Congenital Heart Defects

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Congenital heart defects (CHD) are malformations present at birth that occur during heart development. Increasing evidence supports a genetic origin of CHD.

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1. Introduction

Congenital heart defects (CHD) occurs during heart development, also known as cardiogenesis, which begins very early in gestation. The initial beating embryonic heart is tubular-shaped, and all the while functioning to support somatic growth of the fetus, the embryonic heart loops and is morphed to a complex four-chambered organ [1]. Identification of the regulatory networks controlling all stages of cardiogenesis has led to improved understanding of genes involved in heart development [2]. Conversely, complimentary, genetic studies of CHD patients have identified variants in genes essential to heart development [3].

2. Phenotypic Considerations

2.1. What Is CHD?

CHD refer to malformations of the heart present at birth. We will not consider malformations incompatible with fetal life but will limit our focus on CHD compatible with fetal development resulting in live birth. The anatomic details and clinical significance of the malformations are quite varied. Some may have a profound impact on postnatal clinical well-being and require intervention, usually surgical and often in the neonatal period. On the other hand, some CHD may have no clinical impact and go undetected until discovered incidentally later in life. While such defects may be of little clinical significance, they are highly relevant to the design of genetic studies. This is because statistical evaluation of the co-occurrence between genotype and phenotype sought in a genetic study requires determination of the presence or absence of CHD.

2.2. What Is the Incidence of CHD?

CHD constitute a major portion of clinically significant birth defects. While an incidence of 10 per 1000 (~1%) is often cited [4], depending on the definition of what constitutes CHD, the incidence may be much higher. A history of clinically significant CHD, such as those requiring surgery, may be readily apparent during review of past medical history. However, some CHD may have been overlooked because they were not clinically significant; they cause no symptoms and may only be detected by a cardiac imaging study. Examples of such CHD include isolated aneurysm of the atrial septum, persistent left superior vena cava (LSVC), right aortic arch and bicuspid aortic valve (BAV). BAV, the most common congenital cardiac malformation, has an incidence of 10 to 20 per 1000 of the population [5]; BAV and other malformations of little apparent clinical significance are often excluded from estimates of CHD incidence. Taken together, CHD incidence may be as high as 50 per 1000 (~5%) [6]. This is an important consideration in genetic study design because even though CHD in a research participant lacks clinical significance it may be an indication of genetic abnormality and thereby be of profound genetic significance.

2.3. Tools to Determine CHD Phenotype

Classification of CHD phenotype is based on careful consideration of images of the heart position in the thorax, heart chambers, septa and valves as well as location, anatomy and relationships of vena cava, pulmonary veins and great arteries. A chest X-ray may be useful for determining the position of the heart in the thorax. Angiography, an invasive procedure, may provide useful images of abnormal cardiac anatomy. However, an echocardiogram which uses ultrasound technology has become the gold standard technique for clinical cardiac imaging as it is well adapted for cardiac imaging for patients of all ages including the fetus.

Details of pre- and postnatal medical history, family history and clinical exam may inform about the presence or absence of CHD. Individuals with CHD may have a history of cardiac surgery, previous visits to a cardiologist, and/or records of past cardiac imaging, e.g., echocardiography, that reveal the CHD phenotype. However, the absence of such records does not equate to a phenotype of normal. Extracardiac features relevant to a CHD diagnosis include facial features, skeletal abnormalities including malformed vertebrae and limb anomalies, and abdominal viscera arrangement. For example, from the perspective of an echocardiographer, tetralogy of Fallot due to del22q11, also known as DiGeorge syndrome, may be indistinguishable from that CHD due to the NKX2.5 mutation, whereas in the same scenario a history of cleft palate would drastically alter the genetic focus [3]. A developmental assessment including gross and fine motor skills as well as cognitive development may lead to recognition of developmental delay which is more likely to be associated with certain CHD as part of a syndrome.

3. Genetic Considerations

Much of CHD is thought to have a genetic component, but not all CHD due to genetics clusters in families. Sometimes during the development of germ cells (egg and sperm) sporadic genetic mutations occur. These errors can be as large as additions or deletions of whole chromosomes resulting in trisomies or aneuploidies or as small as an alteration in a single nucleotide variant. Family history coupled with clinical features can be used to identify some syndromic conditions that are not usually inherited, e.g., Down syndrome (trisomy 21). However, absence of a positive family history does not mean that the condition is not inherited; indeed, only in autosomal dominant conditions would one expect an affected child to have an affected parent. Thus, it is important to examine more distant relatives to identify familial clustering.

Family history can distinguish genetic conditions that are not usually inherited, e.g., Down syndrome (trisomy 21), from genetic conditions that exhibit familial clustering, e.g., BAV. The recognition of familial heart disease has been complicated by several genetic phenomena (Table 1) that obscure the familial nature [7]. Further, while most individuals believe family history is important, many are unfamiliar with important, relevant clinical details of familial CHD. Too often, in the hustle and bustle of a busy clinic, family history is asked on the initial visit, recorded and never revisited. This leads to a situation whereby family history is an under-utilized tool in the recognition of genetic etiology. Family history is dynamic, and a current account may require revisiting the questions on more than one occasion and obtaining information from more than one family member. A pedigree is a shorthand way to document and record family history and may give some indication as to the mode of inheritance. However, with electronic medical records, pedigrees may be attached as images that can be reviewed manually and updated as necessary.

Table 1. Definition of genetic phenomena.

Phenomenon	Attribute
Genetic heterogeneity	**Similar phenotypes, different genetic cause.**
Variable expressivity	**Individuals with same disease gene have different phenotypes.**
Reduced penetrance	**Disease absence in some individuals with disease gene.**
Pleiotropy	**Multiple phenotypes associated with the same genetic cause.**

A genetic condition may be identified by recognizing signature cardiac and/or noncardiac findings during evaluation. For example, tetralogy of Fallot is a signature cardiac malformation for 22q11 deletion syndrome (del22q11), but a physician evaluating a patient with right ventricular outflow tract malformation may overlook dysmorphic facial features characteristic of del22q11. The presence of syndromic features is strongly supportive of a genetic condition and may be an indication for genetic testing. Even with what appears to be isolated CHD, typical features of the cardiac phenotype may suggest a genetic etiology with known inheritance.

4. Conclusions

CHD are the result of deviations in heart formation duing the process of cardiogenesis; they are the most common congenital malformations. Many CHD are thought to have a genetic origin but only a small fraction of CHD cases have known etiology[3]; thus while considerable progress has been made in defining the genetic underpinnings of CHD, significant work remains.

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