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Laterality Defects in the National Birth Defects Prevention Study (1998–2007): Birth Prevalence and Descriptive Epidemiology

Angela E. Lin[1,2,*], **Sergey Krikov**[3], **Tiffany Riehle-Colarusso**[4], **Jaime L. Frías**[4,5], **John Belmont**[6], **Marlene Anderka**[2], **Tal Geva**[7], **Kelly D. Getz**[2], **Lorenzo D. Botto**[3], and **National Birth Defects Prevention Study**

[1]Medical Genetics, MassGeneral Hospital for Children, Boston, Massachusetts

[2]Massachusetts Center for Birth Defects Research and Prevention, Boston, Massachusetts

[3]Division of Medical Genetics, Department of Pediatrics University of Utah, Salt Lake City, Utah

[4]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[5]McKing Consulting Corporation, Fairfax, Virginia

[6]Baylor College Medicine, Houston, Texas

[7]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts

Abstract

Little is known epidemiologically about laterality defects. Using data from the National Birth Defects Prevention Study (NBDPS), a large multi-site case-control study of birth defects, we analyzed prevalence and selected characteristics in children born with laterality defects born from 1998 to 2007. We identified 517 nonsyndromic cases (378 heterotaxy, 73.1%; 139 situs inversus totalis [SIT], 26.9%) resulting in an estimated birth prevalence of 1.1 per 10,000 live births (95% confidence interval 1.0–1.2). Prevalence did not differ significantly across sites, over time, or by inclusion of pregnancy termination. Laterality defects were more common among preterm cases compared to term cases, and in children born to mothers who were non-white or younger than 20 years compared to white mothers or those age 25–29 years. The distribution of associated cardiac and extracardiac defects, excluding the expected heterotaxy anomalies, varied by type of laterality defect. Cases with heterotaxy were significantly more likely than those with SIT to have double outlet right ventricle, atrioventricular canal defects, pulmonary stenosis, non-tetralogy of Fallot pulmonary atresia with ventricular septal defect, totally and partially anomalous pulmonary venous return; also more likely to have orofacial clefts, esophageal atresia, bowel atresias, and omphalocele, though not reaching statistical significance. Relatively more common among cases with SIT were Dandy-Walker malformation, anotia/microtia, and limb deficiency. The similarity in the demographic characteristics of heterotaxy and SIT supports the hypothesis that they are part

*Correspondence to: Angela E. Lin, M.D., Medical Genetics, MassGeneral Hospital for Children, 185 Cambridge St., CPZN-2222, Boston, MA 02114. lin.angela@mgh.harvard.edu.

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of a continuum of abnormal left-right axis patterning. These findings on laterality defects may help guide clinical care, future research, and prevention strategies.

Keywords

asplenia; cardiovascular malformations; congenital heart defects; dextrocardia; heterotaxy; isomerism; laterality defects; malposition; prevalence; race/ethnic disparities; situs ambiguous; situs inversus

INTRODUCTION

Laterality defects are also known as defects of embryonic left-right axis patterning or malposition complexes. They include a spectrum of disorders that range in increasing severity from isolated dextrocardia or situs inversus (SI) abdominis to situs inversus totalis (SIT) or heterotaxy. The more severe laterality defects may include situs ambiguous, complex congenital heart defects (CHD), and spleen anomalies (asplenia, polysplenia) [reviewed by Van Praagh, 2006; Chin, 2012]. The cause of most cases of laterality defects remains unknown, although chromosome abnormalities [reviewed by Iida et al., 2006], other genetic causes [Zhu et al., 2006; Fakhro et al., 2011; Cohen, 2012], and maternal environmental influences [Martínez-Frías, 2001] are being increasingly identified as potential causes. Most cases of laterality defects do not have a monogenic etiology [Ferencz et al., 1997; Lin et al., 2000; Aylsworth, 2001], with a few notable exceptions, including X-linked heterotaxy [Gebbia et al., 1997; reviewed in Zhu et al., 2006], autosomal dominant heterotaxy [Alonso et al., 1995], and Kartagener syndrome (a form of autosomal recessive primary ciliary dyskinesia [PCD]) [Kennedy et al., 2007; Brueckner, 2007]. Regardless of the specific cause, laterality defects can be viewed as the result of a broad range of developmental disorders that impact right-left axis patterning [Brueckner, 2012].

In contrast to the abundance of genetic and developmental research, there have been few epidemiologic studies of laterality defects. Previous prevalence estimates drawn from hospital-based [Lin et al., 2000] and population-based studies [Ferencz et al., 1997; Reller et al., 2008; Khoshood et al., 2012] range from 0.9 to 1.7 per 10,000 births. The variability of these estimates is likely due to small sample size or differences in methodology, including case classification and ascertainment. The National Birth Defects Prevention Study (NBDPS) offers a unique opportunity to conduct descriptive epidemiologic analyses in a nationally representative population-based cohort of a relatively large sample of well-classified non-syndromic laterality defect cases.

METHODS

The NBDPS is an ongoing, multi-site population-based case-control study of genetic and environmental risk factors for more than 30 categories of major structural defects [Yoon et al., 2001]. Cases were ascertained from birth defects surveillance systems at 10 study sites: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey (through 2002), New York, North Carolina (beginning 2003), Texas, and Utah (beginning 2003). Study cases are livebirths (all sites), fetal deaths ≥20 weeks (Arkansas, California, Iowa, Massachusetts,

North Carolina, Texas, and Georgia), and elective pregnancy terminations (Arkansas, California, Iowa, Texas, and Georgia). Controls are singleton livebirths without major birth defects selected randomly from the same source population as cases through review of birth certificates or hospital records, matched for geographic area and birth year [Cogswell et al., 2010]. Cases are identified from the existing state surveillance systems and abstracted data are reviewed for study inclusion by the NBDPS clinical geneticist at each site [Rasmussen et al., 2003]. The NBDPS excludes cases with (1) the mildest end of the clinical spectrum of laterality defects, i.e., isolated dextrocardia or SI abdominis; or (2) a recognized or strongly suspected single-gene condition or chromosome abnormality. This means excluding cases with PCD, an etiologically heterogeneous Mendelian syndrome which overlaps with heterotaxy. In addition to the abstracted medical record data, mothers of both cases and controls are asked to consent to a computer-assisted telephone interview on potential risk factors for birth defects. The NBDPS has been approved by the CDC Institutional Review Board and the institutional review board for each participating site.

Study Subjects

We included in the analyses all NBDPS-eligible laterality defect cases and controls with an estimated date of delivery (EDD) from January 1, 1998, to December 31, 2007 regardless of whether their mother participated in the interview. The analysis for small for gestational age excluded twins for both cases and controls, as well as stillbirths and pregnancy terminations, for consistency with available reference values [Alexander et al., 1996].

Laterality Defects Definitions, Coding and Classification

All potential laterality defect cases were reviewed by clinical geneticists with expertise in pediatric cardiology. CHDs were included in the NBDPS only if diagnosed by echocardiography, catheterization, cardiac surgery, magnetic resonance imaging (MRI), or autopsy. Diagnosis by prenatal ultrasound and/or fetal echocardiography was accepted if performed by a pediatric cardiologist or at a prenatal diagnosis center with expertise in this area. CHD cases were evaluated and classified according to phenotype and severity using consistent case definitions; details of the methods have been reported [Botto et al., 2007]. For laterality defect cases, the CHD severity was either simple (i.e., anatomically discrete or uncomplicated CHD) or complex (i.e., multiple CHDs).

All NBDPS centers use modified 6-digit ICD-9-CM codes based on the *International Classification of Disease, Ninth Revision, Clinical Modification, and British Paediatric Association* (currently known as The Royal College of Paediatrics & Child Health) [Correa et al., 2007] which had been expanded for the NBDPS. Cases were coded as complete SI with dextrocardia (SIT) 759.300; SI with levocardia (equivalent to SI abdominis) 759.310; SI thoracis 759.320; SI abdominis 759.330; situs ambiguous, right; right isomerism 759.350; situs ambiguous, left; left isomerism 759.360; situs ambiguous, sidedness unclear 759.370; situs ambiguous, sidedness not otherwise specified (NOS), 759.380; heterotaxy, NOS 759.395; dextrocardia 746.800 (Supplemental Table SI-I, online, includes codes for the CHDs found in these cases). Cases with the description of “polysplenia” or “asplenia” (Ivemark syndrome) required confirmation by imaging or autopsy.

Using inclusion criteria adapted from leading cardiology reviews [Van Praagh, 2006; Foerster et al., 2008; Chin, 2012], laterality defect cases were classified by a single reviewer (A.E.L.) into SIT (mirror image reversal of the normal heart and visceral situs) and heterotaxy (abnormal symmetry of the viscera and/or situs discordance between visceral organs, usually with CHD) (Table I). The diagnosis of heterotaxy required at least three categories of visceral and cardiac anomalies [nosology specified by Foerster et al., 2008] modified to accommodate the NBDPS coding system. For example, a case with complex CHD (totally anomalous pulmonary venous connection, complete atrioventricular canal), abdominal situs ambiguous (transverse liver), bilateral morphologic left bronchi, and polysplenia documented at autopsy would be classified as heterotaxy. We included milder forms of heterotaxy that lacked the characteristic complex CHD if a combination of distinctive extracardiac defects was present, such as situs or spleen anomaly, biliary atresia, bronchial isomerism, similar atrial appendage morphology, great vein anomalies, or intestinal malrotation (refer to “II. Heterotaxy” in Table I). For example, a case of situs ambiguous with asplenia documented by postnatal ultrasound, accompanied by bilateral superior vena cava, malrotation, and interruption of inferior vena cava would also be included. Cases with only SI abdominis or dextrocardia alone were excluded.

Statistical Analyses

We estimated birth prevalence, crude prevalence ratios, and 95% confidence intervals (CI) for laterality defects overall and by subtype in relation to various demographic and clinical characteristics. Total birth prevalence was estimated from the number of affected cases (livebirths, stillbirths, and pregnancy terminations where available) per 10,000 livebirths among the source population from which the cases were ascertained. Time trends in prevalence were evaluated using Cochran–Armitage trend test. Prevalence from states ascertaining terminations was compared to the prevalence in states which do not ascertain terminations, using maximum likelihood estimates. Small-for-gestational-age (SGA) was defined as a birth weight below the 10^{th} centile for a given gestational age, based on sex-specific standardized birth weight distributions of US live births [Alexander et al., 1996]. Logistic regression was used to calculate the unadjusted odds ratios (OR) and associated 95% CI comparing the occurrence of SGA among cases of heterotaxy and SIT to that of non-malformed controls in the NBDPS. To eliminate potential confounding by twinning, the SGA analysis was restricted to singletons. All analyses were performed using SAS version BASE 9.3 (SAS Institute, Cary, N.C.).

We compared the frequency of CHDs occurring in cases with situs ambiguous/right atrial appendage isomerism (“asplenia”) and situs ambiguous/left atrial appendage isomerism (“polysplenia”), using Fisher’s Exact Test to test for significance.

Assessment of Cases With Syndromes Excluded From the NBDPS

To estimate the impact on prevalence of excluding cases with recognizable chromosome and Mendelian syndromes, we compared laterality defect cases in NBDPS to laterality defect cases excluded from NBDPS in the surveillance program of a single NBDPS site, Massachusetts. Details of the Massachusetts Birth Defects Monitoring Program (MBDMP) are described elsewhere [National Birth Defects Prevention Network, 2013]. As an NBDPS

site, Massachusetts uses the same aforementioned NBDPS-modified 6-digit ICD-9-CM codes to classify and code its cases. Using any code for laterality defects as defined above, we selected and reviewed the cases which were excluded from NBDPS due to a chromosomal abnormality or diagnosis of single gene disorder.

RESULTS

The study ascertained 517 cases with nonsyndromic laterality defects (heterotaxy 378, 73.1%; SIT 139, 26.9%) for an estimated birth prevalence of 1.1 per 10,000 (95% CI:1.0–1.2). The prevalence of heterotaxy (0.81, 95% CI: 0.73–0.89) was more than twice that of SIT (0.30; 95% CI: 0.25–0.35) (Table II). Prevalence varied across sites, but not significantly (for heterotaxy, ranging from 0.6 per 10,000 in New Jersey and New York, to 1.9 per 10,000 in California, and for SIT, ranging from 0.3 in New Jersey to 1.4 in California). Prevalence did not vary significantly over time (see Supplemental Table SI–II), or by the inclusion of pregnancy termination (data not shown). Laterality defects as a group, as well as the subtypes of heterotaxy and SIT, were significantly more common among preterm cases (less than 37 weeks gestational age) compared to term cases, and in mothers who were non-white (Hispanic, black, other) compared to those who were white non-Hispanic. All laterality defects combined were also more common among mothers younger than 20 years compared to those age 25–29.

The analysis for SGA included 8029 controls and 469 cases (344 heterotaxy, 125 SIT). Compared to controls, heterotaxy cases were nearly three times more likely to be born SGA (16.9% were SGA vs. 6.5% in controls; OR 2.92, 95% CI 2.17–3.92). This was not the case with SIT (8.0% vs. 6.5%, OR 1.25, 95% CI 0.65–2.40).

The majority of laterality defect cases (350/517, 67.7%) had complex CHD, whereas 9.3% (48/517) had simple CHD, and 23.0% (119/517) had no CHD (Table III). However, the presence and type of CHD varied significantly among laterality defect subtypes. Most cases of SIT had no CHD (82/139, 59.0%); conversely, complex CHD was present in 82.8% (313/378) of heterotaxy cases. For example, the following CHDs were more common among cases with heterotaxy compared to SIT (Table IV): double outlet right ventricle, complete atrioventricular canal defects, pulmonary stenosis, non-tetralogy of Fallot pulmonary atresia with ventricular septal defect, totally and partially anomalous pulmonary venous return, all ventricular and atrial septal defects, vena caval anomalies, and persistent left superior vena cava. A comparison of two familiar forms of heterotaxy showed patterns of CHD frequency (Supplemental Table SI–III), which are roughly similar to previous postmortem and clinical studies [Van Praagh, 2006; Foerster et al., 2008]. Among 66 (48.5%) patients with situs ambiguous, bilateral right-sidedness/right atrial isomerism (“asplenia”), there were significantly (P <0.001) more cases of totally anomalous pulmonary venous return, complete atrioventricular canal defect, and pulmonary atresia with ventricular septal defect (an NBDPS code which differs from tetralogy of Fallot). Also common, but less significantly, were all forms of single ventricle (P <0.01), d-loop transposition of the great arteries (P <0.05), and total cases of valvar pulmonary stenosis and pulmonary atresia/ventricular septal defect (not tetralogy of Fallot) (P <0.5). In contrast, among 70 (51.5%) cases with situs ambiguous, bilateral left-sidedness/left atrial isomerism (“polysplenia”),

there were more cases of interrupted inferior vena cava (P <0.001) and primum-type atrial septal defect (P <0.01). As a group, extracardiac defects were more common in cases with heterotaxy than those with SIT, though this finding was statistically unstable due to small numbers in each defect category. Orofacial clefts, esophageal atresia, bowel atresia, and omphalocele were more frequent among heterotaxy cases than among SIT cases, while Dandy-Walker malformation, anotia/ microtia, and limb deficiencies were more frequent among SIT cases than heterotaxy cases (Table IV). In this comparison of extracardiac defects between heterotaxy and SIT, we excluded the abdominal defects that define the complex (i.e., situs ambiguous, spleen anomalies, malrotation, liver anomalies) and occur in many cases with heterotaxy.

Cases Excluded From the NBDPS

To assess the proportion of excluded cases having a laterality defect with a chromosomal or Mendelian syndrome, we analyzed cases from the MBDMP from 1998 t0 2007. Of the 93 cases with a laterality defect ascertained by the MBDMP, three (3.2%) were excluded from the NBDPS. One case of clinically diagnosed PCD, i.e., without molecular testing, had SIT, “corrected transposition in dextrocardia”, unspecified ventricular septal defect, valvar pulmonic stenosis, and absent kidney. Another excluded case with spondylocostal dysostosis, without further genetic characterization, had heterotaxy, bilateral superior vena cava, interrupted inferior vena cava, complete atrioventricular canal defect, and severe spinal and vertebral anomalies. The last case was excluded due to an unspecified derivative of chromosome 12 and had SIT, patent ductus arteriosus, malformed small ears, and bilateral pre-axial polydactyly of the feet.

DISCUSSION

Few phenomena are as fundamental in human development as the determination of the position of the body’s organs (sidedness) [Cohen, 2012]. Sidedness is the subject of numerous embryological and anatomic descriptive studies, with extensive research into its molecular genetic basis and developmental biology [Vandenberg and Levin, 2013]. Although laterality defects have been recognized for over a century, there is a lack of agreement about the best way to classify them for clinical management, genetic research, and pathologic studies, which has hampered epidemiologic analyses [Houyel et al., 2011]. This study provides a population-based descriptive analysis of laterality defects and its main phenotypic subgroups from a large multi-site study of birth defects using a systematic and common approach to case review and classification, based on detailed description of cardiac and extracardiac defects.

Over the past 30 years, birth prevalence estimates of laterality defects have been generated by hospital-based studies [Lin et al., 2000], regional cardiology programs [Fyler et al., 1980], and population-based [Ferencz et al., 1997; Reller et al., 2008; Bedard et al., 2012; Khoshood et al., 2012] studies (Table V). Estimates from these studies generally hover at slightly more than 1 per 10,000, ranging between 0.88 and 1.7 per 10,000, with variations by inclusion criteria and anatomic definition. Similar to the Baltimore-Washington Infant Study (BWIS), another population-based case-control study of CHDs, the NBDPS excluded

syndromes. Whereas the BWIS used a less specific schema of combining all laterality and cardiac looping defects, the current study separated SIT from heterotaxy subtypes of laterality defects [Ferencz et al., 1997]. Excluded from comparison is the recent large population-based registry data (EUROCAT) [Dolk et al., 2011] which described only "Ivemark atrial isomerism" in their Severity Group II, and provided no data on this group. Despite differences from previous studies in the definition of the phenotypic spectrum (i.e., the inclusion of syndromes or ectopia cordis), the estimated prevalence in our study (1.1 per 10,000) is remarkably similar to that reported by recent population-based studies in Western Canada (1.3 per 10,000) [Bedard et al., 2012] and metropolitan Paris (1.2 per 10,000 [Khoshood et al., 2012], and by a hospital-based study of heterotaxy in Boston (0.99 per 10,000 for heterotaxy) [Lin et al., 2000]. All three studies included some form of familial cases, syndromes (chromosome and Mendelian gene) and/or "other anomalies", which would generally be predicted to increase the prevalence of laterality defects. However, methodologic differences make detailed comparisons difficult. In the current study, prevalence differed insignificantly across sites with a tendency to lower (New Jersey) and higher (California) rates. It is difficult to know whether the variation is related to the surveillance program's abstractors' ability to pursue the type of diagnostic tests and consults which define the phenotypes, or whether there are regional differences among medical specialists such as pediatric cardiologists, geneticists, surgeons, and pathologists who may evaluate these patients differently.

The similarity of the sociodemographic characteristics data between SIT and heterotaxy cases in our study supports the notion that these phenotypes are part of a continuum of laterality maldevelopment. We acknowledge that the studied characteristics, which are relatively imprecise, may be insufficient to distinguish etiologic differences among the phenotypes. The higher rate of SGA among cases of heterotaxy could be related to the higher rate of complex CHDs or could be an indication of a more profound developmental abnormality in this group. Of note, there appears to be no significant impact on prevalence by excluding terminations of pregnancy from the analyses. However, only five sites had available data; terminations were not routinely collected by other surveillance systems.

The detailed analysis of sociodemographic factors in this study differs from other cohorts, notably, the BWIS which did not analyze maternal age and noted only that racial distribution was "slightly different" from controls [Ferencz et al., 1997]. That study compared the sex of births, noting more white females (66.1%) than males (59.1%) and nearly equal frequency of black males (33.1%) and females (31.0%), In the United Kingdom, there was no difference in the male:female sex prevalence ratios of "situs inversus" and "asplenia". Using data from the Metropolitan Atlanta Congenital Defects Program, Miller et al. [2011] focused on CHDs and major structural noncardiac anomalies in which laterality defects (n =161) were classified as a unique malformation complex rather than a CHD. Table III in their paper showed similar trends with a significant difference in race distribution (black or African American more common than White and Other) and maternal age (< 35 years more common than >35 years). The authors noted the lack of homogeneity in their sample across all study years since Hispanic ethnicity was not recorded during entire time period. Sokal et al. [2014] studied major congenital anomalies in the United Kingdom as part of a national population-based study and international meta-analysis. The laterality defects were limited

to “situs inversus” and “asplenia” for which they found no significant difference in the male:female prevalence ratios.

Analysis of Extra-cardiac and Cardiac Defects

While laterality defects span multiple thoraco-abdominal organ systems, relatively few cases in this study had extra-cardiac defects outside of those that are part of the phenotype. Ticho et al. [2000] reported a high incidence of broadly defined “midline-associated” defects in exclusively well-defined 160 autopsied heterotaxy cases (52% among polysplenia, 45% among asplenia). They included many anomalies that are considered ‘minor’ or ineligible in many surveillance programs (e.g., high arched palate, laryngeal cleft, pectus carinatum, fused vertebrae, bifid sacrum, and hypoplastic kidneys), and therefore are not included in NBDPS. However, if a minor anomaly occurs with a major birth defect, it should have been described in the participating programs, and therefore in NBDPS. The marked difference in the frequency of associated extracardiac anomalies between their observation and our study may be explained by the different method of ascertainment. As summarized by Miller et al. [2011], the incidence of extracardiac anomalies associated with CHDs in autopsy studies ranges in selected reports between 45.9% and 66.0%, compared to 14.5%–30.1% in clinical studies, and 16.9%–25.8% in epidemiological studies.

Several complex CHD and certain extra-cardiac defects were more common in cases with heterotaxy than SIT. The types of complex CHD in heterotaxy found in our study have been well-established [Van Praagh, 2006], but the comparison to SIT in a population-based study is new. Comparing the familiar heterotaxy phenotypes based on atrial appendage morphology and spleen status should be viewed with caution. The dichotomy of right and left atrial appendage “isomerism” is more accurately viewed as “more similar than different”, and not necessarily identical (right or left “isomerism”). It is well-known that these phenotypes or mild forms can occur in the same families, supporting the notion that there is a laterality defect in general, but not for a specific phenotype [Zhu et al., 2006]. Information from birth defects surveillance programs differs from the findings of post-mortem analysis [Van Praagh, 2006] and clinical studies [Foerster et al., 2008] in terms of (1) level of anatomic detail, (2) types of available diagnostic modalities (e.g., echocardiogram, MRI, catheterization, autopsy), and (3) ability to confirm and resolve apparent discrepancies or uncertainties. Thus, there were striking similarities between this study and Foerster et al. [2008] for total cases of interrupted inferior vena cava, total bilateral superior right superior vena cava, totally and partially anomalous pulmonary venous return, single ventricle, morphologic left ventricle, d-loop transposition of the great arteries, and tetralogy of Fallot. The apparently high frequency of interrupted inferior vena cava (16.7%) in cases with situs ambiguous/RAI is a puzzling differerence from its absence in a postmortem review [Van Praagh, 2006].

The pathogenesis of laterality defects represents an abnormal developmental sequence in which an early imbalance in cell proliferation, differentiation, and/or migration is thought to lead to an unpredictable cascade of effects on critical cardiac morphogenesis processes. However, whether the origin of the left-right axis is established relatively late in embryogenesis or much earlier, and whether stochastic events play a role is debated

[Vandenberg and Levin, 2013]. Under the general model, the initial gene disturbance or environmental insult could indirectly affect looping, atrioventricular canal growth, or aorticopulmonary septation via some earlier problem in the patterning of the lateral plate mesoderm or the midline. An alternative explanation is pleiotropy, in which the embryonic insult (e.g., genetic mutation) is an independent factor in both left-right patterning and organogenesis. Pleiotropy may explain some of the atypical extra-cardiac defects such as central nervous system malformations.

Study Strengths and Limitations

This is a large population-based study of laterality defects from 10 sites with racial-ethnic and geographic diversity. The cardiac and extra-cardiac defects were verified by detailed and systematic review of diagnostic testing and medical records to ensure accuracy of diagnosis and case classification. A single clinical reviewer then conducted a final review and classification, using a systematic approach, minimizing the variation that can occur with multiple reviewers. The prevalence estimate of the laterality spectrum is reduced slightly because cases with biopsy or mutation proven PCD [Kennedy et al., 2007; Brueckner, 2007; Leigh et al., 2009] and other confirmed or highly suspected monogenic cases are systematically excluded from the NBDPS. Based on Massachusetts data showing that only three cases were excluded for these reasons, the impact of these exclusions seems small.

However, these findings must be interpreted in light of the study's potential limitations. First, the case group may include cases with unrecognized syndromes. The use of genomic microarray technology or molecular testing (e.g., targeted gene analysis) was not prevalent or consistent among all cases during the study years. With refinements and increased use of genetic testing on a clinical basis, it is likely that the proportion of cases with clear genetic etiology will increase. As an example, the contribution of rare de novo DNA copy number variants in causing heterotaxy is increasingly identified [Fakhro et al., 2011]. Secondly, errors in assessment and classification of the laterality defects may have occurred due to incomplete diagnostic records. Ultrasonography, MRI imaging, or post-mortem imaging reports necessary to define spleen anatomy and visceral malposition were not all available for review in all cases. This type of site specific variation was difficult to quantify, but may have impacted ascertainment in subtle ways. A weakness of the comparison between cases with dissimilar spleen phenotypes (asplenia, polysplenia) in a surveillance-based study of laterality defects is lack of consistent, intense diagnostic testing across sites, e.g., spleen imaging and functional studies, assessment of bronchi and atrial appendages morphology, and detailed abdominal vessel and organ imaging. Finally, the impact of terminations on the estimated prevalence of laterality defects might have been greater if additional sites had been able to report terminations.

CONCLUSIONS

Laterality defects pose a challenge to epidemiologic analysis because of their tremendous anatomic complexity and phenotypic diversity which this study tried to address through careful case classification and rigorous review. This study's prevalence estimates from a racial-ethnic and geographically diverse cohort provides helpful information in addressing

the impact of these rare but complex conditions. In addition, the epidemiologic similarities in socio-demographic patterns between heterotaxy and SIT suggest that they are part of a spectrum of abnormalities in the determination of sidedness, and seeking commonalities in etiology and pathogenesis between these two classes of conditions could prove fruitful. This information may help guide clinical care, future research, and prevention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE I

Laterality Defects Inclusion Criteria, National Birth Defects Prevention Study, 1998–2007

I. Situs inversus totalis
II. Heterotaxy: Requires at least three of the following features, selected from group 1–8
1. Characteristic congenital heart defects[a]
Pulmonary venous anomalies
Totally anomalous pulmonary venous connection or drainage
Partially anomalous pulmonary venous connection or drainage
Atrial anomalies
Atrial situsambiguous or inversus
Common atrium
Common atrioventricularcanal(or septal) defects
Complete atrioventricularcanal defect
Partial atrioventricular canal defect
Transitional atrioventricular canal defect
Ventricular abnormalities
Hypoplastic or single left ventricle[b]
Hypoplastic or single right ventricle
Ventricular malposition (e.g., L-loop, superior-inferior, criss-cross)
Ventriculo arterial alignment abnormalities
Double-outlet ventricle
D-loop transposition of great arteries
L-loop transposition of great arteries
Truncusarteriosus
TOF (including TOF/PS, TOF/PA, and TOF/APV)
Ventricular outflow abnormalities
Subvalvar/valvar pulmonary stenosis
Pulmonary atresia with intact ventricular septum
Pulmonary atresia with ventricular septal defect (not TOF-type)
Valvar or subvalvar aortic stenosis
Coarctation of the aorta
2. Biliary atresia
3. Abdominal situs abnormality
Abdominal situs inversus
Situs ambiguous (midline or transverse liver, midline aorta, ipsilateral aorta, and IVC)
4. Spleen abnormality (confirmed by imaging, autopsy, or by Howell-Jolly bodies)
Asplenia
Polysplenia
Single right-sided spleen
5. Isomerism of bronchi
Bilateral left bronchial morphology
Bilateral right bronchial morphology

6. Isomerism of the lungs
Bilateral two lobes (left-sidedness)
Bilateral three lobes (right-sidedness)
7. Similar morphology of the atrial appendages (“isomerism”)
8. Two of the following
Systemic venous anomalies
Bilateral superior vena cava
Interrupted inferior vena cava
Unroofed (absent) coronary sinus
Intestinal malrotation
Malrotation, nonrotation colon
Malrotation, small intestine
Absent gallbladder

APV, absent pulmonary valve; CHD, congenital heart defect; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot.

[a] Adapted from Foerster et al. [2008, Table II].

[b] Hypoplastic left ventricle or single right ventricle, and hypoplastic right ventricle or single left ventricle were coded with specific CHD codes such as tricuspid atresia or hypoplastic left heart syndrome.

TABLE II

Birth Prevalence of Laterality Defects by Clinical and Demographic Characteristics, National Birth Defects Prevention Study, 1998–2007[a]

		All laterality defects			Heterotaxy			Situs Inversus		
	Total births	**Cases**	**Prev [/10,000]**	**PR (95% CI)**	**Cases**	**Prev [/10,000]**	**PR (95% CI)**	**Cases**	**Prev [/10,000]**	**PR (95% CI)**
Total	4,664,529	517	1.1	-	378	0.8	-	139	0.3	-
Sex[b]										
Male	2,386,550	241	1.0	Ref	170	0.7	Ref	71	0.3	Ref
Female	2,277,918	275	1.2	1.2 (1.1–1.4)	207	0.9	1.3 (1.0–1.6)	68	0.3	1.0 (0.7–1.4)
Race-Ethnicity[c]										
White, non-Hispanic	2,539,028	221	0.9	Ref	167	0.7	Ref	54	0.2	Ref
Black, non-Hispanic	590,567	95	1.6	1.8 (1.4–2.4)	69	1.2	1.8 (1.3–2.4)	26	0.4	2.1 (1.3–3.3)
Hispanic	1,252,835	153	1.2	1.4 (1.1–1.7)	110	0.9	1.3 (1.1–1.7)	43	0.3	1.6 (1.1–2.4)
Other	281,936	47	1.7	1.9 (1.4–2.6)	31	1.1	1.7 (1.1–2.4)	16	0.6	2.7 (1.5–4.7)
Maternal age at delivery (years)										
< 20	492,255	76	1.5	1.4 (1.1–1.9)	53	1.1	1.4 (1.0–1.9)	23	0.5	1.6 (1.0–2.7)
20–24	1,102,421	131	1.2	1.1 (0.9–1.4)	95	0.9	1.1 (1.0–1.4)	36	0.3	1.1 (0.7–1.8)
25–29	1,243,123	135	1.1	Ref	99	0.8	Ref	36	0.3	Ref
30–34	1,133,316	116	1.0	0.9 (0.7–1.2)	87	0.8	1.0 (0.7–1.3)	29	0.3	0.9 (0.5–1.4)
35–39	571,145	49	0.9	0.8 (0.6–1.1)	38	0.7	0.8 (0.6–1.2)	11	0.2	0.7 (0.3–1.3)
>=40	121,747	9	0.7	0.7 (0.4–1.3)	5	0.4	0.5 (0.2–1.3)	4	0.3	1.1 (0.4–3.2)
Gestational age (weeks)										
<37	474,986	126	2.6	2.8 (2.3–3.5)	98	2.1	3.1 (2.4–3.9)	28	0.6	2.3 (1.5–3.4)
>=37	4,095,238	381	0.9	Ref	274	0.7	Ref	107	0.3	Ref
Plurality										
Singletons	4,500,939	503	1.1	Ref	368	0.8	Ref	135	0.3	Ref
Twins or more	157,721	14	0.9	0.8 (0.5–1.4)	10	0.6	0.8 (0.4–1.4)	4	0.3	0.8 (0.3–2.3)
Site of Maternal Residence										
Arkansas	383,606	39	1.0	0.7 (0.5–1.1)	27	0.7	0.7 (0.4–1.1)	12	0.3	0.8 (0.4–1.7)
California	624,998	117	1.9	1.4 (1.0–1.8)	88	1.4	1.4 (1.0–2.0)	29	0.5	1.3 (0.7–2.2)
Georgia	510,427	70	1.4	Ref	51	1.0	Ref	19	0.4	Ref
Iowa	385,435	38	1.0	0.7 (0.5–1.1)	26	0.7	0.7 (0.4–1.1)	12	0.3	0.8 (0.4–1.7)

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		All laterality defects			Heterotaxy			Situs Inversus		
	Total births	**Cases**	**Prev [/10,000]**	**PR (95% CI)**	**Cases**	**Prev [/10,000]**	**PR (95% CI)**	**Cases**	**Prev [/10,000]**	**PR (95% CI)**
Massachusetts	632,264	76	1.2	0.9 (0.6–1.2)	56	0.9	0.9 (0.6–1.3)	20	0.3	0.8 (0.4–1.6)
North Carolina	227,707	34	1.5	1.1 (0.7–1.6)	27	1.2	1.2 (0.7–1.9)	7	0.3	0.8 (0.4–2.0)
New Jersey	573,578	34	0.6	0.4 (0.3–0.6)	18	0.3	0.3 (0.2–0.5)	16	0.3	0.8 (0.4–1.5)
New York	460,432	30	0.6	0.5 (0.3–0.7)	26	0.6	0.6 (0.5–0.9)	4	0.1	0.2 (0.1–0.7)
Texas	605,540	53	0.9	0.6 (0.4–0.9)	40	0.7	0.7 (0.4–1.0)	13	0.2	0.6 (0.3–1.2)
Utah	260,542	26	1.0	0.7 (0.5–1.1)	19	0.7	0.7 (0.3–1.2)	7	0.3	0.7 (0.3–1.7)
Year of Birth										
1998	561,406	48	0.8	0.8 (0.5–1.1)	34	0.6	0.8 (0.5–1.2)	14	0.3	0.8 (0.4–1.7)
1999	488,477	61	1.2	1.1 (0.8–1.6)	42	0.9	1.1 (0.7–1.6)	19	0.4	1.2 (0.6–2.4)
2000	480,951	54	1.1	Ref	39	0.8	Ref	15	0.3	Ref
2001	478,699	57	1.2	1.1 (0.7–1.5)	40	0.8	1.0 (0.7–1.6)	17	0.4	1.1 (0.6–2.3)
2002	444,354	46	1.0	0.9 (0.6–1.4)	37	0.8	1.0 (0.7–1.6)	9	0.2	0.6 (0.3–1.5)
2003	424,780	36	0.8	0.8 (0.5–1.2)	24	0.6	0.7 (0.4–1.2)	12	0.3	0.9 (0.4–1.9)
2004	431,349	58	1.3	1.2 (0.8–1.7)	47	1.1	1.3 (0.9–2.1)	11	0.3	0.8 (0.4–1.8)
2005	434,666	55	1.3	1.1 (0.8–1.6)	41	0.9	1.2 (0.8–1.8)	14	0.3	1.0 (0.5–2.1)
2006	452,743	52	1.2	1.0 (0.7–1.5)	40	0.9	1.1 (0.7–1.7)	12	0.3	0.8 (0.4–1.8)
2007	467,104	50	1.1	1.0 (0.6–1.4)	34	0.7	0.9 (0.6–1.4)	16	0.3	1.1 (0.5–2.2)
Birth Status[d]										
Liveborn	4,664,529	497	1.1	-	362	0.8	-	135	0.3	-
Fetal deaths	-	9	-	-	8	-	-	1	-	-
TOP	-	10	-	-	7	-	-	3	-	-

CI, confidence interval; Prev, prevalence; PR, prevalence ratio; Ref, reference; TOP, termination of pregnancy.

[a] Unless otherwise noted, categories may not sum to totals because of missing values.

[b] For Sex, the missing case was not a case of ambiguous genitalia.

[c] For Race, Other does not include unknown.

[d] ForBirth Status, year and site specific population counts are not available.

TABLE III

Distribution[a] of Laterality Defects According to Presence of Congenital Heart Defects in the National Birth Defects Prevention Study, 1998–2007

Severity of CHD[c]	Total N (%)	Heterotaxy N (%)	Situsinversus, totalis N (%)
Simple[b]	48 (9.3)	28 (7.4)	20 (14.4)
Complex	350 (67.7)	313 (82.8)	37 (26.6)
No CHD	119 (23.0)	37 (9.8)	82 (59.0)
Total	517 (100.0)	378 (100.0)	139 (100.0)

CHD, congenital heart defect.

[a]The National Birth Defects Prevention Study distinguishes between case coding and case classification. For example, any case with isolated situs abdominis will be *coded* with 759.310, even though it is not *classified* as one of the laterality defects which are the focus of this study.

[b]Simple CHD includes atrial septal defect, ventricular septal defect, mild pulmonary valve stenosis, mild aortic stenosis.

[c]Chi-square test value 146.7, $P < 0.0001$ comparing no or absent CHD versus complex CHDs for situs inversus totalis and heterotaxy.

TABLE IV

Major Defects Seen Among CasesWith Laterality Defects, National Birth Defects Prevention Study, 1998–2007

	All laterality defects (N =517)		Heterotaxy (N = 378)		Situs InversusTotalis (N = 139)		Fisher's Exact Test, Two-sided *P*-value[a]
Congenital heart defects. total cases	**425**	**82.2**	**365**	**96.6**	**60**	**43.2**	***
Single ventricle, total	61	11.8	53	14.0	8	5.8	
DIRV, DILV	25	4.8	22	5.8	3	2.2	
Single ventricle indeterminate, unspecified	36	7.0	31	8.2	5	3.6	
Conotruncal	204	39.5	179	47.4	25	18.0	
Truncusarteriosus	4	0.8	4	1.1	0	0	
TOF	20	3.9	16	4.2	4	2.9	
d-loop TGA (includesTGA with VSD)	72	13.9	62	16.4	10	7.2	
Double outlet right ventricle	108	20.9	97	25.7	11	7.9	***
l-loop TGA, not single ventricle	36	7.0	26	6.9	10	7.2	
AVCD (AVSD), complete	190	36.8	183	48.4	7	5.0	***
Left-sided obstructive defects	26	5.0	22	6.3	2	1.4	
Aortic stenosis	10	1.9	10	2.6	0	0	
Coarctation	2	0.4	2	0.5	0	0	
Hypoplastic left heart syndrome	14	2.7	12	3.2	2	1.4	
Right-sided defects	173	33.5	153	40.5	20		
Ebstein anomaly	2	0.4	1	0.3	1	0.7	
Pulmonary stenosis	82	15.9	73	19.3	9	6.5	***
Pulmonary atresia with intact septum	16	3.1	14	3.7	2	1.4	
Non-TOF pulmonary atresia with VSD	73	14.1	65	17.2	8	5.8	***
TAPVR	121	23.4	118	31.2	3	2.2	***
PAVPR	34	6.6	33	8.7	1	0.7	***
Ventricular septal defects, total	63	12.2	45	11.9	18	12.9	***
VSD membranous	25	4.8	15	4.0	10	7.2	
VSD malalignment-type	38	7.4	30	7.9	8	5.8	
Atrial septal defects	119	23.0	100	26.5	19	13.7	***
ASD secundum	82	15.9	68	18.0	14	10.1	
ASD NOS	30	5.8	25	6.6	5	3.6	

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	All laterality defects (N =517)		Heterotaxy (N = 378)		Situs InversusTotalis (N = 139)		Fisher's Exact Test, Two-sided *P*-value[a]
Congenital heart defects. total cases	**425**	**82.2**	**365**	**96.6**	**60**	**43.2**	***
ASD other	7	1.4	7	1.9	0	0.0	
Absent right AV valve (e.g. tricuspid atresia)	9	1.7	8	2.1	1	0.7	
Absent left AV valve (e.g., mitral atresia)	26	5.0	20	5.3	6	4.3	
Vena cava, OS (e.g., interrupted IVC)	161	31.1	153	40.5	8	5.8	***
SVC/persistent left or bilateral	145	28.0	137	36.2	8	5.8	***
Visceral defects, total cases[b,c]	517		378		139		
Situs inversus totalis	163	31.5	24	6.3	139	100.0	
Situs ambiguous, right isomerism	66	12.8	66	17.5	0	0.0	
Situs ambiguous, left isomerism	70	13.5	70	18.5	0	0.0	
Situs ambiguous, sidedness unclear, or NOS	169	32.7	169	44.7	0	0.0	
Heterotaxy NOS	104	20.1	104	27.5	0	0.0	
Spleen anomalies	240	46.4	230	60.8	10	7.2	
Asplenia (absent spleen)	149	28.8	144	38.1	5	3.6	
Polysplenia	77	14.9	72	19.0	5	3.6	
Right-sided spleen	14	2.7	14	3.7	0	0.0	
Malrotation	147	28.4	136	36.0	11	7.9	
Extracardiac defects, total cases	41		33		8		
Central nervous system, all	7	1.4	5	1.3	2	1.4	
Neural tube defects, all	2	0.4	2	0.5	0	0.0	
Anencephaly and craniorachischisis	1	0.2	1	0.3	0	0.0	
Spina bifida	1	0.2	1	0.3	0	0.0	
Central nervous system, not NTD	5	1.0	3	0.8	2	1.4	
Holoprosencephaly	1	0.2	1	0.3	0	0.0	
Hydrocephaly	1	0.2	1	0.3	0	0.0	
Dandy-Walker malformation	3	0.6	1	0.3	2	1.4	
Craniosynostosis	1	0.2	1	0.3	0	0.0	
Orofacial clefts	5	1.0	5	1.3	0	0.0	
Cleft lip +/− cleft palate	2	0.4	2	0.5	0	0.0	
Cleft palate	3	0.6	3	0.8	0	0.0	
Anotia/microtia	4	0.8	2	0.5	2	1.4	

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	All laterality defects (N =517)		Heterotaxy (N = 378)		Situs InversusTotalis (N = 139)		Fisher's Exact Test, Two-sided *P*-value[a]
Congenital heart defects. total cases	**425**	**82.2**	**365**	**96.6**	**60**	**43.2**	***
Esophageal atresia	3	0.6	3	0.8	0	0.0	
Bowel atresia/all	7	1.4	7	1.9	0	0.0	
Intestinal atresia/stenosis	2	0.4	2	0.5	0	0.0	
Anorectal atresia/stenosis	5	1.0	5	1.3	0	0.0	
Diaphragmatic hernia	4	0.8	3	0.8	1	0.7	
Sacral agenesis or caudal dysplasia	5	1.0	3	0.8	2	1.4	
Omphalocele	3	0.6	3	0.8	0	0.0	
Hypospadias second/third degree	1	0.2	1	0.3	0	0.0	
Bilateral renal agenesis or hypoplasia	2	0.4	1	0.3	1	0.7	
Cloacalextrophy	2	0.4	2	0.5	0	0.0	
Biliary atresia	2	0.4	2	0.5	0	0.0	
Transverse limb deficiency	1	0.2	0	0.0	1	0.7	
Intercalary limb deficiency	1	0.2	0	0.0	1	0.7	

ASD, atrial septal defect; AV, atrioventricular; AVCD (AVSD), atrioventricular canal defect (atrioventricularseptal defect); DIRV, DILV, double inlet right ventricle, double inlet left ventricle; IVC, inferior vena cava; NOS, not otherwise specified; NTD, neural tube defect; OS, other specified; SVC, superior vena cava; T/PAPVR, totally/partially anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

[a]For congenital heart defects, significance is indicated by two asterisks for <0.01, three for 0.001.

[b]For all extracardiacdefects, the Chi-square test, *P*-value was 0.3207, not significant; we did not calculate this for individual defect types because of small numbers.

[c]For Heterotaxy or situs inversus totalis, there were no cases of encephalocele, anophthalmos/microphthalmos, cataracts, choanal atresia, duodenal atresia/stenosis, gastroschisis, or bladder exstrophy.

TABLE V

Comparison of Laterality Defects Prevalence (per 10,000) in the Literature and the National Birth Defects Prevention Study, 1998–2007

Author Year	Study (years)	Total births Total CHD cases Years of study	Method/Population	Definitions (verbatim from article)	Total No. cases prevalence	Heterotaxy No. cases prevalence	SI, Totalis No. cases prevalence
Fyler et al., 1986	New England Regional Infant Cardiac Program (1968–1974)	1,083,083 2,381 6 years	Cardiology centers New England Approximates population-based	Heterotaxia (Dextro-, meso-, levo-, asplenia); included ectopia cordis	95 0.9	NS	NS
Ferencz et al., 1997	Baltimore-Washington Infant Study (1981–1989)	906,626 4,390 8 years	Population-based Metropolitan Baltimore-Washington, D.C.	Laterality and cardiac looping defects (excluding ectopiacordis)	104 1.4	0.50	0.1
Lin et al., 2000	Brigham and Women's Hospital (1972–3/99, except 1975–78	201,084 489 nontransfers 24 years	Hospital-based Boston, MA Includes TOP	Heterotaxy Syndromes included	NS	58 total 20 nontransfers 0.99	NS
Reller et al., 2008	Metropolitan Atlanta Congenital Defects Program (1998–2005)	398,140 3,240 6 years	Population-based Plus local cardiology center. Metropolitan Atlanta, GA	"Heterotaxy Syndromes" broadly defined	68 1.7	NS	NS
Bedard et al., 2012	Alberta Congenital Anomalies Surveillance System (1995–2002)	301,899 3,751 8 years	Population-based Passive registry, Plus two cardiology centers Western Canada Includes TOP	Heterotaxy NBDPS classification Not subdivided into situsinversus and heterotaxy. Syndromes included	39 1.3	NS	NS
Khoshnood et al., 2013	EPIdemiologie des CARDiopathiescongenitales (EPICARD) (2005–2008)	317,538 births 2,867 cases 3 years	Population-based Greater Paris Includes TOP	Heterotaxy Including isomerism and "mirror-imagery". Exclusion of chromosome or "other" anomalies applied to total CHD analysis, not specific CHDs	37 1.2	NS	NS
Lin et al., 2014 (This study)	NBDPS (1998–2007) All sites	4,664,529 12,445 10 years	Population-based 10 sites National USA 5 sites with TOP	Situsinversustotalis and heterotaxy. Syndromes excluded.	517 1.11	378 0.81	139 0.30

CHD, congenital heart defects; National Birth Defects Prevention Study (NBDPS); NS, not stated; TOP, termination of pregnancy.