Heterotaxy: Associated conditions and hospital-based prevalence in newborns

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Purpose: To provide insight into the possible etiology and prevalence of heterotaxy, we studied conditions associated with heterotaxy in a consecutive hospital population of newborns. **Methods:** From 1972 to March, 1999 (except February 16, 1972 to December 31, 1978), 58 cases of heterotaxy were ascertained from a cohort of 201,084 births in the ongoing Active Malformation Surveillance Program at the Brigham and Women's Hospital. This registry includes livebirths, stillbirths, and elective abortions. Prevalence among nontransfers (i.e., patients whose mothers had planned delivery at this hospital) was calculated as approximately 1 per 10,000 total births (20 of 201,084). **Results:** We analyzed a total of 58 patients consisting of 20 (34%) nontransfers and 38 (66%) transfers. Patients were categorized by spleen status as having asplenia (7 nontransfers, 25 total), polysplenia (8, 20), right spleen (4, 11), normal left (0, 1), and unknown (1, 0). Among the 20 nontransfer and 59 total heterotaxy patients, the following associated medical conditions were present: chromosome abnormality (1 nontransfer, 2 total), suspected Mendelian or chromosome microdeletion disorder (1 nontransfer, 6 total), and maternal insulin-dependent diabetes mellitus (1 nontransfer, 2 total). There were 6 twins (1 member each from 6 twin pairs including 1 dizygous, 4 monozygous, 1 conjoined; 2 were nontransfers). An associated condition occurred in 5 (25%) nontransfer and 16 (28%) total patients, or among 10 of 53 singleton births (19%). **Conclusions:** Although most cases of heterotaxy in this series were sporadic events, an associated condition was present in about one-fourth of the cases. Not all of these conditions would be considered causative etiologies. Based on this small series alone, maternal insulin-dependent diabetes cannot be viewed as a risk factor for heterotaxy. However, the specific association of diabetes with polysplenia with/without left atrial isomerism is noteworthy, and adds weight to animal and epidemiologic case-control data. ***Genetics in Medicine*, 2000:2(3):157–172.**

Key Words: *Asplenia, cardiovascular malformations, congenital heart defects, defects of right, left determination, genetic epidemiology, heterotaxy, isomerism, laterality defects, maternal diabetes, polysplenia, prevalence, situs ambiguous, situs inversus*

Errors in the development of the normal right-left axis in humans can produce a variety of laterality defects. The classification of these complexes is most meaningful when information about the heart, lungs, cilia, spleen, and abdominal organs is combined. Classical heterotaxy refers to abnormal abdominal and thoracic visceral situs, which may include the presence of symmetry (i.e., right or left isomerism), ambiguous or inverted situs, abnormalities of the spleen and complex cardiovascular malformations (CVMs) (Table 1).[1–3] Right and left atrial appendage isomerism are not always associated with asplenia and polysplenia, respectively, nor does spleen phenotype predict appendage morphology.[2]

Many articles have described the anatomic components of heterotaxy[1–13] and more recent reviews outline its genetic basis.[14–19] Equally abundant and often confusing are the terms that refer to this large category of malformations. Some describe classic heterotaxy (e.g., asplenia, polysplenia, right/left isomerism), others apply to the entire spectrum of cardiac malpositions (e.g., laterality defects, defects of right-left determination, right-left-axis malformations). Although one large epidemiologic study presented clear case definition,[17] minimum diagnostic criteria are often omitted, a situation that hampers both clinical and molecular studies. Perhaps the clearest definition is based on what heterotaxy is not: any arrangement of organs across the left-right axis differing from complete situs solitus or complete situs inversus.[14]

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Supported in part by the National Center for Environmental Health, Centers for Disease Control and Prevention through a grant to the Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health; Massachusetts Developmental Disabilities Council and the Charles H. Hood Foundation.

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Received: February 21, 2000

Accepted: March 24, 2000.

Table 1
Cardiac, pulmonary, and abdominal manifestations of situs solitus, situs inversus, and heterotaxy[a]

	Defects of Right–Left Determination		
	Situs Solitus	Heterotaxy[b]	Situs Inversus
Abdominal aorta and IVC relationship to spine	abdominal aorta on left	IVC/aorta on same side	IVC on left
	IVC on right	IVC interruption	abdominal aorta on right
Atrial appendage shape	right atrial appendage triangular	right atrial appendage isomerism	left atrial appendage triangular
	left atrial appendage J-shaped	left atrial appendage isomerism	right atrial appendage J-shaped
		indeterminate appendage shape	
		normal appendage shape	
Spleen morphology, location	single left spleen	polysplenia	single right spleen
		asplenia	
		single right spleen	
Gallbladder/liver location	gallbladder/liver on right	gallbladder/liver midline, left, right	gallbladder/liver on left
Bronchial branching	right bronchi epiarterial	bilateral epiarterial	right bronchi hyparterial
	left bronchi hyparterial	bilateral hyparterial	left bronchi epiarterial
		inverted	
		normal	
Lung lobation	right lung trilobed	bilateral trilobed	right lung bilobed
	left lung bilobed	bilateral bilobed	left lung trilobed
		inverted	
		normal	

[a]See references 1–3.
[b]Listed are possible anomalies. Not all cases of heterotaxy include a selection from each category or pair.
IVC, inferior vena cava.

A variety of clinically recognizable genetic conditions has been reported in humans with heterotaxy.[9,15,17] In addition, major advances in the identification of gene mutations in animals and humans support a growing body of knowledge about causes of laterality defects.[14,18–20] Most cases of heterotaxy are sporadic occurrences without a recognizable cause.[17] We analyzed births at a tertiary care urban hospital to determine the type and frequency of conditions associated with heterotaxy. We also compared the hospital-based newborn prevalence with reported population estimates.

METHODS

Classification of heterotaxy

There is no agreement as to the best way to classify heterotaxy patients. Most authors have used spleen number and morphology.[1,2,4] Others prefer atrial isomerism[6] or cilia morphology.[15] The population-based Baltimore-Washington Infant Study assigned a hierarchical allocation and included looping abnormalities with laterality defects.[17] We chose spleen number and morphology as a reasonable, though imperfect, system for categorizing patients. The minimum diagnostic criteria (Table 2) for heterotaxy required the presence of (1) complex CVM, plus at least 2 of the following: ipsilateral abdominal aorta and IVC, or IVC interruption, isomerism of the atrial appendages, isomerism of the lobes of the lungs or bronchial branching, spleen anomaly, inverted or symmetric liver, gallbladder, and stomach. If applied retrospectively, this definition would encompass most heterotaxy patients in the literature. Because heterotaxy is a spectrum with milder forms, and because certain anomalies carry greater diagnostic weight, we also included patients with (2) IVC interruption and a spleen anomaly who had no CVM or one which was trivial, and those with (3) polysplenia, other anomalies, and a mild CVM. Also included were (4) fetuses with highly suggestive anomalies in whom precise definition was precluded by a destructive termination procedure. Similarly, we included (5) a pair of siblings in whom heterotaxy was diagnosed confidently in the first pregnancy, but less certainly in the second. When evaluated as a pair, heterotaxy is a reasonable diagnosis for both.

Exclusions

We excluded patients with isolated asplenia, those with 1 or 2 accessory spleens (which differ from the multiple splenuli of polysplenia) and poor anatomic description. We excluded patients with isolated abdominal situs inversus or dextrocardia. Strictly speaking, these are not heterotaxy although they are laterality defects; they are not ambiguous or symmetric. Rele-

Table 2
Minimum diagnostic criteria for heterotaxy in 58 patients

Criteria	Patients (ID# of patients listed in Appendix)	
	Nontransfers	Transfers
Total	20	38
I. Classic	11 (55%)	30 (79%)
1. Complex cardiovascular malformation plus 2 of the following:	(ID #1–9, 11, 15)	(#1t–6t, 8t–17t, 22t, 24t–33t, 35t, 37t, 38t)
• Ipsilateral abdominal aorta and IVC, or IVC interruption		
• Isomerism of atrial appendages		
• Isomerism of lung lobation and/or bronchial branching		
• Spleen anomaly (asplenia, polysplenia, right spleen)		
• Inverted or symmetric liver/gallbladder, gallbladder, stomach		
II. Incomplete		
2. IVC interruption, spleen anomaly, absent or trivial CVM	7 (35%)	3 (8%)
	(#12–14, 16–19)	(#21t, 34t, 36t)
3. Polysplenia, other anomalies, mild CVM	1 (5%)	2 (5%)
	(#10)	(#20t, 23t)
4. Fetuses with suggestive anomalies, incomplete autopsy	1 (5%)	1 (3%)
	(#20)	(#7t)
5. Siblings with suggestive heterotaxy anomalies	0	2 (5%)
		(#18t, 19t)

CVM, cardiovascular malformation; IVC, inferior vena cava.

vant to our patient ascertainment, situs inversus and dextrocardia are not identified consistently in newborn surveillance programs. The patients in this Surveillance Program were not examined by our staff; the information provided by the pediatricians and other specialists was used to determine the phenotype. Furthermore, the important distinction between dextrocardia (a true cardiac malformation) and dextroposition or dextroversion (altered cardiac position) cannot be made from the brief newborn record.

Patient ascertainment

From February 16, 1972 to March 10, 1999 (except for the period February 15, 1975 to December 31, 1978), we identified patients with heterotaxy among 201,084 births in the ongoing Active Malformation Surveillance Program at the Brigham and Women's Hospital (BWH), a tertiary care hospital. Ascertainment includes livebirths, stillbirths >20 weeks, and elective terminations in the second trimester; spontaneous abortions <20 weeks were not included. Patients were identified up to the day of discharge, usually within 5 days. Active surveillance was conducted by research assistants who identified index cases of CVM 5 days a week in the 1970s and 6 days a week in the 1980s.

The methodology of this surveillance program has been described previously.[21,22] To summarize briefly, the research assistants made frequent visits to obstetric floors, regular nurseries, intensive care nursery, and autopsy suite to ask nurses, pediatricians, pediatric cardiologists, and pathologists to identify all fetuses and infants with a malformation, including heterotaxy. Beginning in the 1980s, each day the research assistant obtained the list of all infants that had been born in the previous 24 hours and reviewed that infant's hospital record for the findings by the examining pediatrician and any consultants. Demographic and medical data were recorded by research assistants. In the 1990s, ascertainment on Saturdays and holidays was added.

Because BWH is a tertiary care center, we determined the transfer status of the mother of each case. A "transfer" was a mother who had intended to deliver elsewhere, but was transferred to the BWH after the prenatal detection of a fetal abnormality. A "nontransfer" was a mother who had planned to deliver at BWH. Data analysis was performed according to this division of transfer and nontransfer status. Determining the transfer status of mothers evolved during the study period. In 1979 through 1981, data were obtained primarily from medical records or the obstetrician, less frequently from the mother herself. From 1982 onward, we used the maternal interview as the primary source.

The results of cardiology, genetic and cardiac surgical consultations, diagnostic tests, and autopsy reports were also used to establish the diagnosis. Autopsies were performed on approximately two-thirds of the stillborn infants delivered in each year. Cases were classified by suspected or confirmed genetic cause (i.e., chromosome abnormality, single gene) environmental factor (i.e., maternal insulin-dependent diabetes mellitus or exposure to

teratogenic drugs) multifactorial inheritance, twinning (monozygotic, dizygotic, conjoined), and unknown causation.

RESULTS

Heterotaxy prevalence

During a 24 year period, 58 infants with heterotaxy were identified from a cohort of 201,084 births. Thirty four percent were nontransfers and 66% were transfer births (Table 3). The birth prevalence rate for the 20 nontransfers was 0.99 per 10,000 total births (20 of 201,084). This hospital-based prevalence rate is the similar as the published population-based estimate of approximately 1 per 10,000.[10,17]

Clinical features

Classic heterotaxy was less common among nontransfers (55%) than transfers (79%), whereas a less severe form (IVC interruption and spleen anomaly) was more common among nontransfers (35%) than transfers (8%) (Table 2). Among all patients, most were female, white, and liveborn. Most nontransfers were also liveborn, but showed equal sex ratio and race distribution. The 8 elective terminations occurred after 1984 when prenatal diagnosis was commonly available, and the frequency was similar among nontransfers (3, 15%) and transfers (5, 13%). All of the older mothers had been transferred. Comparing the two most common spleen phenotypes among all patients, asplenia was more likely than polysplenia to be associated with neonatal death among livebirths (13 of 21, 62%).

Associated conditions

Noncardiac, nonpulmonary malformations occurred with similar frequency among nontransfers (12, 60%) and transfers (34, 59%) (Table 4). The CVM anatomy was diagnosed using the following techniques among nontransfer and total patients: fetal echocardiography alone (2, 10%; 4, 7%); fetal echocardiography and another method (12, 60%; 43, 74%); autopsy alone (1, 5%; 4, 7%); and combinations of catheterization, surgery, echocardiography, and autopsy (5, 25%; 7, 12%). The spleen phenotype was diagnosed by autopsy (8, 40%; 20, 34%), ultrasound examination (5, 24%; 14, 24%), isotope scan (3, 15%; 11, 19%), and surgery (0; 1, 2%). In one nontransfer patient, the spleen status was unknown because a disruptive termination procedure precluded complete examination. In the absence of a definitive study, the spleen status was defined by the pediatric cardiologist's assignment based upon characteristic CVMs[1–5] in 3 (15%) nontransfer and 10 (17%) total patients.

Table 3
Demographic information on 58 patients with heterotaxy

	Spleen location and number											
	Asplenia		Polysplenia		Single Right		Normal Left		Unknown		Total	
Total	25 (43%)		20 (34%)		11 (19%)		1 (2%)		1 (2%)		58	
	NON	TX	NON	TX	NON	TX	NON	TX	NON	TX	NON	TX
	7 (35%)	18 (47%)	8 (40%)	12 (32%)	4 (20%)	7 (18%)	0	1 (3%)	1 (5%)	0	20 (34%)	38 (66%)
Female	1	11	5	11	4	4	0	1	0	0	10	27
Male	6	7	3	1	0	3	0	0	1	0	10	11
Older mother (>35 years)	0	3	0	1	0	2	0	0	0	0	0	6
Mean age (yrs)												
Mother	27	30	26	27	23	27	0	32	16	NA	23	30
Father	30	33	31	31	26	29	NA	NA	NA	NA	29	31
Race												
White	2	13	4	8	1	6	0	1	0	0	7	28
Black	1	0	4	1	1	0	0	1	1	0	7	1
Other	4	5	0	3	2	1	0	0	0	0	6	9
Birth Status												
Liveborn	6	15	7	9	4	7	0	1	0	0	17	32
Stillborn	0	0	0	1	0	0	0	0	0	0	0	1
Eab	1	3	1	2	0	0	0	0	1	0	3	5
Neonatal death	6	7	2	2	0	0	0	0	0	0	8	9
(% among LB)	(100)	(47)	(28)	(22)	0	0	0	0	0	0	(47)	(28)

NON, nontransfer (mother who planned to deliver at BWH); TX, transfer (mother who transferred care to BWH because of the prenatal detection of a fetal abnormality eab, elective abortion; LB, liveborn.

Table 4
Maternal history, family history and associated malformations identified in 58 patients with heterotaxy

	Spleen location and number in proband											
	Asplenia		Polysplenia		Single Right		Normal Left		Unknown		Total	
Total	25 (43%)		20 (34%)		11 (19%)		1 (2%)		1 (2%)		58	
	NON	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX
	7 (35%)	18 (47%)	**8 (40%)**	12 (32%)	**4 (20%)**	7 (18%)	**0**	1 (3%)	**1 (5%)**	0	**20 (34%)**	38 (66%)
Maternal history			2 IDDM	(**1 NON**, 1 TX)							2 (3%)	
											NON 1 (5%)	
Other family history, total											16 (28%)	
											NON 3 (15%)	
Heterotaxy											5	
Family 1	**brother (NON)**		sister (TX)									
Family 2	brother (TX)							sister (TX)				
Family 3			sister (TX)									
			(sister with heterotaxy, but not in study, TX)									
CVM	1 cousin CHD NS (TX)		1 MU AS (TX)		1 brother CVM NS (TX)						5	
	1 FOB, GGF PS (TX)		1 PGM possible AVC (TX)									
Malformation			**1 NS relative spina bifida (NON)**								2	
			1 brother jejunal atresia (NON)									
Specific syndrome	1 brother DGS (TX)										4	
	1 MU Poland anomaly (TX)											
	1 eab sib Trisomy 18 (TX)											
	1 twin tetraploidy/diploidy (TX)											
Other malformations	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX
none	**3**	9	**4**	2	**1**	5	**0**	0	**0**	0	**8**	16
"typical" heterotaxy	**1**	4	**1**	9	**1**	1	**0**	0	**0**	0	**3**	14
multiple	**3**	5	**3**	1	**2**	1	**0**	1	**1**	0	**9**	8

CVM, cardiovascular malformation; DGS, DiGeorge sequence; eab, elective abortion; FOB, father of baby; GGF, great grandfather; IDDM, insulin-dependent diabetes mellitus; MU maternal uncle; NON, nontransfer; NS, not stated; PGM, paternal grandmother; PS, pulmonic stenosis; TX, transfer.

Table 4 presents details of a positive family history of heterotaxy, CVM, other malformation and specific syndromes. If only patients with a first degree relative with a CVM or heterotaxy are analyzed, the frequency of this more relevant family history figure decreases to 10% (1 nontransfer) and 9% (5 total). These families include the 3 sib pairs with heterotaxy, i.e., a brother with asplenia/sister with polysplenia, brother with asplenia/sister with normal left spleen, sister with polysplenia/sister with unspecified spleen morphology born outside of the study, and 2 patients who had a relative with a CVMs, i.e., a sister with a right spleen/brother with unspecified CVM, and girl with asplenia/father and great-grandfather with pulmonic stenosis. In addition to the two patients whose mothers had insulin-dependent diabetes mellitus (IDDM), there was one mother with "gestational" diabetes who was not tabulated. Heterogeneity among the associated conditions (Table 5) was apparent. Excluding twinning as an associated condition, 10 of 52 (19%) singleton births were associated with a condition.

DISCUSSION

In contrast to the multitude of studies that define the anatomic aspects of heterotaxy and the growing number of molecular biology articles that report individual gene mutations, there are few studies reporting associated conditions derived from epidemiologic surveys.[17] We analyzed associated conditions and newborn prevalence in a consecutive hospital-based series. Of the associated conditions observed in our study, some can be viewed as a genetic etiology (e.g., chromosome abnormality), whereas others lack proof of causation (e.g., maternal IDDM, twinning).

Table 5
Associated conditions in 58 patients with heterotaxy

	Spleen location and number in proband											
	Asplenia		Polysplenia		Single Right		Normal Left		Unknown		Total	
Total	25 (43%)		20 (34%)		11 (19%)		1 (2%)		1 (2%)		58	
	NON	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX
	7 (35%)	18 (47%)	**8 (40%)**	12 (32%)	**4 (20%)**	7 (18%)	**0**	1 (3%)	**1 (5%)**	0	**20 (34%)**	38 (66%)
I. No associated condition	17 (29%)		14 (24%)		10 (17%)		0		1 (2%)		42 (72%)	
	NON	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX	**NON**	TX
	5	12	**6**	8	**3**	7	**0**	0	**1**	0	**15**	27
II. Associated condition											16 (28%)	
											NON	TX
											5	11
Possible genetic defect											*6 (10%)*	
3 sib pairs with heterotaxy											5	
											(1 NON/4 TX)	
Family 1	**brother (NON)**		sister (TX)									
Family 2	brother (TX)						sister (TX)					
Family 3			sister (TX)						(sister not in study, TX)			
1 sibs with possible DGS	brother (TX) (brother not in study)										(1 TX)	
Chromosome abnormality											*2 (3%)*	
			1 47,XX+mar mosaic (Cat-Eye Syndrome)(NON) 1 Trisomy 13 (TX)								**(1 NON/1 TX)**	
											2 (3%)	
Environmental factor			2 IDDM **(1 NON,** 1 TX)								**(1 NON/1 TX)**	
											6 (10%)	
Twinning	1 conjoined (TX) **1 MZ (NON)** 3 MZ (TX)				**1 DZ (NON)**						**(2 NON/4 TX)**	

DGS, DiGeorge sequence; DZ, dizygotic; IDDM, insulin-dependent diabetes mellitus; MZ, monozygotic; NON-nontransfer; R, right; TX, transfer.

Challenges in analyzing heterotaxy

Because so many organs are involved in heterotaxy patients, information is often incomplete (Table 1). Situs ambiguous, implying indeterminate sidedness of the liver, gallbladder, and stomach, should not be diagnosed until a diligent search has been made. To define the spleen phenotype, imaging studies (ultrasound, radionuclide), inspection at surgery or autopsy is needed. Clinicians may deem them unnecessary in patients who have certain complex CVMs that typify polysplenia (i.e., IVC interruption, atrioventricular canal) or asplenia (i.e., bilateral superior vena cava, ipsilateral IVC and abdominal aorta, transposed great arteries, pulmonary stenosis/atresia, total anomalous venous return).[1–3] Analysis of the bronchial anatomy on standard or overpenetrated chest radiographs is convenient and reliable, but overlooked. Lung lobation can be determined only at autopsy. A description of the atrial appendage morphology can be attempted with echocardiography, but autopsy is definitive. Family studies have suggested that the spectrum of heterotaxy encompasses less severe forms.[15] For this study, we included as "incomplete heterotaxy" patients with IVC interruption or polysplenia without complex CVMs and lung isomerism (Table 2).

Previous studies

Because of the plethora of anatomic terms and study designs, publications about heterotaxy should be scrutinized to ensure valid comparison. One study to which these findings can be com-

Table 6
Heterotaxy and chromosome abnormalities*

Author	Pt#	Chromosome # Abnormality	Situs	Stomach	Spleen	Lung Lobation	CVMs	GI, Other
Genuardi *et al.*, 1993[29]	V-9	Unconfirmed Del or Bal Trans 7q22.1	NS	NS	Asplenia	NS	RAI, DORV, AVC, TAPVR	Split hand-split foot
Koiffmann, *et al.*, 1993[28]		Ins (7;8)(q22;q12q24)	Inversus	Right	Polysplenia	Bilateral bilobed	L-TGA, IVC inter, PSsub	Annular pancreas
Devriendt *et al.*, 1999[30]	1	Deletion 8p23.1	Solitus	Left	NS	Bilateral bilobed	LAI, DORV, AVC, PSV	
	2		Solitus	Left	NS	NS	LAI, IVC inter, AVC, PSV, ASV	Malrotation
Carmi *et al.*, 1992[37]	1	Deletion 10q21q23	Inversus	NS	2 accessory (? polysplenia)	NS	Partial AVC, CA, VSDmus, BSVC	Malrotation
Freeman *et al.*, 1996[38]	1	Bal Trans (11;20) (q13.1;q13.13)	NS	NS	Asplenia	NS	PS valvar	Hirschsprung
Fukushima *et al.*, 1993[39]	1	Inv 11q	NS (prob solitus)	NS (prob left)	Polysplenia	Bilateral bilobed	Single ventricle, CA, PAtr, AVC	
Wilson *et al.*, 1991[40]	1	Bal Trans (12;13) (q13.1;p13)	Inversus	Right	Asplenia	Bilateral trilobed	TGA, PAt, VSD, ASD1, BSVC, TAPVR	
Carmi *et al.* 1992[37]	2	Derivative 13q311	Solitus	Left	Small	Bilateral bilobed	TGA, AVC, ASD, PSV, PAS	
Lin *et al.* present study	1	Trisomy 13	Solitus	Left	Polysplenia	NS (prob normal)	Single ventricle, L-TGA, CA, PAtr	
Ferencz *et al.*, 1997[17]	1	Trisomy 13	NS	NS	NS	NS	NS	NS
DeCicco *et al.*, 1973[41]	1	Monosomy 22	Solitus	Left	Polysplenia	NS	TOF, CA, BSVC	
Penman-Splitt *et al.*, 1996[15]	1	Deletion 22q11.2	NS	NS	NS	NS	LAI	NS
Lin *et al.* present study	1	Marker 22 mosaic "Cat-Eye syndrome"	Solitus	Left	Probable polysplenia	NS	IVC inter, ASD2, TAPVR, VSDmem	Anal atresia, malrotation, other MCA

ASD1,2, atrial septal defect, primum or secundum type; ASV, aortic stenosis valvar; AVC, atrioventricular canal; BSVC, bilateral superior vena cava; CA, common atrium; DORV, double outlet right ventricle; GI, gastrointestinal; IVC inter, inferior vena cava interruption; LAI, left atrial isomerism; L-TGA, levo-transposition of the great arteries; NS, not stated; PAtr, pulmonary atresia; PSsub, pulmonic stenosis subvalvar; PSV, pulmonic stenosis, valvar; RAI, right atrial isomerism; TAPVR, total anomalous pulmonary venous return; VSD (mem, musc), ventricular septal defect (membranous, muscular type).
*Listed in ascending numerical order. Excludes patients with a laterality anomaly other than heterotaxy, i.e., I. Cross, cited in Penman-Splitt *et al.*[15] (dextrocardia) and Kato *et al.*[42] (probable situs inversus).

pared is the Baltimore-Washington Infant Study[17] despite important differences in methodology. Laterality and looping defects were classified together, and no category was specifically called heterotaxy. Such patients were classified among those with cardio-visceral discordance, subclassified by cardiac position, further by visceral situs, and eschewing subdivision by splenic phenotype. There were analogous categories for patients with l-TGA. Recognizing that there were no homogeneous subgroups, separate analyses were not done. Unlike our study, they excluded conjoined twins. Risk factors were sought systematically. Using multivariate analyses of cases and controls, six risk factors were identified: family history of heart defects, family history of noncardiac anomalies, maternal diabetes, antitussive use, paternal smoking, and low socioeconomic status.

Our study showed a hospital-based prevalence of heterotaxy of approximately 1/10,000. Literature reports of population-based prevalence are similar. Penman-Splitt *et al.*[15] cited Torgersen[23] and Campbell[24] who had reported complete situs inversus in 1/10,000, from which they deduced that the prevalence of heterotaxy would be <1/10,000. However, in a subsequent publication,[15] they mentioned a 1/24,000 prevalence for right or left isomerism. In the New England Regional Infant Cardiac Program,[25] the prevalence was 0.9/10,000 among livebirths hospitalized to age 1 year. This was a heterogeneous cohort that included

Table 7

Heterotaxy and maternal insulin-dependent diabetes mellitus*

Author	Pt#	Situs	Stomach	Spleen	Lung lobation, bronchi	CVMs	GI	CNS
Gonzalez *et al.*, 1989[43]	1	Inversus (probably)	NS	polysplenia	R: single lobed L: bilobed Bilaterally hyparterial	IVC inter, truncus, VSD, common atrium		
Carey *et al.*, 1991[44]	1	NS	NS	Polysplenia	Bilaterally bilobed	IVC inter, ASD, VSD, PS, COA		
	2	NS	NS	Polysplenia	Bilaterally bilobed	ASD, VSD, PS, COA		
	3	NS	NS	Polysplenia	NS	AVC, ASD, VSD, PS, PAPVR		
Davenport *et al.*, 1993[45]	1	NS	NS	Polysplenia	NS	NS	Biliary atresia	
	2	NS	NS	Polysplenia	NS	NS	Biliary atresia	
	3	NS	NS	Polysplenia	NS	NS	Biliary atresia	
Carmi *et al.*, 1993[46]	3	NS	NS	NS	NS	VSD, "absent" IVC	Biliary atresia, malrotation bowel	
Slavotinek *et al.*, 1996[47]	1			Asplenia		LAI		
	2			Polysplenia				
	3	Inversus						
Morelli *et al.*, 1998[48]	1	Solitus	Left	Left	Solitus	AVC		NTD
	2	Solitus	Left	Polysplenia	Solitus	DORV, PS, VSD		Caudal regression
						IVC interruption		Caudal regression
Gerritsen *et al.*, 1999[49]	1	Inversus	Right	Right	Left isomerism	ASD, VSD	Malrotation	
	2	Inversus	Right	Right	NS	VSD		
	3	Inversus	Right	Polysplenia	NS			
Splitt *et al.*, 1999[50]	1	Inversus	Right	Right polysplenia	Left isomerism	LAI DILV, VSD, AS		
	2	NS	NS	Polysplenia	Left isomerism	LAI IVC inter, AVC	Malrotation	
	3	NS	NS	Polysplenia	Left isomerism	LAI IVC inter, HLHS		
	4	NS	NS	Polysplenia	Left isomerism	IVC inter, AVC, CA, RAA		
	5	NS	NS	Polysplenia	Left isomerism	LAI IVC inter, AVC, PSsub, PSV	Malrotation	
	6	NS	NS	NS	Left isomerism	LAI IVC inter, VSD, TGA, aortic hypo		
	7	NS	NS	Polysplenia	Left isomerism	LAI VSD, RAA	Malrotation	
	8	Inversus	Right	Polysplenia	Left isomerism	LAI dextrocardia, AVC, CA, TGA		
Julius**	1	Inversus	Right	Polysplenia	Left isomerism	DORV, VSDmem, PAPVR, IVC inter	Malrotation	Exencephaly
Lin *et al.*	1(NON)	Solitus	Left	Polysplenia	Right isomerism	ASD2	Diaphragmatic hernia, SUA	
	2 (TX)	Inversus	Right	Polysplenia	Symmetric	IVC inter ASD2, BAV, VSDmusc, COA	Malrotation Absent GB	
Total # patients	25							

AS, aortic stenosis; ASD(2), atrial septal defect (secundum); AVC, atrioventricular canal; BAV, bicuspid aortic valve; CA, common atrium; CNS, central nervous system; COA, coarctation; CVMs, cardiovascular malformations; DILV, double inlet left ventricle; DM, diabetes mellitus; DORV, double outlet right ventricle; GB, gallbladder; HLHS, hypoplastic left heart syndrome; IDDM, insulin dependent diabetes mellitus; IVC inter, inferior vena cava interruption; L, left; LAI, left atrial isomerism; NON, nontransfer; NS, not stated; NTD, neural tube defects; PAPVR, partial anomalous pulmonary venous return; PS, pulmonic stenosis; PSsub, sub-pulmonic stenosis, PSV, valvar pulmonic stenosis; PV, pulmonary vein; R, right; RAA, right aortic arch; SUA, single umbilical artery; TGA, transposition great arteries; TX, transfer; VSD mem, musc, ventricular septal defect, membranous, muscular.

*Excludes the patients whose mothers had gestational diabetes reported by Reynolds *et al.*[51] and Davenport *et al.*[45] (patient 4).

**Personal correspondence, 1999.

isolated dextrocardia, slightly inflating the heterotaxy prevalence. Likewise, Ferencz *et al.*[17] reported laterality and looping defects in 1.44/10,000 livebirths to age 1 year in their population-based Baltimore-Washington Infant Study. After excluding isolated dextrocardia and situs inversus, an approximation of heterotaxy prevalence is 1.0/10,000.

Familial occurrence and syndromes

The recurrence of heterotaxy in siblings suggests autosomal recessive inheritance, but multifactorial inheritance is also a possibility.[26] To investigate this, cardiac and visceral imaging studies of extended family members, and mutation analysis for heterotaxy genes will be needed. As noted by others,[15,26] our series reports asplenia and polysplenia occurring in the same family. A single sibship suggested the role of a possible single gene. This was a male proband with autopsy proven asplenia, complex CVMs, and absent thymus. His brother, born 2 years earlier, had been diagnosed as having DiGeorge syndrome. Though unproven, the second boy may have had the same. Chromosomes were normal (46,XY) in the proband. Molecular analysis for deletion 22q11 was not available, nor was there was parental investigation. There were no patients in our series with any of the "Oral-Facial-Skeletal syndromes" (e.g., Ellis-van Creveld syndrome, short rib-polydactyly syndromes). It has been hypothesized that they represent overlap with heterotaxy because of the common occurrence of similar CVMs, notably common atrium and the spectrum of atrioventricular canal defects.[27]

Chromosome abnormality syndromes

Chromosome abnormalities in heterotaxy patients were uncommon in the literature and our series (Table 6), but provide tantalizing clues about the location of possible genes. One boy with polysplenia, left isomerism, and a CVM had an insertion involving chromosomes 7q22 and 8q12–24.[28] This same chromosome locus may have been altered in another boy with split hand-split foot, asplenia, right isomerism, and complex CVM whose mother had a balanced translocation involving 2q21.1 and 7q22.1 that segregated in the pedigree with split hand-split foot.[29] Unfortunately, the child himself did not have a chromosome analysis, and it remains unproven whether he carried the same balanced translocation or a corresponding deletion involving 7q22.1. The association of deletion 8p23.1 and atrioventricular canal defects provides a possible locus.[30] An association between 8p23 and heterotaxy has not been noted before, but the presence of left atrial isomerism in two of nine patients, accompanied by bilateral left lung lobation, IVC interruption, and intestinal malrotation supports this notion.[30] One of our patients and another from the Baltimore-Washington Infant Study had trisomy 13. This trisomy and other forms of aneuploidy are uncommon among heterotaxy syndromes.[17] Interestingly, none of the chromosome abnormality breakpoints on Table 6 correspond to the location of known molecular loci.[18]

Maternal diabetes

Although maternal diabetes has been reported with situs inversus,[31] the association with a broader spectrum of laterality defects has been proposed only recently (Table 7). It is difficult to interpret the significance of the 1 (10%) nontransfer and 2 (3%) total heterotaxy patients with maternal IDDM in this series. The frequency of maternal IDDM in the underlying BWH population, i.e., births with a malformation besides heterotaxy (nontransfer and total), is not available. At the BWH in 1998, figures are available for the frequency of pregestational diabetes (0.8%), gestational diabetes (3.6%), and insulin treatment (31% of 3.6% = 1.1%) (Dr. Ellice Lieberman, personal communication). These figures compare with reported estimates of 0.1–0.4%, 3–5% and 10%, respectively.[32] Based on this small case series alone, diabetes can not be reported to be a risk factor for heterotaxy. However, the predominance of polysplenia with/without left atrial isomerism in the literature and our patients is noteworthy (Table 7). Furthermore, an increased odds ratio with "overt" diabetes was noted among infants in the Baltimore-Washington Infant Study.[17,33,34] Malformations of the left-right axis in the offspring of nonobese diabetic (NOD) mice provide a model system to investigate the molecular basis of diabetic embryopathy.[35,36]

Implications for genetic counseling

Identifying an underlying etiology would improve recurrence risk assessment. In most cases, empiric risk estimates (e.g., sibling recurrence of 4%)[15,26] have been used. All heterotaxy patients require a careful family history in which the entire spectrum of laterality defects should be sought. Individual family members may require an echocardiogram, chest radiograph, or abdominal ultrasound. Prenatal ultrasound diagnosis of heterotaxy and CVMs warrants antenatal chromosome analysis. Given the current expanding knowledge of the number of mutations associated with the spectrum of laterality defects,[18] families with heterotaxy may be candidates to participate in molecular studies on a research basis.

Acknowledgments

We thank Dr. Carmen Julius for allowing us to list a previously unreported patient (Table 6). Dr. Susan Morelli provided additional clinical information about 2 patients mentioned in an abstract. Dr. Ellice Lieberman provided information on the prevalence of diabetes at the Brigham and Women's Hospital. The opinions and interpretations by the authors are their own and do not necessarily reflect those of the Massachusetts Department of Public Health, its Commissioner, or any of its agents or governing authorities.

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[1]We listed only those features which were specifically noted.
A, asian; a, autopsy; Amb, ambiguous; Ao, aorta; ASD1, atrial septal defect, primum-type; ASD2, atrial septal defect, secundum-type; ASV, aortic stenosis valvar; AV, atrioventricular valve; AVC, atrioventricular canal; B, black; BAV, bicuspid aortic valve; BSVC, bilateral superior vena cava; c, catheterization; CA, common atrium; CAVC, complete atrioventricular canal; CL/CP, cleft lip/cleft palate; COA, coarctation; CVM, cardiovascular malformation; D, dextro; DOMV, double outlet mitral valve; DORV, double outlet right ventricle; dTGA, dextro-transposition of the great arteries; DWM, Dandy-Walker malformation; DZ, dizygotic; e, echo; Eab, elective abortion; F, female; fe, fetal echo; GB, gallbladder; HC, hydrocephalus; HLH, hypoplastic left heart; IDDM, insulin-dependent diabetes mellitus; Inv, inversus; IVC, inferior vena cava; L, latino; LAI, left atrial isomerism; LB, liveborn; LTGA, levo-transposition great arteries; M, male; MA, mitral atresia; meso, mesocardia; MS, mitral stenosis; MV, mitral valve; MZ, monozygotic; ND, neonatal death; NOS, not otherwise specified; NRGA, normally related great arteries; PAP, postaxial polydactyly; PAPVR, partial anomalous venous return; PAS, pulmonary artery stenosis; P At, pulmonary atresia; PGM, paternal grandmother; PSV, pulmonic stenosis valvar; RAA, right aortic arch; RAI, right atrial isomerism; RV, right ventricle; SB, stillborn; SI, situs inversus; Sol, solitus; s, surgery; SUA, single umbilical artery; sym, symmetric; TAPVR, total anomalous pulmonary venous return; TOF, tetralogy of Fallot; Tx, transfer; Tri At, tricuspid atresia; TVS, tricuspid valve stenosis; US, ultrasound; VSD, ventricular septal defect (mal-type, malalignment-type; mem, membranous; mus, muscular).

Appendix. Clinical and cardiac features in 58 patients with heterotaxy

Patient #	Gender	Race	Birth status (death)	Method of CVM diagnosis	Cardiac position other than solitus (i.e., left), visceral situs	Spleen status, how diagnosed	Atria appendage, lung lobation, bronchial branching	Liver + gallbladder situs	IVC and aorta situs	Stomach situs
Nontransfer patients: Asplenia										
1	F	W	LB (ND)	c, s, a	Inv	Asplenia (autopsy)	Bilateral trilobed	sym	IVC on left	right
2	M	L	LB (ND)	e, c, s	Dextro, Amb	Asplenia (clinical)	Bilateral trilobed	sym	IVC inter	mid
3	M	W	LB (ND)	fe, e	Inv	Asplenia (clinical)		sym	Ao & IVC on left	right
4	M	L	LB (ND)	fe, e, c, a	Dextro, Inv	Asplenia (autopsy)	Bilateral trilobed	sym, left	IVC on right	right
5	M	A	LB (ND)	fe, e, a	Sol	Asplenia (autopsy)	Bilateral trilobed, epiarterial	sym, midline GB		
6	M	A	Eab	fe, a	Inv	Asplenia (autopsy)	RAI, Bilateral trilobed, epiarterial	sym, absent GB		right
7	M	B	LB (ND)	fe, e, c	Inv	Asplenia (US)		sym, left GB	IVC inter	right
Nontransfer patients: Polysplenia										
8	F	B	Eab	fe, a	Amb	Polysplenia (autopsy)	Indeterm atrial isomerism, bilateral bilobed	sym, left GB	IVC inter	left
9	F	B	LB	fe, a	Dextro, Sol	Polysplenia (autopsy)	Bilateral bilobed, bronchi inverted	sym	IVC inter	left
10	F	W	LB (ND)	a	Sol	Polysplenia (autopsy)	LAI, bilateral trilobed			
11	M	B	LB	e, a	Inv	Polysplenia (autopsy)	LAI, bilateral bilobed	sym	IVC inter	right
12	M	B	LB	e	Sol	Polysplenia (isotope)		right	IVC inter	left
13	F	W	LB	fe, e, c, s	Sol	Polysplenia (clinical)		right	IVC inter	left
14	F	W	LB	fe, e	Inv	Polysplenia (US)		left	IVC inter	right
15	M	W	LB (ND)	fe, e, a	Sol	Polysplenia on left (US)	Bilateral bilobed		IVC inter	
Nontransfer patients: Right spleen										
16	F	O	LB	fe, US	Inv	Right spleen (US)		sym	Ao & IVC on left, IVC inter	right
17	F	L	LB	e	Inv	Right spleen (isotope)		left	IVC post to Ao, IVC inter	right
18	F	W	LB	fe, e	Sol	Right spleen (isotope)		sym, right GB	IVC inter	left
19	F	B	LB	fe, e	Inv	Right spleen (US)		sym, GB not seen	IVC inter	right
Nontransfer patients: Unknown spleen status										
20	M	B	Eab	fe, a	Inv	Unknown			Ao & IVC on left	right

Ventricle loop	Looping other than solitus, great arteries	Great veins	Atria, ventricles	Valves	Noncardiac malformations	Associated condition
D	dTGA DORV	TAPVR	CAVC, CA, ASD1, ASD2	PSV	Anomalous ureter, fused adrenal glands	MZ twin
L	DORV	TAPVR	CAVC, CA	P At	Bilateral cervical ribs	
D, single RV	dTGA	TAPVR	CAVC, CA	P At	Mild HC, NOS	
D	DORV	TAPVR	incompl AVC, ASD1, ASD2	P At, Tri At, DOMV, BAV		
single RV	DORV	TAPVR BSVC	CAVC, CA, single RV		Malrotation	Sister (Tx): heterotaxy, polysplenia
D	dTGA	PAPVR	ASD1	P At, MV hypo	Bilateral CL/CP, absent gallbladder	
D, single RV	DORV		CAVC, CA, VSD inlet PSV			
D	DORV (TOF), RAA		CAVC, CA, VSD inlet	PSV, subPS		
L	RAA	BSVC	ASD2, VSD mus			
D			ASD2		SUA, diaphragmatic hernia	Mother: IDDM
D			partial AVC, CA	cleft MV		
D			ASD2		Duodenal atresia, malrotation	Brother: jejunal atresia
D		TAPVR	ASD2, VSD mem	TVS	Anal atresia, ear pits, absent vagina, uterus, malrotation, absent R kidney, cervical ribs, bifid uvula	Mosaic 46,XX/47,XX + mar/47,XX del 22q
D				BAV, AS		
D	COA		incompl AVC, ASD1	PSV, cleft MV, MS, subAS	DWM, malrotation, fusion ribs 10–12	Relative NOS: spina bifida
D			ASD2		Biliary atresia	
D			ASD2, VSD mus			
D			ASD2		HC, thin corpus callosum	
D					11 ribs, malrotation	DZ twin
D	poss "TGA"		CAVC	probable P At	SUA	
D, single RV	dTGA		CAVC, CA, ASD1	PSV, subPS	Abdominophagi, omphalocele, fused heart, sternum, intestine, GB, liver	Conjoined twin

Appendix continues on the next two pages.

Appendix. (*Continued*)

Patient #	Gender	Race	Birth status (death)	Method of CVM diagnosis	Cardiac position other than solitus (i.e., left), visceral situs	Spleen status, how diagnosed	Atria appendage, lung lobation, bronchial branching	Liver ± gallbladder situs	IVC and aorta situs	Stomach situs
Transfer patients: Asplenia										
1t	M	W	LB (ND)	fe, a	Inv	Asplenia (autopsy)	Bilateral trilobed	sym		right
2t	F	O	LB (ND)	fe, a	Amb	Asplenia (autopsy)	Bilateral trilobed	sym		
3t	F	W	LB (died 2 yrs)	fe, e, c, s, a	Dextro, Inv	Asplenia (autopsy)	Bilateral trilobed		IVC midline	right
4t	M	W	LB (died 2 mos)	fe, e, a	Inv	Asplenia (autopsy)	Bilateral trilobed	sym, right GB	IVC on right	right
5t	M	W	LB	fe, e, c, s	Sol	Asplenia (US)	LAI	sym, right GB	Ao & IVC on right	
6t	F	W	Eab	fe, a	Sol	Asplenia (autopsy)	Bilateral trilobed, epiarterial	right		left
7t	F	A	Eab	fe, (a)	Dextro, Inv	Asplenia (clinical)				
8t	F	W	LB (ND)	fe, e, s	Amb	Asplenia (clinical)		sym	Ao & IVC on right	mid
9t	F	A	LB	fe, e, c, s	Inv	Asplenia (clinical)		sym	Ao & IVC on right	
10t	M	W	LB (ND)	fe, e, c, s, a	Meso, Inv	Asplenia (autop)	Bilateral trilobed, epiarterial	left, left GB	IVC on left	right
11t	F	W	LB	fe, e, c, s	Dextro, Sol	Asplenia (US)		sym	IVC & Ao on left	
12t	F	A	LB (ND)	fe, e, s	Sol	Asplenia (US)		sym		
13t	F	W	LB (ND)	fe, e, a (lungs)	Dextro, Amb	Asplenia (clinical)	Bilateral trilobed			
14t	F	L	LB	fe, e, c	Dextro, Amb	Asplenia (isotope)		sym	IVC & Ao on left	mid
15t	M	W	LB (ND)	fe, e, s	Dextro, Inv	Asplenia (clinical)	Atria and bronchi inverted		IVC on left	right
16t	F	W	LB	fe, e	Amb	Asplenia (US, scan)	Bilateral epiarterial		IVC & Ao on left	left
17t	M	W	LB	fe, e	Dextro, Inv	Asplenia (US, peripheral blood smear)		left	IVC on left	right
18t	M	W	Eab	fe, a	Inv	Asplenia (clinical)			IVC inter	right
Transfer patients: Normal left spleen										
19t	F	W	LB	fe, e	Sol	Left spleen (US)	Atrial and bronchial inversion	sym right, right GB	IVC inter, Ao midline	left
Transfer patients: Polysplenia										
20t	F	B	SB	a	Inv	Polysplenia (autopsy)	Bilateral bilobed			right
21t	F	W	LB	e	Sol	Polysplenia (surgery)		right	IVC inter	left
22t	M	W	Eab	a	Sol	Polysplenia (autopsy)		right		left
23t	F	W	LB (ND)	a	Inv	Polysplenia (autopsy)	Bilateral bilobed	sym, absent GB		right

Ventricle loop	Looping other than solitus, great arteries	Great veins	Atria, ventricles	Valves	Noncardiac malformations	Associated condition
D	dTGA	TAPVR	CAVC, CA	P At	Myelomeningocele, HC, uterus unicollus, malrotation	
L, single RV	DORV, RAA	TAPVR	CAVC, CA	PSV	Synophrys, slender fingers, large halluces	
D	dTGA	TAPVR	CAVC, CA, VSD mus	PSV, PAS, subPS	Epicanthal folds, absent thymus (possible DiGeorge syndrome)	Brother: DiGeorge syndrome, possible familial DGS. (mother: gest DM)
D, single RV	DORV, RAA	TAPVR	CAVC, CA	PSV		Maternal uncle: Poland anomaly; MZ twin
D	dTGA, RAA	TAPVR	CAVC, CA, ASD1, ASD2	P At	SUA	MZ twin. Co-twin: female, tetradiploidy mosaic without heterotaxy
D, single RV	indeterminate		CAVC, CA	PSV		
D	dTGA, RAA	TAPVR	CAVC	P At		
D	dTGA, RAA	TAPVR	CAVC, ASD2	P At, right PAS	Malrotation, hiatal hernia	
D	DORV, RAA	TAPVR BSVC	incompl AVC, ASD2	P At	Malrotation	
L	LTGA, RAA	TAPVR	CAVC	P At, right PAS	Malrotation	Cousin: CVM NS
D	dTGA	TAPVR	CAVC	PSV		Previous Eab: Trisomy 18
D	DORV	TAVPR, BSVC	CAVC, ASD1	PSV, subPS	Bilateral cervical ribs, 11 thoracic ribs	
indet, single ventr	DORV, RAA	TAPVR, BSVC	CAVC, CA	P At, right AV valve atresia	Thoracic hemivertebrae	
L	DORV vs TGA	BSVC, TAPVR	CAVC, CA, single ventricle	P At		
D	dTGA, DORV, RAA		CAVC, HLH, ASD1, ASD2	subPS	Malrotation	FOB: PS, GGF: died PS, MZ twin
L	DORV, RAA	TAPVR	CAVC, CA, single ventricle	PSV		
L	DORV		CAVC	P At		Sister (also Tx): heterotaxy, see below
L	Inverted (NRGA for SI), RAA	PAPVR	ASD2		Right duplex kidney, ureter	Brother (also Tx): heterotaxy, see above
D			VSD mem	TV abn	Malrotation	
D			ASD2		Duodenal atresia, annular pancreas, malrotation	
L, single LV	LTGA		CA	P At	PAP, horseshoe kidney, absent cerebellar vermis, scalp defect	Trisomy 13
D			ASD1		Malrotation, absent GB	
L	Indeterm, RAA hypo Ao	BSVC	CAVC, CA	subAS, ASV	Malrotation, duodenal web	Maternal uncle: AS; PGM: probable septal defect, NS

Appendix continues on the next two pages.

Appendix. (*Continued*)

Patient #	Gender	Race	Birth status (death)	Method of CVM diagnosis	Cardiac position other than solitus (i.e., left), visceral situs	Spleen status, how diagnosed	Atria appendage, lung lobation, bronchial branching	Liver ± gallbladder situs	IVC and aorta situs	Stomach situs
24t	F	W	LB (ND)	e,c,a	Dextro, Inv	Polysplenia (autopsy)	LAI, bilateral bilobed	left, left GB	IVC & Ao on right, IVC inter	right
25t	F	W	LB	fe, e, c, s	Amb	Polysplenia (US)		sym	IVC inter	
26t	F	O	LB	fe, e	Sol	Polysplenia (US)	Bilateral hyparterial	right	IVC inter	left
27t	F	W	Eab	fe, a	Sol	Polysplenia (clinical)	LAI	sym		left
28t	F	W	LB (died 11 mos)	fe, e, c, a	Sol	Polysplenia (autopsy)		right	IVC inter	left
29t	F	W	LB	fe, e	Inv	Polysplenia		sym	IVC & Ao on left	right
30t	F	A	LB	fe, e, c, s	Inv	Polysplenia (clinical)			IVC inter	right
31t	F	L	LB fe, e	Inv	Polysplenia (US)		sym	IVC inter	right	D
Transfer patients: Right spleen										
32t	M	W	LB	fe, e	Inv	Right spleen (isotope)		sym	IVC inter	
33t	M	W	LB	fe, e, c, s	Inv	Right spleen (isotope)	Atrial and bronchial inversion	sym, right GB	IVCinter	right
34t	F	W	LB	fe, e, s	Dextro, Inv	Right spleen (US)		sym	IVC on left, IVC inter	right
35t	F	A	LB	fe, e	Inv	Right spleen (isotope)			IVC & Ao on right	right
36t	M	W	LB	fe, e	Inv	Right spleen (isotope)		sym, left, left GB	IVC inter	right
37t	F	W	LB	fe, e	Inv	Right spleen (isotope)		sym	IVC inter	right
38t	F	W	LB	fe, e	Dextro, Inv	Right spleen (isotope)		sym	IVC on left	right

Ventricle loop	Looping other than solitus, great arteries	Great veins	Atria, ventricles	Valves	Noncardiac malformations	Associated condition
D	DORV, COA	PAPVR BSVC	CAVC, ASD1, ASD2, VSD mus	M At, subAS		
D	hypo ao		CAVC, CA, ASD1, VSD multiple	MV cleft	Malrotation	
D	DORV	CAVC, VSD mal-type	PSV		Sister: heterotaxy (not in study)	
D	DORV, hypo Ao	BSVC	CAVC, ASD cor sinus, VSD mus	subAS	Malrotation, SUA	
D		PAPVR, BSVC	CAVC, CA	MV cleft	Malrotation	PGM: possible AVC; Maternal great great aunt: CVM NS
D		BSVC	CAVC, CA, VSD mus	PSV, BAV, subAS	Duodenal stenosis, malrotation	Brother: heterotaxy, asplenia (Non)
	COA		ASD2, VSD mus	BAV	Malrotation, absent GB	
L	DORV, RAA		CAVC, CA			
D, single RV	dTGA, RAA		CAVC, CA, VSD mus	P At		
L	Inverted (NRGA for SI), RAA		ASD1	MV cleft, subAS	Duodenal stenosis, malrotation, hypothyroid	
L	DORV (LTGA in SI), RAA	TAPVR	CAVC, CA	PSV		
D						
L	DORV	PAPVR	CA, VSD mal-type	TVS, P At		Brother: CVM NS
D	DORV, RAA	BSVC	CA, VSD inlet	P At	Dandy-Walker malformation, malrotation, hemivert T12-L1	