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Consanguinity and the Risk of Congenital Heart Disease

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Short Title: Consanguinity and Congenital Heart Disease

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ABSTRACT

Consanguineous unions have been associated with an increased susceptibility to various forms of inherited disease. Although consanguinity is known to contribute to recessive diseases, the potential role of consanguinity in certain common birth defects is less clear, particularly since the disease pathophysiology may involve genetic and environmental/epigenetic factors. In this study we ask whether consanguinity affects one of the most common birth defects, congenital heart disease, and identify areas for further research into these birth defects, since consanguinity may now impact health on a near-global basis. A systematic review of consanguinity in congenital heart disease was performed, focusing on non-syndromic disease, with the methodologies and results from studies of different ethnic populations compared. The risks for congenital heart disease have been assessed and summarized collectively and by individual lesion. The majority of studies support the view that consanguinity increases the prevalence of congenital heart disease, however the study designs differed dramatically. Only a few (n = 3) population-based studies that controlled for potential sociodemographic confounding were identified, and data on individual cardiac lesions were limited by case numbers. Overall the results suggest that the risk for congenital heart disease is increased in consanguineous unions in the studied populations, principally at first cousin level and closer, a factor that should be considered in empiric risk estimates in genetic counseling. However, for more precise risk estimates a better understanding of the underlying disease factors is needed.

Key words: Consanguinity, congenital heart defects, risk factors, genetics, environment, genetic counseling
INTRODUCTION

Consanguineous unions afford the possibility that susceptibility genes identical by descent may be inherited through the relatedness of child-bearing couples, potentially leading to disease depending on the prevalence of consanguineous unions and the genetic contribution to disease. For common birth defects such as congenital heart disease (CHD), which are thought to have a genetic component, consanguinity may contribute to the risk of disease, particularly since the prevalence of consanguinity reaches over 50% in some areas of the world and in certain populations [Bittles 2008; Modell and Darr 2002]. The purpose of this article is to determine the potential role of consanguinity as a risk factor for CHD. First cousin unions (where the individuals share 1/8 of their genes) are very common in some cultures (www.consang.net) and could affect disease risk. From a medical genetics perspective, unions have been considered consanguineous if the individuals are related as second cousins or closer ($F \geq 0.0156$). With the recent demonstration of previously undetected autozygosity [Broman and Weber 1999; Gibson et al. 2006; McQuillan et al. 2008; Nalls et al. 2009; Browning et al. 2010], genetic relatedness may play a larger role than initially expected. Furthermore, health care providers need to care for families involved in consanguineous unions and discuss and manage potential health concerns in an appropriate manner [Bennett et al. 2002].

CHD encompasses a range of structural abnormalities of the heart, and in many cases, the factors that predispose an individual to disease are not well understood. At an early stage, Victor McKusick, a pioneer in medical genetics, summarized this issue well when he noted the common occurrence and complex basis of CHD [McKusick 1964].

CHD associated with well-known genetic syndromes often has a known genetic basis or a defined Mendelian inheritance pattern. In contrast, many forms of non-syndromic CHD are
thought to usually result from the combined effects of a number of factors, presumably both genetic and epigenetic [Nora and Nora 1978]. Despite this complexity, consanguinity could increase the likelihood of disease, particularly if the disease has a recessive or multifactorial inheritance pattern. This possibility has been explored by a number of groups, who have attempted to quantify the potential degree of increased risk. However, these studies have varied in their scope, design and analysis, and as a result the conclusions drawn have been varied. For this review we performed a detailed analysis of recent published literature addressing consanguinity and congenital heart disease, in order to focus efforts on disease prevention.

MATERIALS AND METHODS

We searched for all articles from MEDLINE (January, 1950 – March, 2010) using the Medical Subject Headings (MeSH) terms “heart defects, congenital” and “consanguinity,” limited to the English language, which yielded 207 articles. We focused on more recent articles that studied non-syndromic CHD given its greater incidence and its unclear genetic etiology, and excluded articles that considered CHD as a component of a multiple congenital anomaly syndrome or other well-known genetic syndromes. We compared study methodologies and results, and categorized studies by their different designs.

RESULTS

Consanguinity in CHD cases compared to population data for consanguinity

During 1998 Becker et al. examined 1013 patients with congenital heart disease in a major tertiary-care hospital in Riyadh, Saudi Arabia, with demographic and consanguinity information obtained on 891 cases by in-person interview [Becker et al. 2001]. The data were
then compared to rates of consanguinity from an earlier structured study of 3212 Saudi families [el-Hazmi et al. 1995], and the comparison indicated a statistically significant association between first-cousin marriage and congenital heart disease in the study population. The data were intriguing, however the findings may be limited as case and control groups were ascertained differently, although they were based on the same national population. Some potential confounders were mentioned, although critical factors such as socioeconomic status were not included in the published analyses. Nonetheless, the study was compelling as it used quite large subject numbers to address the role of consanguinity in CHD (Table I).

A study by Nabulsi et al. in Lebanon from 1997-2000 investigated CHD patients at the American University of Beirut Medical Center [Nabulsi et al. 2003]. The consanguinity profile of the 759 CHD patients was compared to the rate of consanguineous marriage in a control group from a national collaborative study covering approximately the same time period. When all CHD were considered together, 20.2% of CHD patients were born to first cousins, whereas first cousin marriage in the control group was maximally 13.2%, if individuals from the region with the highest rate of consanguinity (Bekaa) were considered. The difference in cases and controls may suggest an association between CHD and consanguinity, however confounders are important to consider. The authors analyzed a number of demographic variables in their case group, e.g. gender, age, education level, but limited demographic data on the control group were presented. It was concluded that consanguinity could lead to the segregation of autosomal recessive genes, but the contribution of the genes to heritability of cardiac malformations was not well understood. The authors also acknowledged the potential role of a multifactorial etiology in CHD.
Consanguinity in CHD cases compared to selected controls

A number of studies have investigated the issue of consanguinity and congenital heart disease, mostly utilizing smaller study sizes. Roodpeyma et al. used a case-control design with 346 cases of CHD admitted to Taleghani Hospital in Tehran, Iran and an equal number of controls enrolled over the same five-year period from admissions to the same hospital [Roodpeyma et al. 2002]. Their goal was to investigate the risk factors for congenital heart disease, and they investigated a number of variables including consanguinity. In this study, consanguinity was present in 22.0% of cases versus 19.1% of controls and the results did not attain statistical significance at p<0.05. As the study was not primarily focused on consanguinity, no details were published on the types of degree of relationships studied or the mean coefficient of inbreeding of cases and controls.

In South India, Ramegowda and Ramachandra aimed to maintain comparability in the ethnic and socio-economic backgrounds of the cases and controls groups in their study [Ramegowda et al. 2006]. They analyzed 144 cases of congenital heart disease ascertained from three major hospitals in Mysore in the state of Karnataka over two years versus 200 randomly-selected controls selected from the same region. To assess the potential risk of consanguinity on CHD, they interviewed all families and obtained family histories, and representative pedigrees from consanguineous families were shown. As with many studies, the details of the interviews to assess either consanguinity or CHD were not published, leading to an assumption that the ability to ascertain a family history of disease was similar in cases and controls. The authors also incorporated parental ages into a logistic regression analysis. The parents of 15.5% of the control group were consanguineous versus 40.3% of the CHD families, and it was concluded that the study suggested an approach to studying the recessive contributions to sporadic CHDs via
consanguinity. Although patient age was utilized as a covariate in the analyses, further information regarding the specific characteristics of the case and control groups would have been even more helpful in interpretation of this study.

Yunis et al. in a study based in Beirut, Lebanon studied 173 cases of CHD from a perinatal collaborative network, and their 865 controls were selected from the same hospitals’ neonatal intensive care units [Yunis et al. 2006]. Mothers were interviewed in their native language and consanguinity was categorized by degrees of parental relationship. Data regarding neonatal variables and maternal factors were also assessed. At first-cousin level, after controlling for a number of factors an adjusted odds ratio (OR) for the effect of first cousin relationships ($F = 0.0625$) on CHD of 1.8 (95% confidence interval (CI) 1.1-3.1) was reported. More distant consanguinity ($F <0.0625$) revealed an OR of 1.7 for CHD, although the 95% CI was 0.8-3.5.

The study included control for a number of potential confounders, and the authors concluded that the study confirmed an association between consanguinity and CHDs among newborns in Beirut.

In a larger study, Chehab et al. studied 1585 cases of non-syndromic CHD from a pediatric heart disease registry also in Beirut, Lebanon and 1979 controls without CHD from the same registry [Chehab et al. 2007]. An additional control group from a UNICEF study also was utilized. Although the details of the collection of registry information were not described in the article, the authors comparatively analyzed the data from these reasonably large groups. Consanguinity was present in a higher proportion of CHD cases versus controls when the analysis was performed on first-cousins (consanguinity in 19.4% of cases versus 14.4% in controls) and when first- and second-cousin parental relationships ($F \geq0.0156$) were co-analyzed. On the latter basis it was concluded that all degrees of consanguinity were greater in patients with congenitally malformed hearts compared to controls. In recognizing differences between
cases and controls the authors did address potential limitations of their study. They also acknowledged the importance of identifying the specific genetic risk factors in CHD and emphasized that the identification of genes involved in congenital malformations would improve counseling.

Some studies addressed the potential caveats in their data, e.g. Bassili et al. performed a case-control study in Alexandria, Egypt using the public health system to select 894 cases of CHD and an equal number of controls [Bassili et al. 2000]. The mothers were interviewed and the authors noted that a half hour was dedicated to delineating the family history and detailed drawing of the family pedigree of cases and controls. In this study, the authors outlined the demographics of the case and control groups and described their methods in some detail. Of particular interest was the observation that although the cases were similar to controls in many respects, they were more likely to be rural in residence and they tended to have less education. Interestingly, a history of consanguinity gave an adjusted odds ratio of 2.38 (95% confidence interval 1.92-2.96) for CHD. The authors discussed a number of potential sources of bias, including bias in selection, recall, and referral. It was concluded that consanguineous marriage was associated with an increased risk for CHD, and that further health education could help inform others about the potential effects of inbreeding.

Population-based studies

As hospital-based studies may be affected by factors such as patient referral patterns, some studies have used a community-based, cross-sectional study approach (Table II). For example, Gev et al. tracked all children born between 1976-1983 in five villages in the Western Galilee region of Northern Israel [Gev et al. 1986]. Of the 1546 children born, the authors found
2 that had died of CHD and found 25 additional children with disease. The mothers were interviewed, and 14 of 498 children (2.81%) were from consanguineous marriages compared to 13 of 1048 children (1.24%) born to non-consanguineous couples, which was statistically significant (p<0.02). Badaruddoza et al. studied a population of North Indian Muslims where ~38% of marriages were consanguineous [Badaruddoza et al. 1994]. They studied 1721 infants and children by tracing their genealogy to establish the degree of consanguinity between parents. Children were examined for potential congenital heart disease, and CHD among the parents was absent. They found that 12 out of 980 children from non-consanguineous parents had CHD (1.22%), the equivalent rates in consanguineous progeny were 13 of 295 children born to first-cousin couples ($F = 0.0625$) (4.41%), 5 of 221 children from first cousins once-removed ($F = 0.0313$) (2.37%), and 7 of 235 children from second-cousin parents ($F = 0.0156$) (2.98%). In total 3.37% of the children of consanguineous parents versus 1.22% of non-consanguineous parents had CHD. The authors concluded that their survey of homogenous population groups combined with the high incidence of consanguinity and the high incidence of CHD suggested a genetic influence and proposed that a combination of recessive genes was important for disease.

The study is interesting in that consanguinity was traced by genealogy (and not by parental interview as in some other studies), potentially diminishing the possibility of reporting bias.

The study by El Mouzan et al. in Saudi Arabia on consanguinity and congenital heart disease utilized household visits by primary care physicians, with responses received on questions about consanguinity and major genetic diseases from 97% of 11,874 randomly-sampled mothers [El Mouzan et al. 2008]. CHD was present in 9.1 per 1000 consanguineous families versus 4.3 per 1000 nonconsanguineous families, giving an OR of 2.12 (95% CI 1.27-3.57). Although studies of this nature avoid some of the limitations of case-control studies,
confounders are difficult to exclude with the data presented, and the proportion of affected individuals identified in both the consanguineous and nonconsanguineous groups appear lower than in other studies.

**Consanguineous unions and individual CHD lesions**

Given that many of the factors that predispose to CHD are unknown, some studies have considered each form of CHD separately and determined the role of consanguinity. This type of analysis could potentially detect effects that may be missed if multiple CHD lesions were considered as a single entity. Yet it is also possible that CHD displays phenotypic heterogeneity and multiple types of CHD may result from a genetic predisposition, as suggested by individual families that harbor individuals with different forms of congenital heart disease.

Considering the effect of consanguinity on disease based on studies that stratified the type of cardiac lesion, the previously discussed study by Becker et al. (2001) concluded that atrioventricular septal defect (AVSD), pulmonary atresia, pulmonic stenosis, ventriculoseptal defect (VSD), and atrial septal defect (ASD) were associated with consanguinity. Conversely, Ramegowda and Ramachandra (2006) concluded that ASD and patent ductus arteriosus (PDA) were strongly influenced by consanguinity, but they found no significant association of consanguinity with VSD or with complex congenital heart disease. Although intriguing, the conclusions of the study could be subject to a few potential limitations. First, the number of cases of ASD or PDA (26 or 14 respectively) was relatively small, although other studies also utilized low numbers of cases. Furthermore, confounding could always be present given the limited information published, and this has been discussed (Bittles 2007).
Bassili et al. reported that VSD (OR 2.70, 95% CI 2.07-3.50) and ASD (OR 2.87, 95% CI 1.85-4.47) were associated with consanguinity. Nabulsi et al. reported a significantly higher proportion of first-cousin marriages with many individual types of CHD including aortic valvular anomalies, ASD, and Tetralogy of Fallot (TOF), VSD, and pulmonic stenosis.

In the study by Chehab et al. a larger number of cases and controls were analyzed. The authors analyzed the degree of consanguinity in certain individual lesions and concluded that cases with ASD (total cases, n=136), valvular aortic stenosis (n=86), and TOF (n=44) demonstrated a significantly stronger association with consanguinity in the cases than the controls. However, consanguinity in cases with valvular pulmonary stenosis (with first-cousin offspring in 46 of 258 cases) did not differ significantly from the controls. VSDs were significantly associated with first cousin parentage, but not when first and second degree cousins were co-analyzed. ASDs were also associated with first and second cousin parentage.

In the article by Yunis et al., congenital heart disease subtype analysis was performed and VSD was associated with first cousin consanguinity. This finding was extended using multivariate analysis, which gave an adjusted OR of 2.5 (95% CI 1.1-5.6). ASD and hypoplastic left heart were also mentioned, although a full analysis was not performed since the numbers of these cases were smaller.

It seems that the majority of studies conclude that there is an increased incidence of septal defects such as VSD and ASD in the setting of consanguinity. This may reflect the fact that with more common forms of congenital heart disease, the higher incidence likely gives more power to determine the effect of consanguinity. Furthermore, conflicting conclusions may be largely based on differences in the groups studied and the methods of analysis.
DISCUSSION

The majority of studies support a relationship between consanguineous parentage and congenital heart disease (Tables I and II). However, it is important that the conclusions drawn from each study are viewed in the light of their respective strengths and limitations. Many studies used a case-control design and included cases of CHD diagnosed by methods such as echocardiography and excluded cases with known chromosome abnormalities or multiple congenital abnormalities. These studies can identify reasonably large numbers to study, however the analyses of cases and controls are critical. A few important points need to be considered:

First, to what extent could confounding play a role in differences between case and control groups? Could the choice of certain cases or controls inadvertently lead to elevated or deflated effect sizes that are attributed to consanguinity? Many of these studies used controls from the same hospital or from the geographic region as the cases to minimize potential confounders.

Second, how was consanguinity defined and determined? Most studies determined consanguinity considering at least first and second cousin unions, although some studies failed to indicate how consanguinity had been defined. Familial consanguinity also relied largely on the report by the parent of a child with congenital heart disease. Given this commonly used technique, it is important to minimize the possibility of reporting bias in eliciting the history of consanguinity to assure that the investigation for consanguinity is equally efficient in cases and controls. Details such as these are important to consider when drawing conclusions from studies.

Despite these potential issues, most studies conclude that certain lesions such as septal defects are increased in incidence in the setting of consanguinity. Whether less common heart lesions follow a similar pattern is unclear. Future population-based studies that capture large numbers of lesions and that quantify relatedness will be helpful.
Counseling families with consanguinity and congenital heart disease is often performed as for other multifactorial conditions. In the absence of a recognizable pattern of disease inheritance, families are presented with an empiric risk for congenital heart disease based on population data that may or may not take into account the type of heart lesion. This risk may be modified depending on the individual family history and other clinical risk indicators, and may be further adjusted due to the presence of consanguinity, although the degree of risk used in counseling has been variable [Bennett et al. 1999]. Based on our review of these studies, we recognize that future large population-based studies of birth defects such as congenital heart diseases should incorporate measures of genetic relatedness into their assessment and analysis.

Since it is uncommon for isolated congenital heart disease to be inherited in a classic Mendelian manner, most cases are assumed to be complex. For such multifactorial diseases, our ability to discuss and present precise risks to a concerned family is directly related to our understanding of the basis of disease. Based on the studies reviewed here, which are the best currently available, we still need to strive to understand the relative contribution of genetics versus the environment in congenital heart disease. If we can determine the proportional effect of consanguinity on disease, this may help determine the genetic contribution to a specific complex condition or the comparative role of genetics versus environmental influences.

As the effect of consanguinity on the risk of congenital heart disease decreases, one would hypothesize that there could be potentially a larger number of low-effect genes involved in the disease (or less of a genetic contribution) and more potential environmental contribution. Indeed, environmental factors such as blood flow are clearly important in early heart development, yet its contribution is difficult to assess in current human studies. Furthermore, if teratogens [Lammer et al. 1985; Malik et al. 2008] such as rubella or alcohol can contribute to
the risk of congenital heart disease, there is clearly a role for understanding how the
environmental influences lead to disease [Jenkins et al. 2007] given a susceptible genetic
background.

The current discussion on consanguinity and risk for congenital heart disease is timely
given the possibility for future more informative studies. Given the enormous growth in the
ability to genotype individuals based on detection of single nucleotide polymorphisms (SNPs),
we now can determine the ethnic ancestry of an individual based on genetics alone, and the
application of next generation methodologies will greatly increase this analytical capacity. Such
genomic identity may be able to more precisely estimate the degree of genetic relatedness and
identify consanguineous relationships that could have been missed or miscategorized based on
self-report.

Genome-scale SNP identification has also identified regions of extended loss of
heterozygosity in normal individuals, which could be a result from past consanguinity [Broman
and Weber 1999; Gibson et al. 2006; McQuillan et al. 2008; Nalls et al. 2009], and further
studies are needed to elucidate the role of these regions in disease [McGregor et al. 2010]. The
volume of genetic information available is rapidly expanding and the technology is available to
sequence entire exomes or genomes for detection of SNPs or small copy number variants that
could influence disease. These types of studies will reveal potentially common or rare variants
associated with disease, and it will be possible to assess the role of these predisposing factors in
the setting of consanguineous families.

The influence of de novo changes on oligogenic disease is also unknown, however it is
possible that these genomic alterations combined with the effects of consanguinity could bring
together the requisite components for disease. Furthermore, the epigenetic factors that contribute
to CHD are largely unknown [Shieh and Srivastava 2009], and it is unclear if consanguinity
results in shared environmental contributions to disease. Different populations may be
differentially susceptible to genetic and environmental perturbations, and it is important to
continue these studies with a global perspective.

If we can develop a better understanding of the relationship between consanguinity and
congenital heart disease, we can implement more accurate genetic counseling and more effective
clinical management. We propose emphasis in four key areas: (1) With patients involved in
consanguineous unions, to discuss potential implications on health based on the family history
and clinical assessment. A consanguineous union may result in a greater risk for congenital heart
disease based on studies presented in the literature, but the bias towards publication of positive
findings merits consideration, and the magnitude of risk should be taken in context of the
individual history and other potential indicators of disease. (2) Continue to educate healthcare
providers and patients about the importance of the medical family history. (3) Promote a
balanced understanding of consanguinity and develop patient skills to effectively manage
familial health risks. (4) Prioritize disease prevention and investigation into genetic
predispositions to disease and integrate cultural issues such as consanguinity into global health
initiatives.

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REFERENCES


Shieh JT, Srivastava D. 2009. Heart malformation: what are the chances it could happen again?

Circulation 120(4):269-271.


Table I. Results of studies of consanguinity and congenital heart disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. subjects</th>
<th>CHD</th>
<th>Controls</th>
<th>CHD</th>
<th>Controls</th>
<th>Reported statistics</th>
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<td>Becker et al. 2001</td>
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<td>891</td>
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<td>Lebanon</td>
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<td>Iran</td>
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<td>19.1%</td>
<td>Χ²</td>
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<td>894</td>
<td></td>
<td>44.1%</td>
<td>23.8%</td>
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</tbody>
</table>

**Notes:**

- a First-cousin consanguinity
- b Data not available
- c Average inbreeding coefficient 0.021 in CHD cases versus 0.011 in controls (P<0.05)
Table II. Results from population studies of consanguinity and congenital heart disease

<table>
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<td>$\chi^2$ P&lt;0.003</td>
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</table>

$^a$ Includes first cousin and other consanguinity

$^b$ First-cousin consanguinity