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Risk of Congenital Heart Disease in Relatives of Probands with Conotruncal Cardiac Defects: An Evaluation of 1620 Families

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Abstract

Current recurrence risk counseling for conotruncal cardiac defects (CTD) is based on empiric estimates from multiple studies. We examined the risk of congenital heart disease (CHD) in relatives of probands with CTDs to assist in counseling practices in the current era. 1,620 probands with CTDs and no reported chromosomal or genetic abnormalities were recruited sequentially. A three-generation pedigree was obtained for each proband by a genetic counselor detailing the presence and type of CHD in each family member. Risks and 95% confidence intervals (CI) were calculated for subgroups of relatives based on degree of relationship for all probands and by individual lesion of the proband. For pairs of affected relatives, concordance rates were calculated. Severity of CHD in the affected relative was assessed. The risk of CHD was higher in siblings (4.4%, 95% CI 3.4–5.4) than in parents (1.5%, 95% CI 1.1–1.9). Risk varied by the cardiac lesion of the proband with the highest risk in first-degree relatives of probands with tetralogy of Fallot and the lowest in D- transposition of the great arteries. 39% of affected parents and 69% of affected siblings had a concordant lesion (i.e. CTD). Most affected siblings of probands with severe CTDs had complex defects (58%), whereas very few affected parents had complex defects (20%). These data suggest that recurrence risk varies by lesion and relationship, with substantial concordance observed by cardiac lesion and complexity of disease, particularly among siblings. These findings contribute to risk counseling in the current era.

Keywords

Congenital heart defects; Conotruncal cardiac defects; Recurrence risk; Genetic counseling

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Conflict of Interest: None

INTRODUCTION

Congenital heart disease (CHD) is a common birth defect occurring in 4–8 per 1000 live births [Ferencz et al., 1985; Dolk et al., 2011; Bjornard et al., 2013]. The cause of most CHDs has yet to be determined, though multiple genetic and environmental causes have been implicated [Nora, 1968; Pierpont et al., 2007; Blue et al., 2012]. Although rare families exhibit Mendelian patterns of inheritance [Schott et al., 1998; Liu et al., 2011], most familial cases of CHD appear to be inherited as complex traits.

Numerous studies have investigated the patterns of familial risk for CHD [Nora and Nora, 1978; Boughman et al., 1987; Oyen et al., 2009]. Current recurrence risk counseling for CHD is based on empiric estimates of 3–4% in siblings of affected patients and 4–10% in offspring of affected parents, with specific risk figures varying by the CHD sub-group [Rose et al., 1985; Nora and Nora, 1988; Whittemore, 1988; Burn et al., 1998; Gill et al., 2003]. For example, recurrence risks have been observed to be highest in the sub-group with left-sided cardiac defects as compared to other forms of CHD [Hinton et al., 2007]. Among cases with conotruncal defects (CTD), studies suggest that recurrence risks vary by individual lesion, with higher risks for relatives of patients with tetralogy of Fallot than for relatives of patients with transposition of the great arteries [Ferencz et al., 1985; Digilio et al., 1997; 2001].

Given the limited number of families and phenotypic description of CTDs included in previous studies, it has been difficult to provide accurate recurrence risk estimates to families of probands with CTDs. Consequently, current recurrence risk counseling for CTDs remains largely non-specific. In addition, recurrence risk estimates in current use are largely based on data collected in the 1980s. Such estimates may not be accurate in the current era of folic acid fortification in grains and maternal use of preconceptual folic acid supplementation, given that such practices have decreased the rates of neural tube defects but have not been as thoroughly studied in CHD [Botto et al., 2000]. Similarly, risk estimates may be different with higher detection rates of CHD with fetal echocardiography and increased numbers of adults with CHD surviving to reproduce [Friedberg et al., 2009; van der Bom et al., 2011; Blue et al., 2012; Levy et al., 2013]. The purpose of this study was to estimate the risk of CHD in relatives of patients with CTDs in the current era, and to assess whether specific subtypes of CTDs influence risk in first-degree relatives, in an effort to contribute to current recurrence risk counseling practices.

MATERIALS AND METHODS

Patients

Between January 1994 to February 2010, 1,993 patients with CTDs were consecutively invited to participate in a study of the genetic basis of congenital heart disease conducted in the Cardiac Center at The Children's Hospital of Philadelphia. Although variable by year, average recruitment was 86% of all subjects approached. The study was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital of Philadelphia. A total of 1,620 patients with a CTD and no known genetic abnormalities at the time of recruitment agreed to participate in the study. The majority of probands (n=1495,

92%) were tested for a 22q11.2 deletion by fluorescence *in-situ* hybridization (FISH), multiplex ligation dependent amplification (MLPA) or microarray as previously described [Goldmuntz et al., 1998; Vorstman et al., 2006] and all were negative for this deletion. Among the remaining 127 (8%) of probands there was no clinical evidence of a genetic syndrome at the time of recruitment. A genetic counselor obtained a three-generation pedigree from each proband at the time of recruitment, detailing the presence or absence of CHD in each family member. Spontaneous miscarriages and elective terminations were documented in the pedigree but were excluded from these analyses.

Classification of CHDs in probands and relatives

Each proband was confirmed to have a CTD by review of all available medical records including echocardiography, cardiac MRI, cardiac catheterization and/or operative notes. CTDs were defined as abnormalities of the outflow tracts [Kirby et al., 1985; Nishibatake et al., 1987; Guo et al., 2011] and included tetralogy of Fallot (TOF), ventricular septal defects (VSD; including conoventricular or perimembranous, conoseptal hypoplasia or sub-arterial, and posterior malalignment type VSD), truncus arteriosus (TA), interrupted aortic arch (IAA; including type A and B), D- and L- transposition of the great arteries (D-, L- TGA), double outlet right ventricle (DORV), isolated aortic arch anomaly (AAA), double inlet left ventricle with malposed great arteries, and tricuspid atresia with malposed great arteries. Anatomic descriptions of the CTDs have been previously detailed [Peyvandi et al., 2013].

Affected relatives of probands were classified by the concordance or discordance of their defect with the proband's. Lesions were considered concordant when the affected relative had a CTD and discordant when the affected relative had a CHD other than a CTD.

In addition, the severity of CHD was assessed in the affected first degree relatives based on the 2008 ACC/AHA guidelines on the Care of the Adult with Congenital Heart Disease [Warnes et al., 2008]. Specifically, lesions that are mild or largely curative were considered "simple" (atrial septal defects, ventricular septal defects, isolated pulmonary valve stenosis, bicuspid aortic valve, patent ductus arteriosus, and isolated aortic arch anomalies), whereas other lesions were considered complex (TOF, TA, DORV, D- and L- TGA, IAA, coarctation of the aorta and hypoplastic left heart syndrome).

Statistical Analysis

The risk of CHD and its accompanying 95% confidence interval (CI) was calculated for first (parents, siblings), second (aunts, uncles) and third (first cousins) degree relatives. In addition, the risk to parents and siblings were calculated separately for male and female relatives. Where applicable, risks were calculated using data from all relatives within a class, i.e. both those born before and those born after the proband. Risks were calculated for the relatives of all probands with CTDs as well as for the relatives of probands with specific cardiac lesions. Concordance rates were calculated as the proportion of proband-affected relative pairs with or without a CTD.

RESULTS

The study cohort included 1,620 probands with a slight male predominance (59%). The majority of probands were non-Hispanic white (74%). The mean age at the time of recruitment was five years. A range of CTDs was represented among the probands with the most common lesion being TOF (34%) (Table I).

A total of 4,950 first-degree relatives (3,238 parents and 1,712 siblings), 6,738 second-degree relatives and 8,246 third-degree relatives were included in the analysis. The risk of CHD was higher in siblings (4.4%, 95% CI 3.4–5.4) than in parents (1.5%, 95% CI 1.1–1.9) with no apparent difference by gender in the relative. Risks in second and third degree relatives were lower as compared to first-degree relatives (0.8%, 95% CI 0.6–1.1 and 0.9%, 95% CI 0.7–1.2 respectively) (Table II). Risk of CHD in parents and siblings varied with the proband's cardiac anatomy. Among the relatives of probands with the most common lesions (TOF, VSD, D-TGA), risk was highest for first-degree relatives of probands with TOF (2.1% among parents and 6.4% among siblings) and lowest for D-TGA (0.16% among parents and 1.38% among siblings) (Table III).

Overall, among the affected parents of probands with CTDs, 39% had a concordant lesion (i.e. CTD) whereas 69% of affected siblings had a concordant lesion. Similar patterns were also observed for individual lesions. For example, of the 38 affected siblings of probands with TOF, 28 (74%) had a concordant CTD, the majority (n=17) of which also had TOF.

The severity of CHD in affected parents and siblings was examined. Probands with simple defects (VSD and AAA) were analyzed separately from those with complex CTDs. Most affected siblings of probands with complex CTDs had complex defects (58%), whereas very few affected parents had complex defects (20%). Affected parents and siblings of probands with simple defects (VSD and AAA) also had simple defects (57% of affected parents and 72% of affected siblings) (Table IVa, IVb).

DISCUSSION

Our results indicate that the risk of CHD in a sibling or parent of an affected proband with a CTD is elevated as compared to the general population, consistent with previous literature [Nora and Nora, 1988; Hinton et al., 2007; Blue et al., 2012]. However, our large cohort of patients with phenotypically well-characterized CTDs enabled us to identify particular lesions that influence risk in first-degree relatives in the current era, thus updating and assisting in recurrence risk counseling.

In our cohort, risk of CHD varied by the relationship to the proband. Risk in first-degree relatives was much higher as compared to that observed in second and third degree relatives. The steep decline in risk for second and third degree relatives may reflect under-reporting of CHD in more distant relatives. Furthermore, the slightly higher risk seen in third-degree relatives (cousins) than in second-degree relatives (aunts/uncles) may reflect survival bias in younger generations and less knowledge about conditions in older generations.

Previous studies have evaluated recurrence risk among sub-groups of CHD and individual lesions. For example, the Baltimore-Washington Infant Study (BWIS) classified CHD into sub-categories based on embryologic similarities including conotruncal defects and flow lesions (right and left heart obstruction) [Boughman et al., 1987; Maestri et al., 1988]. They found marked differences in precurrence risk rates between sub-categories with the highest precurrence risk in flow lesions. Other studies have identified higher recurrence risks for individual lesions such as TOF and VSD and lower rates for TGA [Digilio et al., 1997; 2001; Loffredo et al., 2004; Meijer et al., 2005; Calcagni et al., 2007]. Our study observed similar variable risks based on individual lesions. Among the most common lesions, risk was highest in TOF and lowest in D-TGA. Less common lesions such as TA and IAA had risk profiles similar to that of TOF. These findings suggest a potential pattern of recurrence risk where lesions with normally related great arteries demonstrate higher risk in relatives as compared to those with transposed great arteries. Of interest, although DORV is anatomically similar to TGA with malposed great arteries, observed risk patterns in relatives of probands with DORV were similar to those seen in TOF and VSD. However, the sample size of probands with DORV is relatively small, limiting our ability to conclude whether their risk profile is closer to that of TOF or TGA.

Just as recurrence risk varies by individual lesions among CTDs, an increasing body of data suggests etiologic differences between subgroups of CTDs. In particular, while DORV and TGA represent abnormalities of the outflow tracts and are thus classified as CTDs, an increasing body of evidence suggests that a subset of these lesions may share a genetic basis with laterality disorders [Goldmuntz et al., 2002; Chhin et al., 2007; Obler et al., 2008; De Luca et al., 2010; D'Alessandro et al., 2013]. In contrast, DORV and TGA are rarely seen in the context of a 22q11.2 deletion, while CTDs with normally related great arteries (e.g. TOF, IAA, VSD, TA, AAA) are commonly seen [Goldmuntz et al., 1998; Peyvandi et al., 2013].

Recurrence Risk Counseling

Although risk of CHD was elevated for both parents and siblings as compared to the general population, risk of CHD was higher among siblings as compared to parents for all CTDs. In addition, concordant defects (i.e. CTD) were more often seen among affected siblings than parents. In fact, most affected parents had simple CHD regardless of the proband lesion, whereas siblings tended to have similar complexity of CHD to the proband. The discordance between parents and their offspring, and the lower frequency of affected parents as compared to siblings may reflect survival bias and reproductive fitness. Simple defects may be more common in the current population as compared to future generations of affected parents given medical and surgical advances. Of note, the specific parental CHD diagnosis was not always available, and thus either category (simple or complex) may have been underrepresented among the affected parents; the apparent discrepancy between sibling and parental CHD must therefore be interpreted with caution.

These findings contribute to the body of literature assessing recurrence risk in the current era. Based on our data, subsequent siblings of children with CTDs are at higher risk of having CHD as compared to the general population. This is particularly true for lesions such

as TOF and VSD. Although the risk of CHD in siblings of patients with TGA appears to be lower, it is slightly higher than the risk of CHD in the general population. In addition, it appears that the complexity of CHD in a subsequent sibling tends to parallel that of the proband, though further studies are required to confirm this finding.

Study Limitations and Conclusions

Our study is limited by the fact that it is a hospital rather than population-based study, and by the overall size of the study cohort. Although our study is hospital-based, the distribution of lesions within our CTD cohort is similar to that of the population-based National Birth Defects Prevention Study (NBDPS) [Botto et al., 2007], suggesting that findings from this study are likely to be broadly applicable to the general population of CTDs. In addition given the high rate of detection of CHD in the current era, that we are a referral center for CHD, and that all CTDs (other than some VSDs) undergo cardiac surgery, the study cohort is representative of cases seen by pediatric cardiologists and genetic counselors. Despite the potential bias of ascertainment, these data contribute to the field in that: (1) the NBDPS has not published family history data, and (2) although Oyen et al recently published a population-based study from Scandanavia assessing risk of CHD in general for first, second and third- degree relatives, they reported lesion-specific recurrence risk ratios, whereas our study provides lesion-specific risks, a more straightforward statistic when counseling families [Oyen et al., 2009]. Although the presence of CHD was not confirmed by diagnostic methods or review of medical records in most relatives of probands, the pedigree was ascertained by a trained genetic counselor rather than from the medical record. Finally, we do not assess how risk is influenced when more than one family member is affected with CHD or whether birth sequence presents a bias when assessing recurrence risk in siblings. Given the relatively small number of affected siblings in our cohort, we provided an overall estimate of risk, rather than less precise estimates of risk for earlier and later born siblings. However, the sibling recurrence risk reported here may be underestimated if couples alter their desired family size following the birth of a child with CHD.

In summary, as in other studies, our findings suggest that CTDs are complex traits with non-Mendelian patterns of inheritance where multiple genetic and/or environmental factors contribute to disease risk [Ferencz et al., 1997; Guo, 2000; Pierpont et al., 2007; Jenkins et al., 2007; Botto et al., 2007; Oyen et al., 2009; Blue et al., 2012]. Recurrence risk appears to vary by lesion and relationship, with substantial concordance observed both by cardiac lesion and complexity of disease. These results are derived from a well-phenotyped cardiac cohort and well-described pedigrees, and thus contribute to recurrence risk counseling in the current era of folic acid fortification and increased survival of affected cases to reproductive age. Future larger studies should address the complexity of disease in recurrence of CHD and should be repeated as adults with more complex CHDs survive to reproduce.

References

Blue GM, Kirk EP, Sholler GF, Harvey RP, Winlaw DS. Congenital heart disease: current knowledge about causes and inheritance. Med J Aust. 2012; 197:155–159. [PubMed: 22860792]

Bjornard K, Riehle-Colarusso T, Gilboa SM, Correa A. Patterns of Congenital Heart Defects, Metropolitan Atlanta, 1978 to 2005. Birth Defects Res Part A Clin Mol Teratol. 2013; 97:87–94. [PubMed: 23404870]

Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. National Birth Defects Prevention Study. . Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res Part A Clin Mol Teratol. 2007; 79:714–727. [PubMed: 17729292]

Botto LD, Mulinare J, Erickson JD. Occurrence of congenital heart defects in relation to maternal mulitivitamin use. Am J Epidemiol. 2000; 151:878–884. [PubMed: 10791560]

Boughman JA, Berg KA, Astemborski JA, Clark EB, McCarter RJ, Rubin JD, Ferencz C. Familial risks of congenital heart defect assessed in a population-based epidemiologic study. Am J Med Genet. 1987; 26:839–849. [PubMed: 3591826]

Burn J, Brennan P, Little J, Holloway S, Coffey R, Somerville J, Dennis NR, Allan L, Arnold R, Deanfield JE, Godman M, Houston A, Keeton B, Oakley C, Scott O, Silove E, Wilkinson J, Pembrey M, Hunter AS. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. The Lancet. 1998; 351:311–316.

Calcagni G, Digilio MC, Sarkozy A, Dallapiccola B, Marino B. Familial recurrence of congenital heart disease: an overview and review of the literature. Eur J Pediatr. 2007; 166:111–116. [PubMed: 17091259]

Chhin B, Hatayama M, Bozon D, Ogawa M, Schön P, Tohmonda T, Sassolas F, Aruga J, Valard A-G, Chen S-C, Bouvagnet P. Elucidation of penetrance variability of a ZIC3 mutation in a family with complex heart defects and functional analysis of ZIC3 mutations in the first zinc finger domain. Hum Mutat. 2007; 28:563–570. [PubMed: 17295247]

D'Alessandro LCA, Latney BC, Paluru PC, Goldmuntz E. The phenotypic spectrum of ZIC3 mutations includes isolated d-transposition of the great arteries and double outlet right ventricle. Am J Med Genet Part A. 2013; 161A:792–802. [PubMed: 23427188]

De Luca A, Sarkozy A, Consoli F, Ferese R. Familial transposition of the great arteries caused by multiple mutations in laterality genes. Heart. 2010; 96:673. [PubMed: 19933292]

Digilio MC, Casey B, Toscano A, Calabrò R, Pacileo G, Marasini M, Banaudi E, Giannotti A, Dallapiccola B, Marino B. Complete transposition of the great arteries: patterns of congenital heart disease in familial precurrence. Circulation. 2001; 104:2809–2814. [PubMed: 11733399]

Digilio MC, Marino B, Giannotti A, Toscano A, Dallapiccola B. Recurrence risk figures for isolated tetralogy of Fallot after screening for 22q11 microdeletion. J Med Genet. 1997; 34:188–190. [PubMed: 9132487]

Dolk H, Loane M, Garne E. European Surveillance of Congenital Anomalies Working Group. Congenital Heart Defects in Europe: Prevalence and Perinatal Mortality, 2000 to 2005. Circulation. 2011; 123:841–849. [PubMed: 21321151]

Ferencz, C.; Loffredo, C.; Correa-Villasenor, A.; Wilson, D. Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore Washington Infant Study: 1981–1989. New Jersey: Wiley-Blackwell; 1997. p. 463

Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol. 1985; 121:31–36. [PubMed: 3964990]

Friedberg MK, Silverman NH, Moon-Grady AJ, Tong E, Nourse J, Sorenson B, Lee J, Hornberger LK. Prenatal detection of congenital heart disease. J Pediatr. 2009; 155:26–31. [PubMed: 19394031]

Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: an analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. J Am Coll Cardiol. 2003; 42:923–929. [PubMed: 12957444]

Goldmuntz E, Bamford R, Karkera JD, Cruz dela J, Roessler E, Muenke M. CFC1 mutations in patients with transposition of the great arteries and double-outlet right ventricle. Am J Hum Genet. 2002; 70:776–780. [PubMed: 11799476]

Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, McDonald-McGinn D, Chien P, Feuer J, Zackai EH, Emanuel BS, Driscoll DA. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol. 1998; 32:492–498. [PubMed: 9708481]

Guo C, Sun Y, Zhou B, Adam RM, Li X, Pu WT, Morrow BE, Moon A, Li X. A Tbx1-Six1/Eya1-Fgf8 genetic pathway controls mammalian cardiovascular and craniofacial morphogenesis. J Clin Invest. 2011; 121:1585–1595. [PubMed: 21364285]

Guo SW. Familial aggregation of environmental risk factors and familial aggregation of disease. Am J Epidemiol. 2000; 151:1121–1131. [PubMed: 10873137]

Hinton RB, Martin LJ, Tabangin ME, Mazwi ML, Cripe LH, Benson DW. Hypoplastic left heart syndrome is heritable. J Am Coll Cardiol. 2007; 50:1590–1595. [PubMed: 17936159]

Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL. American Heart Association Council on Cardiovascular Disease in the Young. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation. 2007; 115:2995–3014. [PubMed: 17519397]

Kirby ML, Aronstam RS, Buccafusco JJ. Changes in cholinergic parameters associated with failure of conotruncal septation in embryonic chick hearts after neural crest ablation. Circ Res. 1985; 56:392–401. [PubMed: 3971512]

Levy DJ, Pretorius DH, Rothman A, Gonzales M, Rao C, Nunes ME, Bendelstein J, Mehalek K, Thomas A, Nehlsen C, Ehr J, Burchette RJ, Sklansky MS. Improved prenatal detection of congenital heart disease in an integrated health care system. Pediatric Cardiology. 2013; 34:670–679. [PubMed: 23117330]

Liu X-Y, Wang J, Yang Y-Q, Zhang Y-Y, Chen X-Z, Zhang W, Wang X-Z, Zheng J-H, Chen Y-H. Novel NKX2-5 mutations in patients with familial atrial septal defects. Pediatric Cardiology. 2011; 32:193–201. [PubMed: 21188375]

Loffredo CA, Chokkalingam A, Sill AM, Boughman JA, Clark EB, Scheel J, Brenner JI. Prevalence of congenital cardiovascular malformations among relatives of infants with hypoplastic left heart, coarctation of the aorta, and d-transposition of the great arteries. Am J Med Genet Part A. 2004; 124A:225–230. [PubMed: 14708093]

Maestri NE, Beaty TH, Liang KY, Boughman JA, Ferencz C. Assessing familial aggregation of congenital cardiovascular malformations in case-control studies. Genet Epidemiol. 1988; 5:343–354. [PubMed: 3215508]

Meijer JM, Pieper PG, Drenthen W, Voors AA, Roos-Hesselink JW, van Dijk APJ, Mulder BJM, Ebels T, van Veldhuisen DJ. Pregnancy, fertility, and recurrence risk in corrected tetralogy of Fallot. Heart. 2005; 91:801–805. [PubMed: 15894783]

Nishibatake M, Kirby ML, Van Mierop LH. Pathogenesis of persistent truncus arteriosus and dextroposed aorta in the chick embryo after neural crest ablation. Circulation. 1987; 75:255–264. [PubMed: 3791607]

Nora JJ. Multifactorial inheritance hypothesis for the etiology of congenital heart diseases. The genetic-environmental interaction. Circulation. 1968; 38:604–617. [PubMed: 4876982]

Nora JJ, Nora AH. The evolution of specific genetic and environmental counseling in congenital heart diseases. Circulation. 1978; 57:205–213. [PubMed: 338196]

Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. Am J Med Genet. 1988; 29:137–142. [PubMed: 3344765]

Obler D, Juraszek AL, Smoot LB, Natowicz MR. Double outlet right ventricle: aetiologies and associations. J Med Genet. 2008; 45:481–497. [PubMed: 18456715]

Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PKA, Melbye M. Recurrence of congenital heart defects in families. Circulation. 2009; 120:295–301. [PubMed: 19597048]

Peyvandi S, Lupo PJ, Garbarini J, Woyciechowski S, Edman S, Emanuel BS, Mitchell LE, Goldmuntz E. 22q11.2 Deletions in Patients with Conotruncal Defects: Data from 1,610 Consecutive Cases. Pediatric Cardiology. 2013; 34:1687–1694. [PubMed: 23604262]

Pierpont ME, Basson CT, Benson DW, Gelb BD, Giglia TM, Goldmuntz E, McGee G, Sable CA, Srivastava D, Webb CL. American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation. 2007; 115:3015–3038. [PubMed: 17519398]

Rose V, Gold RJ, Lindsay G, Allen M. A possible increase in the incidence of congenital heart defects among the offspring of affected parents. J Am Coll Cardiol. 1985; 6:376–382. [PubMed: 4019923]

Schott JJ, Benson DW, Basson CT, Pease W, Silberbach GM, Moak JP, Maron BJ, Seidman CE, Seidman JG. Congenital heart disease caused by mutations in the transcription factor NKX2-5. Science. 1998; 281:108–111. [PubMed: 9651244]

van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJM. The changing epidemiology of congenital heart disease. Nat Rev Cardiol. 2011; 8:50–60. [PubMed: 21045784]

Vorstman JAS, Jalali GR, Rappaport EF, Hacker AM, Scott C, Emanuel BS. MLPA: a rapid, reliable, and sensitive method for detection and analysis of abnormalities of 22q. Hum Mutat. 2006; 27:814–821. [PubMed: 16791841]

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2008; 118:714–833.

Whittemore R. Maternal transmission of congenital heart disease. Am J Cardiol. 1988; 61:499–500. [PubMed: 3341242]

Table I

Characteristics of Probands with CTDs (n= 1620)

Conotruncal Defects	**Number (%)**
Tetralogy of Fallot	550 (34.0)
Ventricular Septal Defect*	339 (21.0)
D-Transposition of Great Arteries	304 (18.7)
Double Outlet Right Ventricle	134 (8.3)
Isolated Aortic Arch Anomaly	84 (5.2)
L-Transposition of Great Arteries	66 (4.1)
Truncus Arteriosus	51 (3.1)
Interrupted Aortic Arch**	41 (2.5)
Double Inlet Left Ventricle***	28 (1.7)
Tricuspid Atresia***	22 (1.3)
TGA-not otherwise specified	1 (0.1)
Gender	
Male	951 (58.7)
Female	669 (41.3)
Race	
White	1194 (73.7)
Black	196 (12.1)
Asian	53 (3.3)
American Indian	12 (0.7)
Native Hawaiian/Pacific Islander	1 (0.1)
Other	64 (4.0)
Unknown	100 (6.1)

* Includes conoventricular, posterior malalignment and conoseptal hypoplasia type ventricular septal defect.

** Includes interrupted aortic arch type A and B.

*** Double inlet left ventricle and tricuspid atresia with malposed great arteries

CTDs, conotruncal defects

Table II

Risks of CHD for relatives of probands with conotruncal defects

Relationship to Proband	# Affected/Total	Risk % (95% CI)
Parents	49/3238	1.5 (1.1–1.9)
Mother	23/1621	1.4 (0.8–2.0)
Father	26/1617	1.6 (1.0–2.2)
Siblings	75/1712	4.4 (3.4–5.4)
Brother	39/881	4.4 (3.2–5.9)
Sister	36/831	4.3 (2.9–5.7)
2nd Degree Relative	56/6738	0.8 (0.6–1.1)
3rd Degree Relative	78/8246	0.9 (0.7–1.2)

CHD, congenital heart disease

Table III

Risk of CHD in first-degree relatives based on proband cardiac lesion

	Relationship to Proband			
	Parents		Siblings	
Proband Lesion	**# Affected/total**	**% Risk(95% CI)**	**# Affected/total**	**% Risk(95% CI)**
TOF (n= 550)	23/1097	2.1 (1.4–3.1)	38/592	6.4 (4.7–8.7)
VSD (n= 339)	11/678	1.6 (0.9–2.9)	12/311	3.8 (2.2–6.6)
AAA (n= 84)	3/168	1.8 (0.6–5.1)	2/129	1.5 (0.5–5.4)
TA (n= 51)	4/101	3.9 (0.1–7.7)	5/53	9.4 (1.5–17.3)
IAA (n= 41)	4/83	4.8 (1.9–11.7)	4/36	11.1 (4.5–25.4)
DORV (n= 134)	3/267	1.1 (0.4–3.2)	6/135	4.4 (2.1–9.4)
D-TGA (n= 304)	1/610	0.2 (0.1–0.9)	5/362	1.4 (0.6–3.1)
L-TGA (n= 66)	0/129	0	2/106	1.8 (0.6–6.6)

CHD, congenital heart disease; TOF, tetralogy of Fallot; VSD, ventricular septal defect; AAA, isolated aortic arch anomaly; TA, truncus arteriosus; IAA, interrupted aortic arch; DORV, double outlet right ventricle; D-TGA, D- transposition of the great arteries; L-TGA, L-transposition of the great arteries

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Table IVa

Severity of CHD in affected first-degree relatives of probands with complex conotruncal defects.

	CHD severity in affected relative		
Affected Relative	**Simple**	**Complex**	**Unknown/Other**
Parent (n= 35)	16 (46%)	7 (20%)	12 (34%)
Sibling (n= 59)	20 (34%)	34 (58%)	5 (8%)

Table IVb

Severity of CHD in affected first-degree relatives of probands with simple conotruncal defects.

	CHD severity in affected relative		
Affected Relative	**Simple**	**Complex**	**Unknown/Other**
Parent (n= 14)	8 (57%)	1 (7%)	5 (36%)
Sibling (n= 14)	10 (72%)	3 (21%)	1 (7%)

CHD, congenital heart disease; Simple defects included atrial septal defects, ventricular septal defects, isolated pulmonary stenosis, isolated bicuspid aortic valve, patent ductus arteriosus, isolated aortic arch anomalies; Complex defects included tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, D- and L- transposition of the great arteries, interrupted aortic arch, coarctation of the aorta, and hypoplastic left heart syndrome.