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Genetic basis of congenital cardiovascular malformations

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ABSTRACT

Cardiovascular malformations are a singularly important class of birth defects and due to dramatic improvements in medical and surgical care, there are now large numbers of adult survivors. The etiologies are complex, but there is strong evidence that genetic factors play a crucial role. Over the last 15 years there has been enormous progress in the discovery of causative genes for syndromic heart malformations and in rare families with Mendelian forms. The rapid characterization of genomic disorders as major contributors to congenital heart defects is also notable. The genes identified encode many transcription factors, chromatin regulators, growth factors and signal transduction proteins- all unified by their required roles in normal cardiac development. Genome-wide sequencing of the coding regions promises to elucidate genetic causation in several disorders affecting cardiac development. Such comprehensive studies evaluating both common and rare variants would be essential in characterizing gene–gene interactions, as well as in understanding the gene–environment interactions that increase susceptibility to congenital heart defects.

1. Introduction

Congenital cardiovascular malformations (CVMs) present some of the most interesting and difficult challenges in medicine. They are exceptionally common [Hoffman and Kaplan, 2002; Hoffman et al., 2004] affecting 0.5–0.7% of all liveborn infants. The prevalence for severe CVMs at birth is reported to be ~1.5 cases per 1000 live births [Hoffman and Kaplan, 2002]. Repair of heart defects requires advanced technological interventions, and they are among the most costly birth defects to manage. Even in the era of modern surgery, some cardiac defects continue to have very poor prognosis [Hoffman et al., 2004], and constitute the largest fraction of infant mortality attributable to birth defects [Boneva et al., 2001]. Nevertheless, it is estimated that there are now more than 1 million adults with a history of significant CVM [Marelli et al., 2007].

In trying to define the origin of heart defects one might consider two very broad and non-exclusive models. In the **'embryonic insult'** model a single inciting event in a specific developmental field or process is followed by a cascade of disturbed anatomic relationships, abnormal flow-, oxygen- and pressure-dependent remodeling, and abnormal maintenance of the cardiac muscle, valve, and vessel tissues. This abnormal cascade leads to a range of anatomic outcomes that are then classified by their clinical implications and management. Embryonic insults could involve genetic and/or environmental agents. There are a handful of well-established teratogens that greatly increase the chance of heart defects [Arpino et al., 2000; Cooper et al., 2006; Correa et al., 2008; Czeizel et al., 1996; Hernandez-Diaz et al., 2000; Jimenez-Solem et al., 2012; Levy et al., 2001; Loser and Majewski, 1977; Nora et al., 1974; Obican and Scialli, 2011; Tabacova et al., 2003; van Beynum et al., 2010; Weinstein and Goldfield, 1975; Wichman et al., 2009; Wurst et al., 2010]. These include maternal diabetes, first trimester rubella infection, and isotretinoin (Accutane) exposure [Jenkins et al., 2007]. The second model invokes **'developmental pleiotropy'** i.e. the inciting factor(s) affect multiple independent processes in heart development. In this model the anatomic outcome reflects the specificity of the disturbed developmental process e.g. tetralogy of Fallot resulting from direct impairment of pulmonary subinfundibulum growth rather than some earlier abnormality in cardiac precursor differentiation or growth. Genetic factors, either causal mutations or risk-increasing variants, could easily operate through either of these mechanisms.

Genetic disorders make up the most complex and numerically significant category of known causes of CVM. A broad range of genetic mechanisms are either known to participate or strongly suspected in causing cardiovascular malformations. Like most traits that exhibit complex inheritance, there are still many unknowns and the relative importance of various genetic factors (common variants, rare variants, copy number variations (CNVs), *de novo* mutations, epistasis, epigenetics, etc.) remains to be defined.

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Despite important advances over the last 15 years, the etiology of the vast majority of CVM cases is unknown. There is a distinct lack of data concerning molecular mechanisms that are required for normal human cardiac development and very little direct observation of abnormal human embryos and fetuses. There is additional difficulty in making the connection between normal cardiac development and CVMs because there are no direct methods for determining in any single affected individual which developmental step(s) were disturbed. Many CVMs have an ambiguous embryologic origin and they may be interpreted as arising from multiple alternative early events or later and more specific processes.

2. Genetic epidemiology of congenital cardiovascular malformations

About 20% of infants born with a CVM have non-cardiac malformations [Ferencz et al., 1989]. These children are considered to have either 'multiple congenital anomalies' or 'syndromic CVM' to contrast them with those who have only 'isolated' CVM. Epidemiology studies usually distinguish between these groups but the published literature is inconsistent in the criteria that are applied. The high birth incidence together with the substantial sibling recurrence risk (1–4%) has suggested the hypothesis that CVMs have a multifactorial etiology [Burn et al., 1998; Gill et al., 2003]. Supporting this supposition is the fact that a much larger number of infants have minor anomalies of the heart at birth such as small atrial and ventricular septal defects, if imaging studies are performed without regard to symptoms. Bicuspid aortic valve (BAV) is a very common anomaly with studies in healthy adults indicating a prevalence of 1.3% [Roger et al., 2011]. BAV does not cause symptoms in early life; however, it is an important risk factor for subacute bacterial endocarditis, late onset aortic valve calcification/stenosis, aortic aneurysm and dissection [Michelena et al., 2008; Tzemos et al., 2008].

There are generally very similar rates of CVM in all major geographical regions. For some CVM there are measurable differences in rates between population groups [Canfield et al., 2006; Fixler et al., 1990; Grech, 1998, 1999; Ho, 1991; McBride et al., 2005a, 2005b; Muir, 1960; Pradat et al., 2003; Schrire, 1963; Shann, 1969]. The most likely explanation for these differences lies in the distinctive genetic history of different populations. There may be some increase in rate of CVM over the last decade (Oyen et al., 2009a, 2009b]. This will require verification as previous studies are consistent with stable birth prevalence rates of CVM over the last 60 years [Hoffman and Kaplan, 2002]. Changes in rates over relatively short time frames have typically been interpreted as reflecting environmental factors. However, the rapid change in mean parental age must also be accounted for and this could still involve increased rates of single gene mutation mechanisms.

High heritability of congenital heart defects means that genetic factors have a very large role in the overall occurrence of heart defects in the population and that the aggregate impact of genetic factors is apparently far larger than all environmental factors combined. Studies of some types of CVM have been consistent with heritability of 50–90% [Burn et al., 1998; Cripe et al., 2004; Hinton et al., 2007; Insley, 1987; McBride et al., 2005a, 2005b]. Several factors cause heritability to be underestimated in CVM: (1) heart defects are approximately 10-fold more common in miscarried pregnancies and, as a consequence, many affected offspring may not be counted in population surveys; (2) affected individuals have fewer children than people without heart defects; (3) families whose first born is affected may decide against having further offspring. Family history of CVM is one of the most consistently identified risk factors in CVM [Loffredo et al., 2000, 2001; Oyen et al., 2009a, 2009b; Wollins et al., 2001; Zavala et al., 1992]; the rate of occurrence in close relatives of affected individuals being substantially (5- to 40-fold) higher than the general population rate. Across all CVM, sibling and or offspring recurrence risk is estimated at 1–4% [Burn et al., 1998; Digilio et al., 2001; Gill et al., 2003; Hoess et al., 2002; Hoffman, 1990; Lewin et al., 2004; Meijer et al., 2005; Oyen et al., 2009a, 2009b, 2011; Piacentini et al., 2005; Siu, 1998; Whittemore et al., 1994]. Several studies have also demonstrated increased rates of cardiovascular malformations in populations with increased inbreeding and consanguineous parentage [Badaruddoza et al., 1994; Becker and Al Halees, 1999; Becker et al., 2001; Chehab et al., 2007; Nabulsi et al., 2003; Ramegowda and Ramachandra, 2006]. This is most likely to result from autosomal recessive inheritance of CVM-causing mutations. Inbreeding and the consequent reduced effective population size also makes it more likely that CVM risk increasing genetic variants could be present in one or both parents, thus increasing the occurrence of oligogenic traits.

3. Developmental epidemiology

A major problem is to explain why severe CVM are so common given that there should be severe selective constraints on the persistence of causal variants in the population. There are several potential explanations:

3.1. Dosage sensitivity

Developmental pathways are exquisitely sensitive to the amount of gene product available at specific times and in very specific locations in the embryo. A prominent role for mutation in transcription factors and chromatin modulators in cardiovascular malformations has emerged. With few exceptions these cause defects through either haploinsufficiency or imbalanced expression. The sensitivity of cardiac development to these dosage imbalances makes both *de novo* mutation and dominant transmission the most common modes of inheritance.

3.2. Large mutation target

We know from the study of animal models that more than 300 genes are required for normal heart development [Bentham and Bhattacharya, 2008]. Even though mutations in each individual gene might be quite rare, the large number of potential causal mutations might make heart defects very common.

3.3. Genetic loci with high mutation rates

We know of a few examples of genomic regions that experience much higher than average mutation rates. The deletion of 22q11 (which underlies the DiGeorge/Velocardiofacial syndrome, observed in about 1 in 4000 liveborn children) is an example of this mechanism. If there are more such genomic regions or mutation-prone loci that have yet to be uncovered, they might be contributing to an important fraction of total cases.

4. Genetic architecture of CVM

It is useful to consider the classes of genetic aberrations and the allele frequency spectrum of gene and genomic variants that contribute to cardiovascular malformations. Chromosomal abnormalities detected by conventional karyotyping account for approximately 10–12% of all CVMs in liveborn infants [Hartman et al., 2011]. Within this group, trisomy 21 is the most common cause, constituting about half of cases [Hartman et al., 2011]. The