Heart Malformation
What Are the Chances It Could Happen Again?

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Congenital heart disease (CHD) is the most common human birth defect worldwide,1 taking a tremendous toll on affected families, caregivers, and healthcare systems. Approximately 40,000 children are born each year in the United States with a heart malformation, and at least another 40,000 are born annually with subclinical malformations that result in heart disease later in adulthood. Significant advances in cardiac care and surgery have lowered mortality, and there are now >1 million survivors of CHD in the United States. As a result, the economic effects of CHD are substantial, particularly when lifetime costs of management are considered.

As an increasing proportion of the CHD population reaches reproductive age, questions of the genetic contribution to disease and risk of transmission have become paramount. Such individuals also often suffer age-dependent complications in heart function that may be related to the initial developmental and/or genetic insult that resulted in the CHD. Although their causes remain generally unknown, most CHDs are thought to have a multifactorial origin with an interplay of genetic and environmental effects.2 However, the relative contributions of genes and the environment have been difficult to discern. In this issue of Circulation, Øyen et al3 use a uniquely sized and annotated population to estimate recurrence risk for specific CHDs in families and thereby indirectly assess the role of genetic inheritance in CHD.

A number of studies have attempted to quantify the risks conferred by a family history of CHD, demographic qualities, or environmental exposures.4-5 Gestational insults such as rubella infection and gestational diabetes can predispose to CHD, as can exposure to ethanol and other teratogens like retinoic acid.6,6 Although the incidence of CHD is higher in the setting of these exposures, most fetuses remain unaffected, suggesting that only a subpopulation may be at risk. In contrast, several syndromic and familial cases of CHD are caused by rare single-gene mutations that have major effects, sometimes with 100% penetrance.7–9 Thus, the more common types of CHD that appear to be sporadic may, in fact, be caused by inherited genetic variants that modestly affect protein expression or function and manifest as disease only when combined with additional genetic, epigenetic, environmental, or hemodynamic insults (Figure 1). However, experimental evidence for this theory remains elusive.

Øyen et al address the epidemiological aspect of this theory by examining familial aggregation of CHD using an unusually large and well-defined Danish population that has been annotated in multiple registries.3 The authors used a population-based design that uniquely captured all residents of Denmark (>1.7 million) over a 28-year period. They identified ~18,000 individuals with CHD and capitalized on the Danish Family Relations Database to link affected individuals with first-, second-, and third-degree relatives. Disease information for relatives also was available in the database and allowed phenotype-based development of pedigrees. Using this population, the authors estimated the contribution of a family history of CHD to an individual’s risk of CHD, and they estimated the population risk conferred by such family histories.

They found the relative risk of recurrence for all types of CHD to be ~3 when a first-degree relative had CHD. This relative risk diminished when the family history of CHD was in only second- and third-degree relatives. These findings are consistent with the commonly used empirical risks provided to families faced with a potential recurrence of CHD. Even after the authors accounted for cases with known chromosome abnormalities or other congenital anomalies, the increased relative risks of recurrence persisted. Therefore, their findings might be applicable to the most common scenario in which CHD is an isolated finding. Furthermore, the authors analyzed the relative risk of recurrence of disease in unlike-sex twin pairings (presumably dizygotic twins), and this estimate was similar to the relative risk found in those individuals with affected first-degree relatives. Interestingly, same-sex twins, which likely include some monozygotic twins, demonstrated an ~3-fold higher relative risk of recurrence than unlike-sex twins. These data strongly suggest a genetic component to “sporadic” congenital heart disease (Figure 1).

Interestingly, when the authors analyzed recurrence of the same type of CHD within families, the relative risk of recurrence was significantly higher for certain malformations. For example, heterotaxy, atrioventricular septal defect, and left and right ventricular outflow tract obstructive lesions had particularly higher relative risks of recurrence, with heterotaxy having a relative risk of ~80. Although the numbers available for analysis were inevitably smaller than when CHD was analyzed as a collective group, the large initial size of this population still provides compelling evidence for a
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10,11 It is intriguing to consider that the high relative risk of recur-
for lesions such as heterotaxy or aortic valve disease
may reflect the presence of inherited variants of genes already
implicated in autosomal-dominant disease that have more mod-
est genetic effect on many forms of CHD. These findings
are similar to the high incidence of aortic valve disease found
in first-degree relatives of individuals with aortic valve
atresia associated with hypoplastic left heart syndrome.10,11 Given these findings from Øyen et al and related studies,11,13
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atresia associated with hypoplastic left heart syndrome.10,11

Despite these interesting findings, the study by Øyen et al
found that the contribution of CHD family history to the
overall prevalence of CHD was only \( \approx 2\% \) to 4\%, suggesting
that most of the cases of CHD in the population did not have
a family history of disease. This observation suggests that
predisposition to disease involves multiple factors, including
different genetic loci, epigenetic factors (eg, DNA methyl-
ation or histone modifications that affect gene expression;
Figure 2), environmental influences, subtle hemodynamic
factors during cardiac development, or a combination of these
factors. In this scenario, a potential disease-susceptibility
allele could lead to disease penetrance or nonpenetrance
(Figure 1), depending on the size of the effect of the
susceptibility allele and the presence of “second hits” that
modify the phenotype.

Given these findings from Øyen et al and related studies,11,13
where should we direct our efforts to better understand and
combat cardiac birth defects? This study emphasizes the grow-
ing need to understand cardiac phenotypes that may have
multifactorial origins so that we can direct efforts toward
prevention and, eventually, novel therapies. Family-based
genetic mapping studies and population-based association
studies will play important roles in elucidating the rare and
common genetic variants that predispose to CHD. Such
studies are becoming increasingly feasible with rapidly
evolving genome-wide technologies that can survey the
genome for potential genetic changes. For example, high-
density SNP detection with microarrays and, more recently,
next-generation deep sequencing for whole exome analyses
are tremendously powerful tools to detect human genetic
variation. However, the ability to associate genetic changes
with disease involves complex bioinformatics analyses that
will need to be developed as the compendium of human
genetic variation is discovered. In addition, a rate-limiting
step will likely be access to sufficient numbers of patients
with similar heart defects for association studies. This effort
will require nationwide biobanks with high-quality pheno-
typic information.

Despite the current and future advances in genetic discov-
ey in cardiac disease, there will undoubtedly be further
complexities that underlie sporadic and familial disease. For
example, noncoding regions of the genome have traditionally
been understudied or overlooked altogether, and these and
other regions of the genome need to be effectively interro-
gated to identify small noncoding RNAs (eg, microRNAs; see
Figure 2), introns, and novel sequences potentially associated
with disease.14,15 Furthermore, as the genetic bases of CHDs
are elucidated, our understanding of environmental contribu-
tions and fetal hemodynamics to disease predisposition needs
to grow substantially.

What does this mean practically for a family dealing with
a child suffering from CHD? Currently, there is often no clear
explanation of causality for the family. In fact, CHD, as with
many other conditions, appears to fall into the conundrum of
probabilistic causality.16 That is, it cannot be assumed that the
purported “cause” (be it genetic or environmental) is always
related to the expected “effect.” Given this uncertainty, when
dealing with potential future pregnancies for a family already
affected by disease, the current status of the field promotes

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**Figure 1.** Multifactorial origin of CHD. A parent may harbor a genetic predisposition to disease (susceptibility allele) and transmit this genetic risk to offspring. However, this would result in CHD only in conjunction with variants in other genetic loci or with epigenetic factors, resulting in disease penetrance. The susceptibility allele alone may not be sufficient to cause disease in offspring (nonpenetrance), but the individual would still be at risk for vertical transmission of increased risk.

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**Figure 2.** Epigenetic regulation of gene expression. In addition to genetic variation affecting gene expression, cellular levels of proteins can be regulated by many nongenetic mechanisms, including histone modifications (eg, acetylation) affecting chromatin structure, DNA methylation of CpG residues affecting transcription, or microRNA interaction with mRNA targets leading to translational regulation.
the use of the empirical recurrence risks to provide further information. The challenge that lies ahead is to provide better insight into the likelihood of disease. Identification of the predisposing genetic variants may lead to approaches involving modification of the environmental factors that might be able to lower penetrance even in the presence of susceptibility allele. We hope that studies such as those by Øyen et al can translate into further research from the field toward more precise testing for disease, sensitive and universal prenatal screening, and improved genetic counseling. For the sake of families faced with recurrent disease and for those that will encounter their first birth defect, it is incumbent on the field to engage in a focused effort to determine the underlying cause of the high recurrence risk reported here for subtypes of CHD and to ultimately identify effective preventive measures.

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References

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