Recurrence of Discordant Congenital Heart Defects in Families

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Background—Variation within a single gene might produce different congenital heart defects (CHDs) within a family, which could explain the previously reported familial aggregation of discordant CHDs. We investigated whether certain groups of discordant CHDs are more common in families than others.

Methods and Results—Using Danish national population and health registers, we identified CHDs among all singletons born in Denmark during 1977–2005 and their first-degree relatives. In a cohort of 1 711 641 persons, 16 777 had CHDs, which we classified into 14 phenotypes. We estimated relative risks of discordant CHDs by history of specific CHDs in first-degree relatives. The relative risk of any dissimilar CHD given the specified CHD in first-degree relatives was as follows: heterotaxia, 2.00 (95% CI, 0.96 to 4.17); conotruncal defects, 2.78 (95% CI, 2.12 to 3.66); atrioventricular septal defects, 2.25 (95% CI, 1.39 to 3.66); anomalous pulmonary venous return, 1.76 (95% CI, 0.66 to 4.64); left- and right-ventricular outflow tract obstruction, 2.55 (95% CI, 1.87 to 3.48) and 3.09 (95% CI, 2.03 to 4.71), respectively; isolated atrial septal defects, 2.76 (95% CI, 2.11 to 3.61); isolated ventricular septal defects, 2.27 (95% CI, 1.75 to 2.94); persistent ductus arteriosus, 1.92 (95% CI, 1.32 to 2.79); other specified CHDs, 3.29 (95% CI, 2.51 to 4.32); and unspecified CHDs, 2.30 (95% CI, 1.76 to 3.00). Relative risks for all pairwise combinations of discordant CHD phenotypes gave no indications that certain constellations of CHDs cluster more in families than others.

Conclusion—We documented strong familial aggregation of discordant CHD phenotypes. However, we observed no excess clustering of specific CHD phenotypes among the first-degree relatives. (Circ Cardiovasc Genet. 2010;3:122-128.)

Key Words: heart defects, congenital ♦ epidemiology ♦ genetics ♦ heart septal defects ♦ population

Clustering of similar congenital heart defects (CHDs) in first-degree relatives suggests that various gene mutations underlie specific heart defect phenotypes. However, variation within a single gene might also produce different phenotypes (pleiotropy) within a family, which could explain the aggregation of different CHDs in families reported in several case studies, case-control studies, and population-based cohort studies.

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It has been hypothesized that certain dissimilar CHDs may arise through common pathways that involve shared susceptibility genes or epigenetic factors, suggesting that familial clustering of dissimilar CHDs warrants attention. For example, although septum defects may be isolated and circumscribed, some also may represent arrested major CHDs (forme fruste). Thus, a proportion of ventricular septal defects (VSDs) may represent a forme fruste of the tetralogy of Fallot. Similarly, transposition of the great arteries also may represent a severe extension of a septum anomaly.

If there is a continuum from simple VSDs to tetralogy of Fallot to transposition of the great arteries (outlet defects), we would expect to observe an increased risk of major CHDs in relatives of individuals with septum defects and vice versa. Similarly, we also would expect to observe familial clustering of other apparently unrelated CHDs, such as atrial septum defects (ASDs) and abnormal connections of the veins with the atria (inlet defects) or atrioventricular septal defects and valve defects (primitive ventricle defects).

Despite the general assumption, based on case reports, that clustering of specific constellations of dissimilar CHDs occur, familial aggregation of CHDs of different types to our knowledge has never been formally investigated. We investigated an individual’s risk of being born with CHDs given different CHDs in first-degree relatives.
Methods

Data Sources
Since April 1, 1968, the Danish Civil Registration System has registered demographic, vital status, and kinship information on all persons residing in Denmark, aided by the unique personal identification number assigned to each Danish resident. The personal identification number permits accurate linkage of individual-level information from Denmark’s nationwide population-based registers, including Statens Serum Institut’s Danish Family Relations Database,13,14 the National Patient Register, the Medical Birth Register, the Causes of Death Register, and the Danish Cytogenetic Central Register.

The Danish Family Relations Database is based on parent-child links registered in the Civil Registration System. Because most individuals born in Denmark since 1950 have links to their parents, the database can identify parents, siblings, and half-siblings residing in Denmark for nearly all persons born in 1950 or later. The National Patient Register contains information on inpatient diagnoses assigned since 1977 and outpatient diagnoses from 1995 onward. Consequently, heart defects may not be registered in older individuals, but incomplete family history of heart defect results in negligible bias in relative risk estimates when disease prevalence is <1%.15 The Medical Birth Register has collected information on gestational age for all births since 1978. The Causes of Death Register has registered death certificate information, including underlying cause of death and up to 3 contributing causes of death since 1970. The Danish Cytogenetic Central Register was established in 1968 and contains information on all pre- and postnatal chromosomal analyses performed in Denmark since 1970 and 1960, respectively.

Case Ascertainment and Classification of CHDs
CHDs were ascertained using the National Patient Register and the Causes of Death Register, with International Classification of Disease (ICD) codes, 8th revision, for diagnoses registered from 1977–1993 (746.00 to 747.49, 759.00, 759.01, 759.09) and 10th revision codes thereafter (Q200 to Q269, Q893). We considered an individual to have a CHD at birth if a defect was ever diagnosed, irrespective of age at diagnosis. The coding of CHD diagnoses was performed by hospital cardiologists at the time of hospital discharge. CHDs were classified into phenotypes based on those used by Botto et al,16 as reported previously.17 Briefly, they were classified into the following 14 heart phenotypes by grouping specific ICD codes hierarchically: (1) heterotaxia, (2) conotruncal heart defect, (3) atrioventricular septal defect, (4) anomalous pulmonary venous return, (5) left ventricular outflow tract obstruction, (6) right ventricular outflow tract obstruction, (7) isolated ASD; (8) isolated VSD, (9) ASD and VSD, (10) complex defects, (11) associations (conotruncal heart defect + atrioventricular septal defect, septal defect + left ventricular outflow tract obstruction, septal defect + right ventricular outflow tract obstruction), (12) isolated patent ductus arteriosus, (13) unspecified, and (14) all other specified heart defects. The hierarchical structure implies that all persons with any heterotaxia diagnosis, regardless of other heart defect codes, were allocated to the heterotaxia group. Next, all persons with conotruncal defect codes were identified; given the hierarchical nature of the classification scheme, individuals with heterotaxia were not included in this group. Next, individuals with atrioventricular septal defect but without heterotaxia or conotruncal defects were identified, and so on.

Persons with CHDs also were divided into those with only heart defects and those with extracardiac defects (defects in brain, spinal cord, peripheral nerves, eyes, ears, face, neck, peripheral vessels, respiratory organs, oral facial structures, gastrointestinal organs, reproductive and urinary organs, extremities, skeleton, muscles, skin, and other specified organs; multiple malformations; and syndromes) (ICD-8 codes, 740 to 745, 747.59 to 758, 759.19, 759.69 to 759.99; ICD-10 codes, Q00 to Q18.9, Q27.0 to Q89.2, Q89.4 to Q89.9) and those with and without chromosomal aberrations. (Down syndrome, trisomy 13, trisomy 18, Turner syndrome, other sex chromosome aneuploidy, deletions, and other chromosome abnormalities). Chromosomal abnormalities were identified using standard cytogenetic techniques. In cases of specific structural chromosomal aberrations (eg, deletions, translocations, inversions) or clinical suspicion of chromosomal aberration, karyotype investigations have been supplemented with fluorescence in situ hybridization techniques since 1990 and array-based studies since 2005.

Study Population
All singletons born alive in Denmark between 1977 and 2005 with at least 1 identifiable first-degree relative were included in the study cohort, as reported previously.17 Information on CHDs was retrieved from the National Patient Register and the Causes of Death Register. For each cohort member, older first-degree relatives (mother, father, and older sibling) were identified using the Danish Family Relations Database. CHDs among relatives (exposure of interest) were identified in the same way as those among cohort members.

Statistical Analysis
Familial clustering of dissimilar CHDs was evaluated by estimating the relative risks of any dissimilar CHD by history of specific CHDs in first-degree relatives and the relative risks of specific dissimilar CHDs by history of specific CHDs in first-degree relatives. Only CHDs in family members born before the cohort member were considered to contribute to a family history of CHDs, ensuring that affected pairs in the cohort contributed only once.

Relative risk of any dissimilar CHD by family history of a specific CHD was estimated as a risk ratio, that is, the ratio of the risk of any dissimilar CHD in individuals with a specific CHD in an older first-degree relative (numerator) to the risk of any CHD phenotype other than the specific phenotype of interest in individuals whose older first-degree relatives had no CHDs (denominator). For example, given an older first-degree relative with heterotaxia, the relative risk of any dissimilar CHD in the younger individual was the ratio of the nonheterotaxia CHD risk in individuals with a heterotaxia first-degree family history to the nonheterotaxia CHD risk in individuals without a CHD first-degree family history. Thus, an individual and a family member had dissimilar defects when the cohort member had a CHD other than the family member’s specific defect. Risk ratios were estimated using binomial log-linear regression performed with PROC GENMOD in SAS version 9.1. Relative risks were adjusted for calendar period (1977–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2005).

The relative risks of specific dissimilar CHDs by family history of a specific CHD in first-degree relatives were estimated using polytomous logistic regression. For each pair of discordant CHDs (eg, heterotaxia in the individual and conotruncal heart defects in family members, and conotruncal heart defects in the individual and heterotaxia in family members), the estimated relative risk represented the relative risk of either of the 2 CHDs by family history of the other CHD in the pair. Polytomous logistic regression was used to model the 2 CHD outcomes in each pair simultaneously. For each CHD outcome in the pair, the logarithm of the odds was modeled with parameters for the effects of family histories of the 2 dissimilar CHDs and the effect of family history of the same CHD. The 2 parameters for the effects of family history of the dissimilar CHDs were assumed to be equal. The reported relative risk for any heart defects by family history of the other heart defect in the pair was equal to the exponential function of this common parameter. When estimating the overall relative risk for a CHD different from that reported in a first-degree relative, the parameters were assumed to be the same for all pairs of defects in a simultaneous model. The parameters in the polytomous logistic regression model were estimated using PROC NLMIXED in SAS version 9.1. Adjustment for calendar period was performed as described previously in this article. Estimated numbers were calculated by multiplying the period-specific population prevalence of CHD with the number of persons with a family history of CHD, categorized by period. The project was approved by the Danish Data Protection Agency and the Board of the Danish Cytogenetic Central Register.
Table 1. Absolute and Relative Risks of Any Dissimilar CHD Phenotype by History of Specific CHD Phenotype in First-Degree Relatives in a Cohort of 1 711 641 Singletons Born in Denmark, 1977–2005

<table>
<thead>
<tr>
<th>CHD Phenotype in First-Degree Relative†</th>
<th>Persons at Risk‡</th>
<th>No. of CHDs</th>
<th>%</th>
<th>RR§</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterotaxia</td>
<td>359</td>
<td>7</td>
<td>1.9</td>
<td>2.00</td>
<td>0.96–4.17</td>
</tr>
<tr>
<td>Conotruncal defect</td>
<td>2062</td>
<td>50</td>
<td>2.4</td>
<td>2.78</td>
<td>2.12–3.66</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>743</td>
<td>16</td>
<td>2.2</td>
<td>2.25</td>
<td>1.39–3.66</td>
</tr>
<tr>
<td>Anomalous pulmonary venous return</td>
<td>228</td>
<td>4</td>
<td>1.8</td>
<td>1.76</td>
<td>0.66–4.64</td>
</tr>
<tr>
<td>LVOTO</td>
<td>1655</td>
<td>39</td>
<td>2.4</td>
<td>2.55</td>
<td>1.87–3.48</td>
</tr>
<tr>
<td>RVOTO</td>
<td>702</td>
<td>21</td>
<td>3.0</td>
<td>3.09</td>
<td>2.03–4.71</td>
</tr>
<tr>
<td>Isolated ASD</td>
<td>2156</td>
<td>52</td>
<td>2.4</td>
<td>2.76</td>
<td>2.11–3.61</td>
</tr>
<tr>
<td>Isolated VSD</td>
<td>3005</td>
<td>56</td>
<td>1.9</td>
<td>2.27</td>
<td>1.75–2.94</td>
</tr>
<tr>
<td>Isolated ASD and VSD</td>
<td>416</td>
<td>9</td>
<td>2.2</td>
<td>2.18</td>
<td>1.14–4.16</td>
</tr>
<tr>
<td>Complex defect</td>
<td>37</td>
<td>2</td>
<td>5.4</td>
<td>5.16</td>
<td>1.34–19.9</td>
</tr>
<tr>
<td>Association</td>
<td>256</td>
<td>12</td>
<td>4.7</td>
<td>4.68</td>
<td>2.70–8.14</td>
</tr>
<tr>
<td>Isolated patent ductus arteriosus</td>
<td>1606</td>
<td>27</td>
<td>1.7</td>
<td>1.92</td>
<td>1.32–2.79</td>
</tr>
<tr>
<td>Unspecified CHD only</td>
<td>2777</td>
<td>53</td>
<td>1.9</td>
<td>2.30</td>
<td>1.76–3.00</td>
</tr>
<tr>
<td>Other specified CHD</td>
<td>1662</td>
<td>51</td>
<td>3.1</td>
<td>3.29</td>
<td>2.51–4.32</td>
</tr>
</tbody>
</table>

LVOTO indicates left ventricular outflow tract obstruction; RR, relative risk; and RVOTO, right ventricular outflow tract obstruction.†Any CHD phenotype in the cohort member other than the CHD phenotype present in the first-degree family members.‡No. of persons having a first-degree relative with a CHD.§RR adjusted for calendar period. The reference group comprised cohort members with any CHD phenotype other than the phenotype of interest and with first-degree relatives with no CHDs.

Results

Of 1 711 641 singletons born in Denmark in the period from 1977–2005, 16 777 had 1 or more CHDs, yielding an overall CHD prevalence of 9.8 per 1000 singleton births.17 Chromosomal aberrations and extracardiac birth defects were reported in 1249 (7.4%) and 3783 (22.5%) persons with CHD, respectively. Table 1 presents risk ratios for any CHD phenotype different from the specific CHD phenotype in first-degree relatives. For example, 359 cohort members (persons at risk) had a first-degree relative with heterotaxia; of these persons, 7 (1.9%) had a nonheterotaxia CHD phenotype. This risk was compared with the risk of nonheterotaxia CHD in cohort members with no heterotaxia among first-degree relatives, yielding a relative risk of 2.00. The relative risks of discordant CHDs, given specific CHD phenotypes in first-degree relatives, ranged from 1.76 to 5.16 (Table 1).

Table 1 presents total numbers of individuals with dissimilar CHD phenotypes by the relatives’ specific CHD phenotype. In the online-only Data Supplement Table, cohort members with CHDs also are divided by CHD phenotype, yielding a 14×14 table that consists of all possible pairwise combinations of CHD phenotypes between cohort members and their first-degree relatives. For example, the 7 individuals with a nonheterotaxia CHD and heterotaxia in a relative from Table 1 are shown in the supplemental Table to have conotruncal defects (3 persons), right ventricular outflow tract obstruction, isolated ASD, isolated VSD, and an association defect. Overall, there were 399 cohort member-relative pairs with discordant CHDs; 156.36 pairs were expected. Information on pairs with concordant CHDs (boxes along the diagonal) is published elsewhere.† On either side of the diagonal (supplemental Table), there were 201 pairs observed versus 77.13 expected on the lower left side and 198 pairs observed versus 79.23 expected on the upper right side.

In Table 2, the relative risk for each pair of CHDs represents the relative risk of either of the 2 CHDs by family history of the other CHD in the pair. For example, the relative risk for the pair heterotaxia-conotruncal defect (4.59) combined the relative risk of heterotaxia by history of conotruncal defects in first-degree relatives and the relative risk of conotruncal defects by history of heterotaxia in first-degree relatives. Where there were 3 or more discordant pairs (44 of 91 possible combinations), the relative risks (a measure of familial aggregation of discordant CHDs) ranged from 1.66 to 8.91, with most between 2 and 4.

The pair-wise relative risks did not reveal patterns of association among specific clusters of CHD phenotypes. For example, the relative risks associated with isolated VSD were of similar strength (1.07 to 3.52) for all discordant CHD phenotypes but complex defects (relative risk, 14.3) (Table 2); however, the estimate for the isolated VSD-complex defect combination was based on only 2 discordant pairs. Conotruncal defect combinations also all had similar relative risks. In particular, isolated VSD and conotruncal defects did not seem to aggregate more in families than other pairs of defects (relative risk, 2.16). Likewise, isolated ASD did not seem to co-occur more often with atrial or inlet vessel defects (eg, anomalous pulmonary venous return relative risk, 4.21) than with other phenotypes. With the exception of combinations involving complex defects, most combinations of discordant CHD phenotypes were represented in our data, although in many cases there were only 1 or 2 affected pairs.

The overall relative risk for a CHD phenotype different from that present in a first-degree relative was 2.68 (95% CI, 2.43 to
2.97), as reported previously. Excluding chromosomal aberrations, extracardiac defects, or both, the overall relative risks increased to 2.82 (95% CI, 2.54 to 3.13), 2.86 (95% CI, 2.52 to 3.23), and 3.02 (95% CI, 2.66 to 3.43), respectively.

**Discussion**

We hypothesized that certain constellations of CHDs are similar in etiology and thus might aggregate in families. We previously documented strong familial clustering of similar CHDs and an increased risk of any dissimilar CHD given a prior CHD in a first-degree family member. In contrast to previous studies on familial aggregation of CHDs, this study evaluated familial aggregation for all pairwise combinations of discordant CHD phenotypes. For many combinations, the relative risk—here a measure of familial aggregation of discordant CHDs within families—suggested that individuals...
with a family history of CHDs themselves had a 2- to 4-fold increased risk of CHDs compared with individuals without a family history of CHDs. However, we found no evidence that the specific constellations of the 14 CHD phenotypes aggregate in families.

**Previous Studies**

We showed previously that the presence of any CHD in an older sibling or a parent increases an individual’s risk of any dissimilar CHD almost 3-fold, whereas the relative risks of specific CHDs in an older sibling or a parent range from 1.8 to 5.2. These findings correspond to those from previous population-based studies of familial CHDs, although previous estimates were slightly higher than ours likely because similar and dissimilar CHDs were evaluated together.

In this study, we had the opportunity to classify affected cohort members and family members into specific heart phenotypes, evaluating all pairwise combinations of discordant CHDs. To our knowledge, no population-based evaluation of the familial coaggregation of all possible combinations of discordant CHDs has been published before because large data sets with both codes for CHD diagnoses and pedigree information have been unavailable. Most previous studies of dissimilar heart defects in families have been case reports based on selected pedigrees without comparison groups. Families with several different CHDs have been identified, leading to the hypotheses that different CHDs occurring in families are associated with common genetic factors and that certain constellations of CHDs may cluster in families because shared gene defects or epigenetic mechanisms could produce an inherited susceptibility to CHDs affecting the same embryological segment (eg, arterial or venous pole, primitive ventricle). For example, VSDs and conotruncal defects might co-occur in families. However, in our study, the relative risks for most VSD-discordant CHD combinations were similar. Furthermore, minor CHDs among first-degree family members did not insulate against severe defects, as has been suggested by Gill et al.

**Interpretation of Present Findings**

The surprisingly uniformly increased relative risks for pairs of discordant CHDs could be explained in several ways. The inclusion of syndromic CHDs associated with single-gene or chromosomal defects could contribute to the uniformity of relative risks for a variety of CHD phenotypes if the CHDs arising from the syndrome fell into multiple phenotype classes. Single-gene syndromes featuring multiple CHD phenotypes include Alagille syndrome (right ventricular outflow tract obstruction, conotruncal defects, ASD), Holt-Oram syndrome (ASD, VSD, or both), Noonan syndrome (a wide range of cardiac phenotypes), and CHARGE syndrome (conotruncal defects, ASD). These single-gene syndromes show autosomal dominant inheritance with variable expressivity or reduced penetrance, although a large proportion of single-gene syndromes arise de novo. Most chromosomal aberrations associated with cardiac phenotype arise de novo; theoretically, however, microdeletion syndromes or other cryptic rearrangements could show autosomal dominant inheritance with varying phenotypic expression. However, known chromosomal or syndromic CHDs contributed little to the clustering of discordant CHD phenotypes in our data. When we excluded persons with chromosomal aberrations based on information from the Danish Cytogenetic Register, the overall relative risk of familial recurrence of discordant CHD phenotypes changed very little. Because CHDs co-occurring with other birth defects likely represent a large proportion of the syndromic CHDs, we repeated our analyses, restricting to persons with isolated CHDs and thereby excluding persons with syndromic heart defects and extracardiac defects. Even when only based on presumed nonsyndromic CHDs, the overall relative risk of recurrence changed very little.

Single genes have been reported to be associated with different nonsyndromic CHDs in unrelated persons (see http://www.ncbi.nlm.nih.gov/omim). Allelic variants may produce anatomically different nonsyndromic CHDs, and in a few cases, identical mutations have been reported in different nonsyndromic CHDs. To date, however, there are few examples of inherited single-gene defects associated with familial aggregation of discordant nonsyndromic CHDs (eg, hypoplastic left heart syndrome, coarctation of aorta with intact ventricular septum, aortic stenosis). In this study, these defects were regarded as anatomically similar and collapsed into the left ventricular outflow tract obstruction category and, therefore, were not evaluated against one other.

Shared environmental factors that exert their effects during different stages of embryonic heart development in successive pregnancies and lead to different heart phenotypes in siblings could also underlie the increased relative risks of discordant CHDs. However, such factors would have to be very strong or interact with other factors, such as CHD susceptibility loci. For example, pregestational diabetes is known to increase the risk of CHDs, with relative risks ranging from 3 to 5. The fairly uniform increase in relative risk for different pairs of discordant CHD phenotypes also could reflect the fact that CHD phenotypes are classified according to errors in specific sequences of cardiac development (ie, according to cardiac anatomy and stages of fetal heart development) rather than according to etiologic causes.

Several relative risk estimates were very strong but only based on a single discordant pair; thus, the findings could be due to chance. Should these associations be real, we probably have identified a few rare families with Mendelian conditions expressing different CHD phenotypes. Interestingly, the “complex” and “association” phenotypes were most strongly associated with discordant CHDs within families. Family members of persons with association defects may have had single defects that were part of the association but were classified as having dissimilar defects. If there exists a spectrum of defects with association defects at the most severe end, then part of what we showed as clustering of dissimilar defects would be due to aggregation of defects within the spectrum.

**Limitations and Strengths**

Parents with a previous child or other family member with a CHD may opt for prenatal screening and termination of pregnancy if the fetus is affected, which would reduce the observed number of within-family recurrences of CHD and deflate risk ratio estimates accordingly. However, although prenatal detection of neural tube defects is very sensitive, the sensitivity for
detecting CHDs is still low, meaning that a large proportion of CHDs cannot be avoided by detection and termination of affected pregnancies. Among 1196 affected pregnancies in Odense County, Denmark, from 1980–2007, only 36 (3%) were terminated after prenatal investigation (chromosomal investigation, fetal echocardiography, or both) revealed fetal cardiac anomalies. Thus, although we had no information on the distribution of terminated pregnancies by family history, elective termination of CHD-affected pregnancies after prenatal investigation has only a minor effect on the overall birth prevalence of CHD in Denmark and, therefore, likely had little to no effect on our relative risk estimates.

Likewise, knowledge of CHD in other family members also could lead to increased surveillance for and diagnosis of CHDs. Although this situation theoretically could occur for less severe defects (eg, isolated septal defects), severe CHDs almost always come to medical attention due to either the need for surgery or death. In an additional analysis, ratios between the sums of observed numbers and sums of expected numbers were the same for septal defects by family history of nonseptal defects and for nonseptal defects by family history of septal defects, suggesting that surveillance bias did not appreciably influence our results.

Although CHD diagnoses in the National Patient Register have not been validated, validation of the registration of acute myocardial infarction has yielded a high sensitivity (91%) and positive predictive value (93%) compared with a project-based clinical register. We assume that CHD diagnoses in the National Patient Register, which are coded by cardiologists, have similar or higher sensitivity and positive predictive value than the diagnosis of acute myocardial infarction. Moreover, our phenotype-specific prevalences corresponded with those published by international birth defect registers, such as the International Clearinghouse and EUROCAT; the clinical birth defect register of Odense County, Denmark; and the National Birth Defects Prevention Group in Atlanta.

Mild extracardiac defects not requiring medical intervention and undocumented chromosomal aberrations could have been missed. However, the proportion of persons with reported extracardiac defects or syndromes among those with CHD (22.5%) corresponded well with results from a recent Norwegian population-based study. Furthermore, the proportion of persons with chromosomal aberrations among those with CHDs (7.4%) was actually slightly higher than that reported in Odense County, Denmark (which reports to EUROCAT), from 1980–2005 (6.3%). Therefore, CHD cases with extracardiac or chromosomal defects probably were not misclassified as having isolated CHDs.

Our study had multiple strengths. Because our cohort encompassed all singleton births in Denmark during a 29-year period (more than 1.7 million persons), our study had great overall power, and Denmark’s national registers allowed for complete follow-up of birth cohort members. Additionally, health care is free for all in Denmark, reporting of all hospital diagnoses is mandatory, and registration of severe birth defects is considered virtually complete. The national prevalence of specific defects corresponded well with estimates from comparable population-based registers. Finally, the Danish Family Relations Database allowed us to identify pedigrees for every member of our study cohort and link pedigree information with birth defect information without the need for personal contact with cohort members or their families, which ensured the absence of differential misclassification of CHD diagnoses.

Conclusion

The present study documented a general aggregation of dissimilar CHDs in families. We found no excess clustering of specific CHD phenotypes among first-degree relatives; particularly, the isolated septal defects did not co-occur more often in families with specific major defects. This familial aggregation of discordant CHDs is unlikely to be exclusively environmental in origin but probably has genetic origins as well.

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Disclosures

None.

References

Select congenital heart defects (CHD) could be similar in etiology and therefore might aggregate in families. In contrast to previous studies of familial aggregation of CHD, the present nationwide study evaluated familial aggregation for all common congenital heart defects. J Med Genet. 2007;44:779–783.


Clinical Perspective

Select congenital heart defects (CHD) could be similar in etiology and therefore might aggregate in families. In contrast to previous studies of familial aggregation of CHD, the present nationwide study evaluated familial aggregation for all pairwise combinations of discordant CHD phenotypes (heterotaxia, conotruncal defects, aortoventricular septal defects, anomalous pulmonary venous return, left- and right-ventricular outflow tract obstruction, isolated atrial septal defect, isolated ventricular septal defect, complex defects, associations, persistent ductus arteriosus, other specified CHD, and unspecified CHD) by investigating an individual’s risk of being born with a CHD given one or more different CHD in first-degree relatives. For many combinations, the relative risk—here a measure of familial aggregation—was increased risk of CHD compared with individuals without a family history of CHD.
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SUPPLEMENTAL MATERIAL

1) Supplemental table
Supplemental table. Observed and expected numbers of persons with congenital heart defect (CHD) by history of discordant CHD among first-degree relatives, in a cohort of 1,711,641 singletons born in Denmark, 1977-2005.

<table>
<thead>
<tr>
<th>Heart defect phenotype* in first-degree relative</th>
<th>Heterotaxia</th>
<th>Conotruncal defect</th>
<th>AVSD</th>
<th>APVR</th>
<th>LVOTO</th>
<th>RVOTO</th>
<th>Isolated ASD</th>
<th>Isolated VSD</th>
<th>Isolated ASD and VSD</th>
<th>Complex defect</th>
<th>Association</th>
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* Anomalous pulmonary venous return (APVR); atrial septum defect (ASD); atrioventricular septum defect (AVSD); congenital heart defect (CHD); left ventricular outflow tract obstruction (LVOTO); patent ductus arteriosus (PDA); right ventricular outflow tract obstruction (RVOTO); ventricular septum defect (VSD).