Congenital Heart Disease

Recurrence of Congenital Heart Defects in Families

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Background—Knowledge of the familial contribution to congenital heart diseases (CHD) on an individual and population level is sparse. We estimated an individual’s risk of CHD given a family history of CHD, as well as the contribution of CHD family history to the total number of CHD cases in the population.

Methods and Results—In a national cohort study, we linked all Danish residents to the National Patient Register, the Causes of Death Register, the Danish Central Cytogenetic Register, and the Danish Family Relations Database, yielding 1,763,591 persons born in Denmark between 1977 and 2005, of whom 18,708 had CHD. Individuals with CHD were classified by phenotype. We estimated recurrence risk ratios and population-attributable risk. Among first-degree relatives, the recurrence risk ratio was 79.1 (95% confidence interval [CI] 32.9 to 190) for heterotaxia, 11.7 (95% CI, 8.0 to 17.0) for conotruncal defects, 24.3 (95% CI, 12.2 to 48.7) for atrioventricular septal defect, 12.9 (95% CI, 7.48 to 22.2) for left ventricular outflow tract obstruction, 48.6 (95% CI, 27.5 to 85.6) for right ventricular outflow tract obstruction, 7.1 (95% CI, 4.5 to 11.1) for isolated atrial septal defect, and 3.4 (95% CI, 2.2 to 5.3) for isolated ventricular septal defect. The overall recurrence risk ratio for the same defect was 8.15 (95% CI, 6.95 to 9.55), whereas it was 2.68 (95% CI, 2.43 to 2.97) for different heart defects. Only 2.2% of heart defect cases in the population (4.2% after the exclusion of chromosomal aberrations) were attributed to CHD family history in first-degree relatives.

Conclusions—Specific CHDs showed highly variable but strong familial clustering in first-degree relatives, ranging from 3-fold to 80-fold compared with the population prevalence, whereas the crossover risks between dissimilar cases of CHD were weaker. Family history of any CHD among first-degree relatives accounted for a small proportion of CHD cases in the population. (Circulation. 2009;120:295-301.)

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

Congenital heart defects (CHDs) are a common birth defect. The CHD birth prevalence is 5 to 10 per 1000 live births.1–7 CHDs are gross structural abnormalities of the heart or intrathoracic vessels that are actually or potentially of functional significance.8 In the online database Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/), >400 entries include CHDs. The large proportion of these entries constitute malformation syndromes or chromosomal aberrations, although to date, heart defects have been associated with very few genes. Gene defects have naturally been suspected to contribute to the occurrence of malformations,9,10 but the extent of this contribution is unclear because there are few population-based data with substantial numbers on the familial clustering of CHD.11–15

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To overcome the methodological difficulties previously experienced in studies of the recurrence of heart defects, large population-based studies are required. In practice, such studies can best be undertaken in Scandinavia, where congenital malformations have been registered nationwide for decades and where information on large numbers of persons with specific birth defects can be linked to population-based data sets with pedigree information.

In the present nationwide and truly population-based study, we investigated whether an individual’s risk of being born with specific heart defects is influenced by prior heart defects in family members. Furthermore, we estimated the contribution of a family history of heart defects to the total number of heart defects in the population.

Methods

Data Sources
Since April 1, 1968, the Danish Civil Registration System has registered demographic, residence, 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 Institute’s Danish Family Relations Database,6,17 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 Danish Civil Registration System. Most individuals born in Denmark since 1950 have links to their parents. Therefore, the Danish Family Relations Database can identify parents, siblings, and half-siblings resident in Denmark for most persons born in 1950 or later. Grandparents, aunts/uncles, nieces/nephews, and cousins can also be identified for almost 90% of individuals born in 1985 or later.

The National Patient Register contains information on inpatient diagnoses assigned since 1977 and outpatient diagnoses from 1995 onward. The Medical Birth Register has collected information on gestational age for all births since 1978. The Causes of Death Register contains death certificate information, including underlying cause of death, since 1970. The Danish Cytogenetic Central Register was established in 1968 and contains information on all prenatal and postnatal chromosomal analyses performed in Denmark since 1970 and 1960, respectively.

Case Ascertainment and Classification of CHDs

CHDs were ascertained from the National Patient Register and the Causes of Death Register by use of International Classification of Disease (ICD) codes for diagnoses registered from 1977 through 1993 (the 8th revision [ICD-8 codes 746.00 to 747.49, 759.00, 759.01, and 759.09]) and the 10th revision (ICD-10 codes Q200 to Q269 and Q803) thereafter. We considered an individual to have a heart defect at birth if a defect was ever diagnosed, irrespective of age at diagnosis.

Persons with heart defects were classified into phenotypes based on those used by Botto et al.,18 as reported previously. In short, persons with CHDs were classified into the following 17 heart phenotypes by grouping specific ICD codes in hierarchical fashion: (1) heterotaxia; (2) conotruncal heart defect; (3) aortoventricular septal defect (AVSD); (4) anomalous pulmonary venous return; (5) left ventricular outflow tract obstruction; (6) right ventricular outflow tract obstruction; (7) isolated atrial septal defect (ASD); (8) isolated ventricular septal defect (VSD); (9) ASD and VSD; (10) complex defects; (11) conotruncal heart defect plus AVSD; (12) septal defect plus left ventricular outflow tract obstruction; (13) septal defect plus right ventricular outflow tract obstruction; (14) isolated patent ductus arteriosus (PDA) among infants born at term; (15) isolated PDA in preterm infants; (16) unspecified; and (17) all other specified heart defects. Persons with CHD were also divided into those with only heart defects and those with extracardiac defects (ie, 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: 740 to 745, 747.59 to 758, 759.19, and 759.69 to 759.99; ICD-10: Q00 to Q18.9, Q27.0 to Q89.2, and 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). The hierarchical structure implies, for instance, 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 but without AVSD were identified; by definition, because of the hierarchical nature of the classification scheme, individuals with heterotaxia could not be included in the conotruncal defect group. Next, individuals with AVSD but without heterotaxia or conotruncal defects were identified, and so on.

Study Population

All live births in Denmark between 1977 and 2005 with at least 1 identifiable first-degree family member were included in the study cohort. Date of birth for all cohort members was identified with the Civil Registration System, and information on CHD was retrieved from the National Patient Register and the Causes of Death Register. For each individual in the study cohort (cohort member), family members (co-twin, and first-, second-, and third-degree relatives) were identified with the Danish Family Relations Database. CHDs among family members (exposure of interest) were identified in the same way as those among cohort members, except they could have been born before 1977.

Statistical Analysis

Familial clustering of CHDs was evaluated with recurrence risk ratios, ie, the ratio between the risk of CHD in individuals with a registered family history of an older affected relative and the risk in individuals with a family history of an older unaffected relative of the same type. The comparison of individuals with the same type of relatives reduced bias due to incomplete registration of family members in older birth cohorts in the Danish Family Relations Database and adjusted the recurrence risk ratio for the effect of having a specific kindship type. Family history of heart defect was defined by kinship and heart defect type. For family history, first-degree relatives were defined as parents or an older sibling; second-degree relatives as grandparents, older half-siblings, or uncle/aunt and nephews/nieces; and third-degree relatives as older first cousins. Only heart defects in family members born before the cohort member was born contributed to a family history of heart defects, which ensured that affected pairs in the cohort contributed only once. In twins, 1 of them was chosen (at random) to be the “first born.” Twins were classified as same-sex twin and unlike-sex twin, because we did not have information on zygoisity.

Family history by defect type was evaluated in first-degree relatives of singletons. The cohort member and family member had “similar defects” when the pair had the same heart defect phenotype and “dissimilar defects” when the cohort member had any other heart defect phenotype than the family member’s specific defect. Recurrence risk ratios for similar defects and dissimilar defects were estimated for family history of the 17 heart phenotypes. The overall recurrence risk ratio (ie, common effects) for similar defects was estimated by combining the 17 similar defects model into 1 simultaneous model. Likewise, the overall recurrence risk ratio for any type of heart defect different from the specific defect in the family member (dissimilar defects) was estimated by combining the 17 dissimilar defect models into 1 simultaneous model. In subanalyses, the estimation of recurrence risk ratios was restricted to persons without chromosomal aberrations or extracardiac defects. Finally, we approximated the recurrence risk ratios (RRs) for monozygotic twins by the equation 

$$RR_{monozygotic twins} = 0.5 \times RR_{same-sex twins} + 0.5 \times RR_{like-sex twins}$$

based on the 2 assumptions that (1) the numbers of same-sex dizygotic twins and same-sex monozygotic twins are equal,19 and (2) the relative risks for unlike-sex twins and all dizygotic twins are equal. Recurrence risk ratios are referred to as relative risks of recurrence and were estimated with binominal log-linear regression performed with PROC GENMOD in SAS (version 9.1, SAS Institute Inc, Cary, NC). Recurrence risk ratios were adjusted for calendar period (1977 to 1979, 1980 to 1984, 1985 to 1989, 1990 to 1994, 1995 to 1999, and 2000 to 2005) and were reported with 95% confidence intervals (CIs).

The population-attributable risk is an estimate of the fraction of the total number of cases of CHD in the populations that would not have occurred if the effect of a specific factor had been eliminated, that is, if the risk could have been reduced to that of the exposure category with the lowest risk.19 Family history of any heart defect among first-degree relatives was regarded as the exposure.

The project has been approved by the Danish Data Protection Agency and the Board of Danish Cytogenetics Central Register. No further approval was needed.

Results

Of 1763 591 persons born in Denmark in the period from 1977 to 2005, 18 207 had 1 or more CHDs, which yielded an overall CHD prevalence of 103 per 10 000 live births, as reported previously. Among persons with CHDs, 3097 (17.0%) had a postnatal chromosomal investigation, and of these, 1272 (41.1%) had a chromosomal aberration. Chromosomal aberrations were found in 1272 (7.0%) persons with CHD and
extracardiac birth defects in 4067 (22.3%). Among persons with a CHD, 1430 (7.9%) were part of a multiple birth.

In twins, the relative risks of any CHD were 12.5 (95% CI 10.9 to 14.3) for same-sex twins and 6.93 (95% CI 5.32 to 9.04) for unlike-sex twins (Table 1). Because twins more often are born preterm, and PDA is more prevalent in infants born preterm, we also estimated relative risks of any heart defect excluding PDA, which yielded relative risks of 9.25 and 3.33 for like-sex and unlike-sex twins, respectively. The approximated relative risks for monozygotic and dizygotic twins were 15.17 and 3.33, respectively.

The relative risks of any CHD in singletons were 3.21, 1.78, and 1.10 for a family history of any CHD in first-, second-, or third-degree relatives, respectively (Table 1). For a CHD family history in first-degree relatives and after the exclusion of cases with chromosomal aberrations or extracardiac defects, the relative risks of any CHD were 3.31 and 3.43, respectively (to be compared with the relative risk of 3.21 for nonexcluded cases).

In Table 2, familial recurrence risk ratios for the same heart defect phenotypes were estimated in singletons, given a family history of heart defect in first-degree relatives. For example, 359 singletons (cohort members) had a first-degree relative with heterotaxia, and among these cohort members, 5 persons (1.4%) were also born with heterotaxia. Comparison of the risk of heterotaxia in cohort members who had an older affected first-degree relative with the risk of heterotaxia in a cohort member without such a family history among first-degree relatives yielded a relative risk of heterotaxia recurrence of 79.1 (95% CI 32.9 to 190). In similar ways, relative risks of recurrence for the other types of heart defects are presented. For the other severe defects, the recurrence risk ratio was 11.7 for conotruncal defects, 24.3 for AVSD, 12.9 for left ventricular outflow tract obstruction, and 48.6 for right ventricular outflow tract obstruction. The isolated septal defects, ASD, VSD, and ASD plus VSD, showed slightly weaker recurrence risk ratios (7.1, 3.4, and 5.6, respectively).

Isolated PDA in preterm infants had a recurrence risk ratio of 19.5, whereas there was only 1 recurrent PDA in related term infants. Unspecified heart defects and other specified heart defects also demonstrated elevated recurrence risk ratios of 5.2 and 12.6, respectively. When we combined all estimates for the same heart defect phenotypes, the overall relative risk of recurrence for the same heart defect phenotype was 8.15.

Recurrence risk ratios for the same heart defect phenotype were also estimated in persons without chromosomal aberrations or extracardiac defects. Except for heterotaxia and AVSD, the relative risks of recurrence changed very little when we restricted the analyses to persons without chromosomal or extracardiac defects. With the exclusion of chromosomal aberrations, extracardiac defects, or both chromosomal aberrations and extracardiac defects, the overall relative risks for the same heart defect phenotype were 8.61 (95% CI 7.31 to 10.1), 8.19 (95% CI 6.71 to 10.0), and 8.38 (6.82 to 10.3), respectively (to be compared with the overall relative risk of 8.15 for nonexcluded cases in Table 2). Heterotaxia and AVSD demonstrated increased relative risks of recurrence, from 79.1 to 113 (95% CI 47 to 273; n=5) and from 24.3 to 54.6 (95% CI 26.0 to 115; n=7), respectively, when chromosomal aberrations were excluded.

Familial clustering of dissimilar types of heart defects was also evaluated. Given each of the specific heart defect phenotypes in a first-degree relative, the relative risks of any other heart defect mentioned ranged from 1.55 to 5.65. When we combined all the estimates for different types of defects, the overall relative risk for any type of heart defect different from the first-degree relative was 2.68 (95% CI 2.43 to 2.97).

Finally, we estimated the population-attributable risk associated with family history of heart defects. Family history of any heart defect among first-degree relatives accounted for 2.2% of the heart defect cases in the population. With the exclusion of cases with chromosomal or extracardiac defects, the population-attributable risks were 4.2% and 3.6%, respectively.

**Discussion**

The present study provides population-based estimates for the familial recurrence risk ratios of same-type CHDs. We found
that the same heart defect phenotype showed strong familial clustering, with relative risks of recurrence of 3-fold to 80-fold in first-degree relatives. Although the crossover relative risks between dissimilar heart defects were weaker, they were not trivial. A family history of any heart defect among first-degree relatives accounted for 2.2% of the heart defects was not type specific. In the present study, probably because the family history of heart defects was not type specific. In the end, the various studies were difficult to compare because the heart defect classifications were not uniform.

### Same Heart Defect Phenotype

The reported familial clustering of the same heart defect phenotypes among first-degree relatives strongly suggests that gene mutations are the underlying cause. A number of selected heart defects have been found to be associated with a variety of single genes or more than 1 gene. Single-gene syndromes that feature heart defects include, for example, Alagille syndrome, with associated right ventricular outflow tract obstruction, conotruncal heart defects, or ASD; the Holt-Oram syndrome, with ASD, VSD, or both; the Noonan syndrome, with a variety of cardiac phenotypes; the CHARGE syndrome, with dysmorphic features and PDA in term infants. These single-gene syndromes show autosomal dominant inheritance with variable expressivity or reduced penetrance, although the majority of single-gene syndromes arise de novo.

The trisomies (trisomy 21, 18, and 13) are the most common chromosomal aberration associated with heart defects in live births, but they cannot explain the recurrence of the same heart defect phenotype. These trisomies arise de novo in almost all cases. Microdeletion syndromes with cardiac phenotypes, such as the 22q11 deletion syndrome, which is often associated with conotruncal defects, and the William-Beuren syndrome, which is associated with left ventricular outflow tract obstruction, show autosomal dominant inheritance, although the large proportion of these microdeletions also arise de novo. New chromosomal microarray technology has further “cryptic” rearrangements (eg, copy-number variations) will be unmasked to reveal loci critical for embryonic heart development. Such copy-number variations (microdeletions or microduplication) probably arise spontaneously but can be passed down to offspring in a mendelian fashion, as has been demonstrated in monozygotic twin sisters with pulmonary atresia and intact ventricular septum.

Even though recurrent chromosomal or syndromic heart defects are described in the literature, as presented above,
they appear to contribute very little to the clustering of same heart defect phenotypes in the present study. By linkage to the national cytogenetic register, we could exclude persons with chromosomal aberrations, and we found that the relative risk of recurrence changed only slightly, from 8.15 to 8.61. Information on specific syndromes was unavailable; however, we had knowledge about extracardiac malformations. Heart defects with additional birth defects likely represent a large proportion of the syndromic heart defects. With restriction of the analyses to persons with an isolated heart defect, the overall relative risk of recurrence did not change (8.15 to 8.19), which indicates that the increased relative risk of same-type recurrence in the present study consisted of recurrent nonsyndromic heart defects.

Recently, single-gene defects have been found in nonsyndromic heart defects, such as isolated ASD,34 and they are suspected to be present in some familial cases of isolated AVSD,35,36 anomalous pulmonary venous return,37 or left ventricular outflow tract obstruction.35,38 These isolated heart defects are proposed to be inherited in an autosomal dominant fashion and in some families with reduced penetrance.

Shared environmental factors in successive pregnancies could also underlie the increased relative risk, but such factors must be very strong or interact with other factors39 (eg, susceptible heart defect loci). Pregestational diabetes, which is known to increase the risk of various types of CHD, with relative risks in the range of 3 to 5,1 is hypothesized to change the expression of a regulatory gene important for the septation of the outlet tract of the heart.40

Dissimilar Heart Defect Phenotype
A single gene or gene pair may also give rise to different phenotypic effects (pleiotropy) in the same family,9,10 which could explain the observed crossover relative risk between different types of heart defects, as reported in several case studies on families with clustering of different heart defects.15

In the present study, given a family history of a specific heart phenotype, the overall relative risk of any other heart defect was 2.68. Alternatively, heart defects could have been misclassified, and similar defects could have been wrongly classified as dissimilar defects and produced apparently familial clustering of dissimilar defects. However, the distribution of pairs with discordant defects was symmetrical; for example, a family member with 1 type of defect and a cohort member with another type of defect and vice versa showed similar distributions and relative risks of recurrence (data not shown). Furthermore, a family history of isolated ASD or VSD also demonstrated an increased risk of any other heart defects. Therefore, misclassifications of heart phenotypes cannot exclusively explain the increased crossover relative risk between different heart phenotypes.

As mentioned above, the single-gene causes of nonsyndromic CHD are examples that could underlie the strong recurrence risks of the same heart defect phenotype but could also contribute to the weaker recurrence risk of different heart defect phenotypes, because a variety of defects are reported to fall into different phenotype classes. This may appear to run counter to our same type–versus–different type defect difference in relative risks; however, to date, we do not know the population prevalence of the single-gene causes in the various defect classes. In addition, other genes may be responsible for the strong inherited component in same-phenotype recurrence that is not present in different-phenotype recurrence.

Twins
Interestingly, the approximated relative risk for CHD in monozygotic twins was much stronger than the relative risk in unlike-sex twins, whereas the relative risks in unlike-sex twins and in singletons with a family history of any CHD in first-degree relatives were similar. The excess relative risk of CHD in monozygous twins, as reported previously,41 and not in unlike-sex twins indicates that twinning per se predisposes to CHDs, whereas the shared in utero conditions do not appear to play a role.

Attributable Risk of Family History
In the present study, we report a strong familial clustering of phenotypes of the same heart defect among first-degree relatives, and we discuss plausible genetic contributions to such clustering, as well as the possibility of repeated environmental exposure in successive pregnancies, particularly in individuals with an inherited heart defect susceptibility. However, the contribution of CHD family history to the overall prevalence of CHD in the populations was only 2.2%, and after the exclusion of chromosomal and extracardiac defects, the attributable risks were 4.2% and 3.6%, respectively. Similar population-attributable risks have been calculated from a hospital-based case-control study in which CHD family history was based on parental interviews.42

The low population-attributable risk from a positive family history can be explained in the following ways. Environmental risk factors for CHD could dominate; however, knowledge of such factors is scarce. In a recent review,1 definitive risk factors include maternal rubella; phenylketonuria; pregestational diabetes; exposure to thalidomide, retinoids, and indo-methacin; and perhaps the use of antiepileptic drugs in pregnancy. The alternative could be that a high proportion of heart defects arise in susceptible individuals who carry low-penetrance genes or gene combinations, as has been proposed for common cancers.43 Susceptible embryos may develop a heart defect if other important genes along the same pathway in embryonic heart development are disturbed owing to additional inherited gene mutations, de novo mutations, copy-number variations, or unfavorable maternal and intrauterine factors. Finally, a heart defect could occur by pure chance errors in heart development.

Study Limitations and Strengths
Parents with a previous child or other family member with CHD may opt for prenatal screening and termination of a pregnancy if the fetus is affected. This could reduce the potential number of recurrences and deflate recurrence risk ratio estimates. However, although prenatal detection of neural tube defect is high, the sensitivity for detecting CHDs is still low,44 which means that a large proportion of CHDs cannot be avoided by detection and termination of affected pregnancies. Among all births with CHDs in the Danish county of Odense from 1980 to 2006, the proportion of terminated pregnancies for fetal cardiac anomaly after prenatal investigation (prenatal chromosomal investigation,
fetal echocardiography, or both) was 3% (excluding PDA). Elective termination after prenatal investigation has a minor effect on the overall CDH birth prevalence in Denmark, although we could not evaluate the effect on the degree of familial clustering.

Information about mild extracardiac defects that did not require medical intervention or milder phenotypes of chromosomal aberrations that were not investigated could have been missed. However, in the present study, the proportion of persons with reported extracardiac defects among those with CHD was 22.3%, which corresponded to a recent population-based study from Norway. The proportion of persons with chromosomal aberrations (7.0%) among those with CHD was slightly higher in the present study than in the Danish county of Odense (6.3% in the period 1980 to 2005), which reports to the European Surveillance of Congenital Anomalies. Therefore, heart defect cases with extracardiac or chromosomal defects probably were not misclassified as isolated heart defects.

We did not have complete family history for all cohort members; however, with a disease prevalence of less than 1%, an incomplete family history results in negligible bias. In addition, the proportion of cohort members with an affected first-degree relative (persons at risk) was similar to the population prevalence of heart defects. We are aware of possible confounding by indication; that is, knowledge of heart defects in other family members could lead to an investigation and diagnosis of a heart defect. Although in theory, this could be the case for less severe defects, such as isolated septal defects, severe CHDs almost always come to medical attention, either owing to the need for surgery or at death.

The present study had multiple strengths. Because the study cohort encompassed the entire Danish population, with more than 1.7 million persons born during a 29-year period, the present study had great overall power. Furthermore, Denmark’s national registers allowed for complete follow-up of birth cohort members. Also, in Denmark, health care is free for all citizens, 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 and link to their birth defect information for every member of the study cohort without having to contact cohort members and their families, which ensured the absence of differential misclassification of disease categorization.

In conclusion, specific CHDs showed very strong familial clustering in first-degree relatives, ranging from 3-fold to 80-fold compared with the population prevalence. The population-based recurrence risk ratio of the same heart defect phenotypes in the present study constitutes familial clustering of nonsyndromic heart defects, whereas chromosomal and syndromic heart defects play only a small role in recurrent heart defects. The presence of increased crossover relative risks between dissimilar heart defects suggests that certain families have susceptibility to heart defects. Because most heart defects represent the only case in the family, a large proportion of heart defects most likely arise in susceptible individuals who carry low-penetration genes or gene combinations, possibly in interaction with maternal or intrauterine factors. Although recurrence risk ratios are strong, very few families experience a second heart defect of any type, which is important to recognize for clinical counseling purposes.

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Disclosures

None.

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