Clinical focus

Congenital heart disease: current knowledge about causes and inheritance

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Congenital heart disease (CHD) affects 6–8 babies in every 1000 live births.[1] It is the most common cause of death from a congenital structural abnormality in newborns in the Western world, and is often associated with fetal loss. In Australia, over 2000 babies are born with CHD each year, with about half of these requiring surgery or catheter interventions. The other half have minor abnormalities (minor valve lesions or very small ventricular or atrial septal defects) that have no functional impact and rarely affect wellbeing or require intervention.

More patients with CHD require treatment each year than those with other significant conditions such as childhood cancer or cystic fibrosis (with 600 and 70 new cases, respectively, presenting each year in Australia). About a quarter of those requiring treatment will need surgery in the first year of life. Most infants and children requiring single interventions can expect to lead a near-normal life. A small group of infants with complex lesions require multiple surgical procedures, intensive support and close monitoring during the first few years of life, although their quality of life may still be good. With the success of contemporary surgical procedures and improved survival, many patients with complex lesions are reaching adult life, and the population of adults with CHD now exceeds the number of children with structural heart abnormality.[2]

However, despite the improved treatment and prognosis of these patients, there is still a large gap in our knowledge of the aetiology of CHD. Determining a cause for CHD is important from a psychosocial perspective for the patient and family (whose main questions when faced with a new diagnosis of CHD are "why" and "how"), but also in regard to family planning for both the parents and the affected child as he or she approaches reproductive age. With the growing adult CHD population, information on recurrence risks and aetiology will become increasingly relevant. Understanding the aetiology of CHD will also benefit clinical management of the patient. It may help identify possible complications and risk factors for surgery or treatment, as patients with genetic syndromes or extracardiac anomalies are generally at higher risk of operative mortality and morbidity.[3]

Novel genetic techniques, such as whole exome and genome sequencing (Box 1), can accelerate gene discovery and assist in identifying causes of diseases of previously unknown aetiology, such as CHD. This review updates our current understanding of the causes and inheritance of CHD in light of the advances being made in genetic technologies.

Summary

- About 80% of congenital heart disease (CHD) is multifactorial and arises through various combinations of genetic and environmental contributors.
- About 20% of cases can be attributed to chromosomal anomalies, Mendelian syndromes, non-syndromal single gene disorders or teratogens. Down syndrome and velocardiofacial syndrome are the most commonly seen syndromes in patients with CHD.
- To date, more than 30 genes have been linked to non-syndromal forms of CHD. Their contribution to CHD remains unknown but is presumed to be relatively small.
- There is limited evidence for the contribution of specific environmental factors to CHD causation. However, folic acid supplementation in the pre- and peri-conception period, ensuring rubella vaccination has been completed before pregnancy, and maintaining good glycaemic control in mothers with diabetes may reduce the risk of CHD in infants.
- Recurrence risks vary between different types of non-syndromal CHD with multifactorial inheritance, and can be as high as 10% when two or more siblings are affected. Generally, the recurrence risk increases if a parent rather than a sibling is affected, particularly when the affected parent is the mother.
- Individualised recurrence risks can be generated for members of families affected by CHD after obtaining a detailed family history, including accurate cardiac diagnoses for all affected members.
- High-throughput genetic techniques can accelerate gene discovery and improve our ability to provide individualised genetic counselling.

Multifactorial congenital heart disease

Currently, about 20% of CHD cases can be attributed to known causes such as genetic syndromes and teratogens, but very little is known about the aetiology of most cases (about 80%). It is generally accepted that the group of CHD lesions with unknown aetiology follows a multifactorial inheritance model, which implicates both genetic and environmental factors in disease development.[4] The prevailing model involves variations in many different genes, each of which contributes only a small amount to the individual's susceptibility to a particular condition. These interact with each other and with environmental factors to raise the likelihood that an individual will have CHD. Most sporadic cases of CHD (ie, isolated cases of CHD without a family history of the condition) would fall into this category.

1 Definitions of new genetic techniques

Whole genome sequencing: Analysis of an individual's entire genetic code using a technique that allows multiple strands of DNA to be sequenced simultaneously, thereby greatly reducing the time required. Highly advanced bioinformatics analysis is essential to filter the large volume of information generated.

Whole exome sequencing: Analysis of the protein-coding region (the exome) that makes up 1% of an individual's entire genome, using a technique that allows multiple strands of DNA to be sequenced simultaneously. The exome is thought to contain the majority of disease-causing mutations. Analysing only 1% of the genome greatly reduces the amount of information to be filtered and the cost of the process.

Genome-wide association studies: Studies in which associations between variations within the genome and diseases are made by rapid screening of a dense array of genetic markers. If variations occur at a statistically higher frequency in individuals with the disease compared with healthy controls, the variations are said to be associated with the disease. ◆

Chromosomal anomalies

Chromosomal anomalies can cause CHD through several different mechanisms. Chromosomal material may be gained, as in Down syndrome, in which individuals have an additional chromosome 21, or it may be lost, as in velocardiofacial syndrome (VCFS), which is caused by loss of part of chromosome 22. Loss or gain of chromosomal material causes abnormality due to the effect on dosage-sensitive genes. For example, haploinsufficiency of *TBX1* is responsible for many of the clinical features of VCFS, including the cardiac phenotype.[5] Some phenotypic aspects could also be due to epigenetic effects and as yet unknown mechanisms. Chromosomal rearrangements, such as reciprocal translocations, can also cause problems by disrupting genes at the breakpoints on affected chromosomes, or by changing the relationship between a gene and its regulatory elements.

Chromosomal anomalies account for about 8%–10% of presenting cases of CHD.[6] Down syndrome is the most common chromosomal anomaly seen in patients with CHD, followed closely by VCFS. About 40%–50% of patients with Down syndrome have a heart defect (Box 2),[10] and 80% of patients with VCFS have CHD, which usually includes lesions affecting the outflow tract and great vessels, such as tetralogy of Fallot (TOF).[11] Although other syndromes, such as Edwards syndrome, may report higher percentages of patients with CHD presentation (Box 2), the prevalence of these syndromes is lower than Down syndrome and VCFS and therefore not seen as often.

Copy number variations (CNV) — variations in the number of copies of a specific section of DNA present in an individual — are another type of chromosomal anomaly. Specific CNV have in the past been associated with diseases such as autism and schizophrenia and, more recently, with CHD. A recent study found that microduplications of the 1q21.1 region accounted for about 1% of the population attributable risk of TOF and that duplication of the *GJA5* gene was associated with a 10-fold increase in risk of TOF.[12]

2 Chromosomal anomalies associated with congenital heart disease (CHD)[7-9]

Syndrome	Chromosomal anomaly	Associated cardiac lesions	Proportion of patients with CHD
Down	Trisomy 21	AVSD, ASD, VSD, TOF	40%–50%
Edwards	Trisomy 18	VSD, ASD, DORV, TOF, CoA, HLHS	90%–100%
Patau	Trisomy 13	ASD, VSD, DORV, HLHS, L-TGA, AVSD, TAPVR, dextrocardia, PDA	80%
Turner	Monosomy X	CoA, AS, HLHS, PAPVR	25%–35%
Klinefelter	47, XXY	ASD, PDA, MVP	50%
Cat eye	Tetrasomy 22p	TAPVR, PAPVR	50%
Pallister–Killian	Tetrasomy 12p	VSD, CoA, PDA, ASD, AS	25%
Velocardiofacial	(Del 22q11.2)	IAA(B), TA, TOF, aortic arch anomalies	75%–85%
Williams	(Del 7q11.23)	SVAS ± PVS, PS, PPS	50%–80%

ASD = atrial septal defect. AS = aortic stenosis. AVSD = atrioventricular septal defect. CoA = coarctation of the aorta. DORV = double outlet right ventricle. HLHS = hypoplastic left heart syndrome. IAA(B) = interrupted aortic arch (type B). L-TGA = congenitally corrected transposition of the great arteries. MVP = mitral valve prolapse. PAPVR = partial anomalous pulmonary venous return. PDA = patent ductus arteriosus. PPS = peripheral pulmonary stenosis. PS = pulmonary stenosis. PVS = pulmonary valve stenosis. SVAS = supravalvular aortic stenosis. TA = truncus arteriosus. TAPVR = total anomalous pulmonary venous return. TOF = tetralogy of Fallot. VSD = ventricular septal defect. ◆

3 Microdeletions and single gene disorders associated with congenital heart disease (CHD)[7-9]

Syndrome	Gene (region)	Associated cardiac lesions	Proportion of patients with CHD
Alagille	*JAG1*, *NOTCH1* (del 20p12)	PPS, TOF, ASD, PS	85%–95%
Noonan	*PTPN11*, *SOS1*, *KRAS*, *RAF1*	PVS, ASD, CoA, HCM	80%–90%
Holt–Oram	*TBX5*	ASD, VSD, AVSD, TOF	80%
Char	*TFAP2B*	PDA	60%
Ellis–van Creveld	*EVC*, *EVC2*	Primum ASD, common atrium, AVSD	60%
Smith–Lemli–Opitz	*DHCR7*	AVSD, primum ASD, VSD, PAPVR	45%
CHARGE	*CHD7*, *SEMA3E*	ASD, VSD, valve defects	50%–80%
Kabuki	*MLL2* in some cases	CoA, ASD, VSD	40%
Heterotaxy*	*ZIC3*	Dextrocardia, L-TGA, AVSD, TAPVR	90%–100%

ASD = atrial septal defect. AVSD = atrioventricular septal defect. CoA = coarctation of the aorta. HCM = hypertrophic cardiomyopathy. L-TGA = congenitally corrected transposition of the great arteries. PAPVR = partial anomalous pulmonary venous return. PDA = patent ductus arteriosus. PPS = peripheral pulmonary stenosis. PS = pulmonary stenosis. PVS = pulmonary valve stenosis. TAPVR = total anomalous pulmonary venous return. TOF = tetralogy of Fallot. VSD = ventricular septal defect.
* Here refers to heterotaxy syndrome, which includes both cardiac and non-cardiac (eg, asplenia, polysplenia) manifestations. Heterotaxy is also an umbrella term for cardiac lesions, including left and right atrial isomerism. ◆

Mendelian syndromes

CHD can be associated with extracardiac anomalies and in some cases can be diagnosed as being part of a syndrome. About 3%–5% of CHD can be attributed to Mendelian syndromes where a single mutation in the DNA results in pathological consequences, following a Mendelian inheritance pattern.[13]

Examples of Mendelian syndromes associated with CHD include Alagille syndrome, Holt–Oram syndrome and Noonan syndrome — these syndromes have a particularly high frequency of cardiac anomalies (Box 3). In most of the known Mendelian syndromes, the causal gene variation can be identified using current molecular genetic tests. As with chromosomal anomalies,

there is variable expression within the cardiac phenotype of each syndrome, resulting in a range of possible cardiac lesions.

Non-syndromal single gene disorders

Research into CHD in the past 15 years has primarily focused on gene discovery in non-syndromal, familial forms of CHD. The proportion of cases falling into this group is still unknown, although it is presumed to be relatively small. Autosomal dominant inheritance is most common; however, the pathogenicity of the reported mutations and the role they play in disease phenotype and segregation is, in most cases, not very clear. Many of the genes reported to date encode transcription factors (proteins that regulate gene expression), but other types of proteins, particularly structural proteins such as cardiac actins and myosins, have also been implicated. The first two genes to be linked to non-syndromal CHD were *NKX2-5* and *GATA4*;[14] more than 30 genes have since been associated. A selection of the more well known genes is shown in Box 4.[1] Gene discovery in the field has relied on traditional techniques, such as linkage analysis and candidate gene approaches. While these techniques have been successful in other research fields, they rely on large families with multiple affected members and prior knowledge of biological pathways — both of which are a rarity in CHD.

Environmental factors and teratogens

Environmental factors influencing CHD can be broadly defined as any "non-genetic" factor with an associated risk of CHD development. These usually occur within a maternal preconceptional or fetal–placental–maternal context. The contribution of specific environmental exposures to the causation of CHD in general is unknown, as most associations have been derived from small observational studies, which have not been replicated and may have been complicated by recall bias and confounding effects.

The best documented maternal risk factor is maternal diabetes, with a reported fivefold increased risk of CHD from pregestational diabetes.[16] As the time of greatest risk for development of CHD is before the 7th week of gestation, the types of CHD most commonly associated with maternal diabetes are those due to defects of primary cardiogenesis, such as heterotaxy, atrioventricular septal defect and outflow tract anomalies.[17] The exact mechanisms by which diabetes induces CHD are unknown. One theory suggests that abnormal glucose levels may disrupt expression of regulatory genes in the embryo, thereby resulting in cell death. Another hypothesis is that oxidative stress and the production of free radicals resulting from changes in metabolism may be to blame. Strict glycaemic control before conception and during pregnancy has been reported to reduce the risk of infants developing CHD.[18]

Other environmental factors have been associated with an increased risk of CHD (Box 5), although findings are generally inconclusive. For example, studies providing supportive evidence of a protective effect of periconceptional folate and folic acid-containing multivitamin supplementation were too small to provide definite answers.[19] Additional population-based studies and randomised clinical trials are needed to confirm their findings. Maternal febrile illness is also questionable as a risk factor, as most studies were unable to distinguish between possible confounding effects of medications taken to reduce illness. Potential confounding effects have also been seen in studies investigating maternal antidepressant use, specifically selective serotonin reuptake inhibitors (SSRIs), although consistent evidence supporting an increase in CHD after use of some SSRIs warrants further study.[20]

Despite the inconclusive evidence reported, it seems reasonable to suggest a few basic recommendations aimed at minimising possible CHD risk factors for women who are or intend to become pregnant:

- Daily folic acid supplementation in the pre- and periconception period
- Ensuring rubella vaccination is complete before pregnancy
- Optimal management of other known risk factors, such as diabetes and phenylketonuria, before and during pregnancy

4 Selected genes associated with non-syndromal congenital heart disease[1,15]

Gene	Function	Associated cardiac lesions
NKX2-5	Transcription factor	ASD–AV block, TOF, HLHS, TGA, DORV, Ebstein anomaly, VSD
NKX2-6	Transcription factor	TA
GATA4	Transcription factor	ASD ± PS, TOF, VSD, DORV
GATA6	Transcription factor	TA, TOF, AVSD
TBX1	Transcription factor	IAA, aortic arch anomalies, VSD
TBX5	Transcription factor	ASD, VSD, AVSD, conduction abnormalities
TBX20	Transcription factor	ASD, VSD, valve defects, LVOTO
CITED2	Transcription factor	ASD, VSD, TOF, TGA
ZIC3	Transcription factor	Heterotaxy, ASD, AVSD, TGA, VSD, TAPVR, PS
ZFPM2	Transcription factor	TOF
FOXH1	Transcription factor	TOF, VSD
HAND1	Transcription factor	HLHS (somatic mutation)
TFAP2B	Transcription factor	PDA
NOTCH1	Membrane ligand–receptor	AS, BAV
NODAL	Membrane ligand–receptor	Heterotaxy, TGA
JAG1	Membrane ligand–receptor	PS, TOF
CFC1	Membrane ligand–receptor	Heterotaxy, TGA, DORV, TOF
MYH6	Sarcomeric protein	ASD
MYH7	Sarcomeric protein	ASD, Ebstein anomaly
MYH11	Sarcomeric protein	PDA
ACTC1	Sarcomeric protein	ASD, VSD
GJA1	Gap junction protein	HLHS (somatic mutation)
GJA5	Gap junction protein	TOF
CRELD1	Matricellular protein	AVSD, dextrocardia
ELN	Structural protein	SVAS
VEGFA	Mitogen	TOF

ASD = atrial septal defect. AS = aortic stenosis. AV = atrioventricular. AVSD = atrioventricular septal defect. BAV = bicuspid aortic valve. DORV = double outlet right ventricle. HLHS = hypoplastic left heart syndrome. IAA = interrupted aortic arch. LVOTO = left ventricular outflow tract obstruction. PDA = patent ductus arteriosus. PS = pulmonary stenosis. SVAS = supravalvular aortic stenosis. TA = truncus arteriosus. TAPVR = total anomalous pulmonary venous return. TGA = transposition of the great arteries. TOF = tetralogy of Fallot. VSD = ventricular septal defect. ◆

- Avoiding medication use before and during pregnancy, if possible. Where the use of medication is unavoidable, it should be discussed with medical professionals.

Contribution of "flow"

Normal circulation in the developing fetus is an important promoter of growth and chamber development.[21] In complex forms of CHD, where multiple anomalies exist, it is conventionally thought that individual structural defects may explain "downstream" changes. For example, severe mitral stenosis or atresia may be associated with underdevelopment of the left ventricle, aortic valve and ascending aorta. It is likely that the situation is more complex than this, with translational studies suggesting that individual genetic mutations may cause a range of abnormalities affecting both cardiac valves and chamber myocardium.[22] Defining the genetic and molecular underpinning of these abnormalities is important in understanding the growth potential of cardiac structures in affected individuals.

Alternative hypothesis

Controversy has surrounded the suggestion that multiple somatic mutations — mutations present in affected tissue but not in the germline — may cause sporadic CHD. However, subsequent studies have not replicated this finding and it appears unlikely that this is an important causal mechanism for CHD.[23]

Recurrence risks in congenital heart disease

In a minority of cases, it is possible to provide a precise recurrence risk for CHD, based on known Mendelian inheritance in a family or on risk figures related to a chromosomal anomaly. In the absence of such information, empirical risk estimates must be used. For most lesions, the reported recurrence risk in siblings of an affected individual, when neither parent is affected, is in the range of 1%–6% (Box 6).[24,25] If more than one sibling is affected, the recurrence risk can increase to 10%.[26] The recurrence risk in offspring of affected parents is generally significantly higher than that in siblings of affected individuals with unaffected parents. Further, if the mother is the affected parent, the risk of disease transmission is higher.[25] The reason for these differences is unknown, and it is difficult to reconcile them with known genetic mechanisms.

Recurrence risks also vary considerably among different types of CHD. Obstructive left heart lesions, including hypoplastic left heart syndrome, aortic valve stenosis and coarctation of the aorta, generally have noticeably higher recurrence risks in siblings of unaffected parents and/or offspring of affected parents compared with other types of CHD.[27] It is reported that up to 20% of the asymptomatic first-degree relatives of patients with obstructive left heart lesions may have undiagnosed CHD, in particular bicuspid aortic valve (BAV).[28] Although not classically considered a childhood heart defect, BAV may require treatment later in life, including valve replacement and aortic surgery.

5 Environmental risk factors associated with congenital heart disease (CHD)[8,9,17]

Teratogenic influence	Associated cardiac lesions	Proportion at risk of CHD
Maternal diabetes	VSD, ASD, L-TGA, AVSD, TAPVR, CoA, TOF, TGA	5%
Maternal rubella	PDA, VSD, ASD, PS, TOF	30%–60%
Maternal phenylketonuria	TOF, VSD, PDA, left-sided lesions	15%–50%
Systemic lupus erythematosus	Complete heart block	Uncertain
Febrile illness	PS, right- and left-sided obstructive defects, tricuspid atresia, VSD	Uncertain
Thalidomide	TOF, ASD, VSD, TA	Up to 30%
Retinoic acid	TA, TOF, IAA, DORV	25%
Anticonvulsants	Any defect	Uncertain
Lithium	Ebstein anomaly, tricuspid atresia	Lower than initially reported
Selective serotonin reuptake inhibitors	VSD, ASD, TOF	Uncertain
Alcohol	VSD, ASD, TOF	Uncertain
Marijuana	VSD, Ebstein anomaly	Uncertain

ASD = atrial septal defect. AVSD = atrioventricular septal defect. CoA = coarctation of the aorta. DORV = double outlet right ventricle. IAA = interrupted aortic arch. L-TGA = congenitally corrected transposition of the great arteries. PDA = patent ductus arteriosus. PS = pulmonary stenosis. TA = truncus arteriosus. TAPVR = total anomalous pulmonary venous return. TGA = transposition of the great arteries. TOF = tetralogy of Fallot. VSD = ventricular septal defect. ◆

6 Recurrence risk (RR) of different types of congenital heart disease (CHD)[6,8,13,24]

Cardiac lesion	RR in siblings with unaffected parents		RR in children of affected parents	
	1 child affected	⩾2 children affected	Mother affected	Father affected
VSD	3%	10%	9%–10%	2%–3%
ASD	2%–3%	8%	6%	1%–2%
TOF	2%–3%	8%	2%–5%	1%–2%
CoA	2%	6%	4%	2%–3%
AS	2%	6%	12%–20%	5%
PS	2%	6%	6%–7%	2%
HLHS	3%	10%	nr	nr
AVSD	3%–4%	nr	10%–14%	1%
PA	1%	3%	nr	nr
TA	1%	3%	nr	nr
TGA	1%–2%	5%	nr	nr
L-TGA	5%–6%	nr	nr	nr
Ebstein anomaly	1%	3%	6%	nr
Heterotaxy	5%–6%	nr	nr	nr
Overall	**1%–6%**	**3%–10%**	**2%–20%**	**1%–5%**

ASD = atrial septal defect. AS = aortic stenosis. AVSD = atrioventricular septal defect. CoA = coarctation of the aorta. HLHS = hypoplastic left heart syndrome. L-TGA = congenitally corrected transposition of the great arteries. nr = not reported. PA = pulmonary atresia. PS = pulmonary stenosis. TA = truncus arteriosus. TGA = transposition of the great arteries. TOF = tetralogy of Fallot. VSD = ventricular septal defect. ◆

Concordance of recurrent CHD (ie, the same subtype of CHD) within members of the same family can vary substantially between different types of CHD. The overall exact concordance of recurrent CHD is reportedly 37%, with a group concordance (ie, within the same spectrum of CHD) of 47%.[29]

Future directions

Recent advances in technology provide us with the potential to better understand conditions with a genetic

component that have not previously been well understood. Revolutionary techniques such as whole genome and exome sequencing still harbour many challenges, including the analysis of large amounts of data and the difficulty in distinguishing benign variants from disease-causing mutations. However, the prospect of novel gene discovery and possible identification of disease aetiology greatly outweighs these challenges. For conditions with complex, multifactorial inheritance, such as CHD, these novel techniques hold much promise. Unlike traditional research techniques, they provide an unbiased approach, in which both rare and common variants can be identified, making them more suitable to the study of complex diseases.

Accelerated gene discovery in CHD will translate into more individualised genetic counselling for patients and their families, and the role of genetics in the clinical care of patients with CHD should continue to evolve. For now, ensuring an accurate family history is obtained, including detailed cardiac diagnoses for all affected family members, could provide valuable clues about possible causation and inheritance. This is particularly relevant to families with multiple affected individuals, and a referral to a genetics service should be considered.

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