortic and mitral valves

as these

lesions involve the conus and truncus arteriosus of the embryonic heart.

TOF, TGA, DORV, and persistent truncus arteriosus are collectively known as conotruncal defects, as these lesions involve the conus and truncus arteriosus of the embryonic heart.

3. Overview of Cardiogenesis and Transcriptional Events during Cardiac Development

Broadly speaking, CHD can be considered as the consequence of normal cardiac development gone awry. Heart development or cardiogenesis, is a complex developmental process ([Figure 1](#)) governed by multiple interlinked and dose-dependent pathways ^[19]. Owing to the complexity of the developmental processes governing morphogenesis of the heart, impairment in any of these steps understandably leads to CHD. These events increase the difficulty of identifying and characterizing the genetic risk factors for CHD, and emphasizes the importance of understanding cardiogenesis at the molecular level. Therefore, an overview of the cardiac developmental events and their transcriptional regulation ([Figure 2](#)) would be pertinent to provide context to understanding the developmental defects causing CHD.

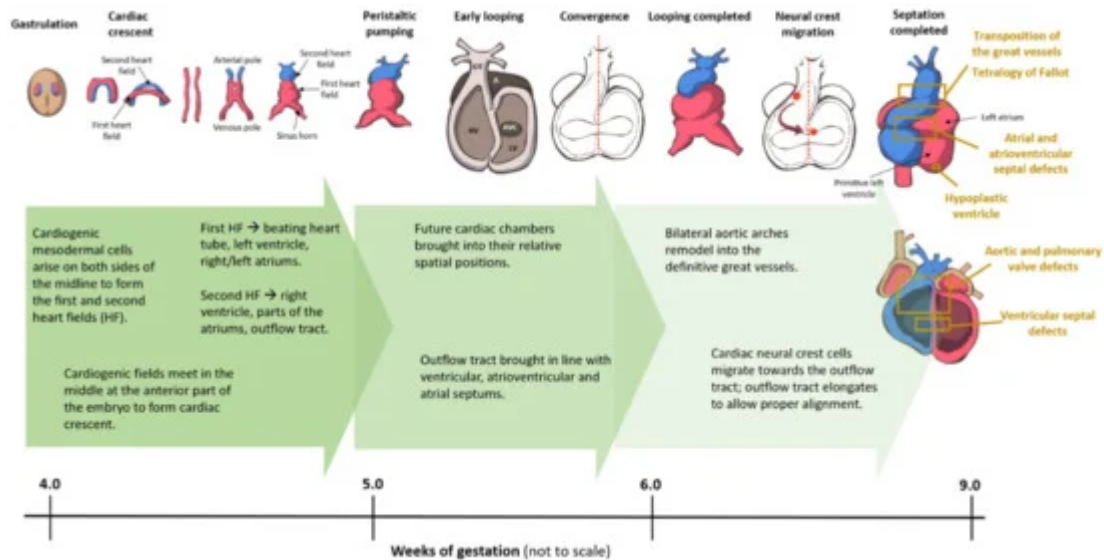


Figure 1. Cardiac development in the human embryo. This schematic shows the embryonic development of the human heart through first and second heart field formation, heart tube formation and pumping, looping, neural crest migration and septation, resulting in a fully developed heart at the end of gestation. HF: heart field.

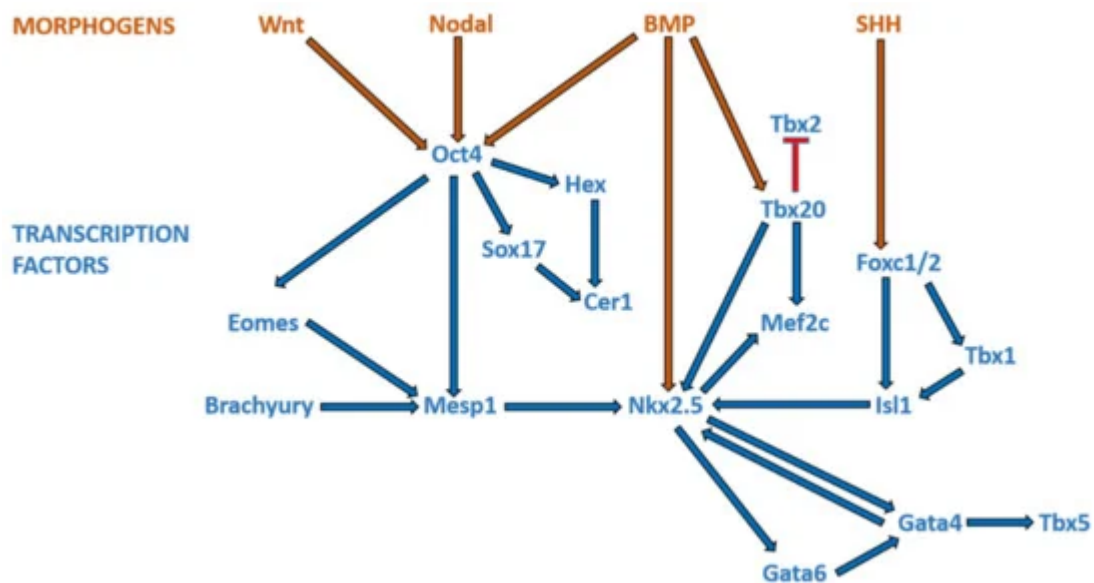


Figure 2. Morphogens and transcriptional factors regulating cardiac cell lineage and differentiation. Note: Blue arrows indicate activation; red arrows indicate inhibition.

4. Epigenetics and Congenital Heart Disease

The expression of thousands of genes in millions of cells in a single organism must be tightly regulated, during development and throughout its life. Although the genotype of most cells of a given organism is the same (except the gametes and the cells of the immune system), multiple cell types and functions emerge owing to highly regulated gene activity. Gene activity is largely mediated by transcriptional regulation, which is in turn orchestrated by epigenetic mechanisms. Although the definition of epigenetics may have evolved over time, Conrad Waddington

in the 1950s proposed that, “An epigenetic trait is a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence” [20]; and this can involve the heritability of a phenotype, passed on through either mitosis or meiosis. The mechanisms that govern epigenetics comprise of DNA methylation, histone modifications, higher-order chromatin structure, and the activity of certain non-coding RNA species [21]. Overall, epigenetics are heritable, and mutations in single gene responsible for these mechanisms can lead to dysregulation on an array of genes leading to polygenic diseases including CHD. Here, we describe the list of genes implicated in CHD across the different mechanisms. [Table 3](#), [Table 4](#) and [Table 5](#) summarize the current available literature of human studies.

Table 3. DNA methylation in CHDs.

DNA Methylation					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
NOX5	21 VSD and 15 controls	Hypermethylation	Fetal myocardial tissue	VSD	[22]
KIAA0310; RAB43; NDRG2	21 VSD and 15 controls	Hypermethylation	Fetal myocardial tissue	VSD	[23]
SIVA1		Hypomethylation			
LINE-1*	32 TOF and 15 controls [24]; 48 TOF patients and 16 controls [25]	Hypomethylation	Right ventricular tissue samples [24]; Right ventricular outflow tracts [25]	TOF	[24]
NKX2.5; HAND1; EGFR; EVC2; TBX5; CFC1B	30 TOF and 6 controls [26]; 41 TOF and 6 control [27]	Hypermethylation	Right ventricular myocardium tissues	TOF, HLHS	[26][27]

DNA Methylation					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
<i>GATA4</i> ; <i>MSX1</i>	6 Down syndrome with CHD, 6 Down syndrome without CHD, 6 isolated heart malformations, and 4 control	Hypermethylation	Whole heart tissue	AVSD, VSD, CoA, TOF, LHH, HAA, DORV, VSD, TOF, MVA, AVA, PFO, TVS; RHH, TA; ADA; TAV	[28]
<i>SCO2</i>	8 TOF, 8 ventricular septal defect, and 4 control	Hypermethylation	Myocardial biopsies	TOF, VSD	[29]
<i>ZFPM2</i>	43 TOF and 6 controls	Hypermethylation	Right ventricular outflow tract	TOF	[30]
<i>p16^{INK4a}</i>	63 TOF and 75 controls	Hypermethylation	Whole blood	TOF	[31]
<i>BRG1</i>	24 CHD and 11 controls	Hypomethylation	Various cardiac tissues.	TOF, VSD, DCRV	[32]
<i>MTHFR</i>	40 Down syndrome without CHD; 40 mothers of Down syndrome with CHD, and 40 age matched control mothers	Hypermethylation	Whole blood	AVSD; VSD, ASD; TOF	[33]
<i>TBX20</i>	23 TOF and 5 controls [34] ; 42 TOF and 6 controls [35]	Hypomethylation	Right ventricular myocardial tissues	TOF	[34]

DNA Methylation					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
<i>ZIC3</i> ; <i>NR2F2</i>	Monozygotic twin pair discordant for DORV	Hypermethylation	Whole blood	DORV	[36]
Histone Modification					
Allele	Clinical Sample Size	Modification	Source Type	Cardiac Disease Phenotype	Reference
<i>WHSC1</i>	Case study	H3K36me3	In vivo mouse models [38]	HLH; WHS	[38][39][40]
<i>MLL2</i> ; <i>CHD7</i> ; <i>WDR5</i> ; <i>KDM5A</i> ; <i>KDM5B</i>	362 severe CHD cases and 264 controls	H3K4me	Whole blood	LVO; CTD	[41]
<i>UBE2B</i> ; <i>RNF20</i> ; <i>USP44</i>		H2BK120		CTD; HTX; LVO	
<i>SMAD2</i>		H3K27		HTX	
<i>EBAF</i>	16 VSD and 16 normal fetuses at 22–28 weeks of gestation.	H4ac	Myocardial tissue	VSD	[42]
<i>RNF20</i> ; <i>RNF40</i> ;	2645 case trios and 1789 control	H2Bub1	Whole blood or sputum	Dextrocardia; RAI; TAPVR; CAVC; PA;	[43]

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Histone Modification					
Allele	Clinical Sample Size	Modification	Source Type	Cardiac Disease Phenotype	Reference
<i>UBE2B</i>	trios.			L-TGA; HLHS; TOF, RAA	
<i>JMJD1C</i> ; <i>RREB1</i> ; <i>MINA</i> ; <i>KDM7A</i>	89 severe CHD cases and 95 controls	H3K27/H3K9	Whole blood	CTD	[44]
<i>KAT2B</i>	400 Chinese Han	HAT	Whole blood	TOF, TA and TGA, VSD, AVSD and PDA	[45]
<i>PRDM6</i>	35 individuals and their extended kindreds	H3K9me2/H4K20me2	Whole blood	N-PDA	[46]
<i>KANSL1</i>	253 diseased patients	H4K16ac	Whole blood	TOF	[47]

Table 5. Non-coding RNA in CHDs.

Non-Coding RNA					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
miR-196a (rs11614913 CC)	1324 CHD and 1783 controls	Increased mature miR-196a expression	Whole blood	TOF, VSD; ASD	[48]

Non-Coding RNA					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
miR-1-1	28 VSD and 9 controls	Upregulates <i>GJA1</i> and <i>SOX9</i>	Heart tissue	VSD	[49]
miR-181c		Downregulates <i>BMPR2</i>		VSD	
miR-1, miR-206	30 TOF and 10 controls	Upregulates Cx43	Myocardium tissue	TOF	[50]
let-7e-5p; miR-222-3p; miR-433	3 VSD and 3 controls	Downregulated	Blood plasma	VSD	[51]
miR-184	10 CHD and 10 controls	Downregulated	Right ventricular outflow tract	Cyanotic cardiac defects	[52]
miRNA-139-5p	5 family individuals	(c.1784T > C) gain-of-function	Whole blood	ASDII	[53]
miR-518e, miR-518f, and miR-528a	7 Down syndrome patients with AVSD and 22 Down syndrome patients without CHD	Downregulates <i>AUTS2</i>	Down syndrome lymphoblastoid cell lines (GSE34457)	AVSD	[54]
miR-518a, miR-518e, miR-518f, and miR-96		Downregulates <i>KIAA2022</i>			

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Non-Coding RNA					
Allele	Clinical Sample Size	Modification	Tissue Type	Cardiac Disease Phenotype	Reference
miR-138 (rs139365823)	857 CHD and 938 controls	Upregulates miR-138	Whole blood	VSD; ASD; TOF; PDA	[55]

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