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Birth defect co-occurrence patterns in the Texas Birth Defects Registry

Renata H. Benjamin¹, Angela E. Scheuerle², Daryl A. Scott^{3,4}, Maria Luisa Navarro Sanchez¹, Peter H. Langlois^{5,6}, Mark A. Canfield⁵, Hope Northrup⁷, Christian P. Schaaf^{3,8,9}, Joseph W. Ray¹⁰, Scott D. McLean¹¹, Han Chen^{1,12}, Michael D. Swartz¹³, Philip J. Lupo^{#14}, A.J. Agopian^{#1}

¹ Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, Texas

² Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, Texas

³ Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas

⁴ Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas

⁵ Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas

⁶ Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Austin, Texas

⁷ Department of Pediatrics, Division of Medical Genetics, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas

⁸ Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas

⁹ Heidelberg University, Institute of Human Genetics, Heidelberg, Germany

¹⁰ Department of Pediatrics, Division of Medical Genetics and Metabolism, University of Texas, Medical Branch, Galveston, Texas

¹¹ Clinical Genetics Section, The Children's Hospital of San Antonio, San Antonio, Texas

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Corresponding author: Dr. A.J. Agopian, UTHealth School of Public Health, Department of Epidemiology, Human Genetics and Environmental Sciences, 1200 Pressler, Houston, TX, 77030, a.j.agopian@uth.tmc.edu, Phone: 713-500-9815.

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RHB contributed to study conception and design, data analysis and interpretation, drafted the article, and approved the final version; AES & DAS contributed to study conception and design, data analysis and interpretation, article revisions, and approved the final version; MLNS & HC contributed to data analysis and interpretation, article revisions, and approved the final version; PHL & MAC contributed to study data acquisition, article revisions, and approved the final version; HN, CPS, JWR, SDM, & MDS contributed to study conception and design, article revisions, and approved the final version; PJJ & AJA contributed to study conception and design, acquisition of data, analysis and interpretation, article revisions, and approved the final version.

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¹² Center for Precision Health, UTHealth School of Biomedical Informatics, Houston, Texas

¹³ Department of Biostatistics and Data Science, UTHealth School of Public Health, Houston, Texas

¹⁴ Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas

These authors contributed equally to this work.

Abstract

Background: The population-level landscape of co-occurring birth defects among infants without a syndromic diagnosis is not well understood.

Methods: We analyzed data from 40,771 infants with two or more major birth defects in the Texas Birth Defects Registry (TBDR; 1999–2014). We calculated adjusted observed-to-expected (O/E) ratios for all two, three, four, and five-way combinations of 138 major defects.

Results: Among 530 patterns with the highest adjusted O/E ratios (top 5% of 10,595 patterns), 66% included only defects co-occurring within one organ system and 28% were suggestive of known patterns (e.g., midline developmental defects). Of the remaining patterns, the combination of defects with the highest O/E ratio (193.8) encompassed diaphragm, spine, spleen, and heart defects. Fourteen patterns involved heart and spine defects with or without rib defects. Ten additional patterns primarily involved two hallmark components of VACTERL association (specifically, vertebral defects, anal atresia, cardiac defects, renal, or limb defects, but not tracheoesophageal fistula).

Conclusions: Our analyses provide a description of the birth defect co-occurrence patterns in a multi-ethnic, population-based sample, and revealed several patterns of interest. This work complements prior work that has suggested etiologic connections between select defects (e.g., diaphragmatic hernia and heart and spleen anomalies; heart and spine defects).

Introduction

An estimated 15–30% of infants born with a birth defect will have more than one malformation.^{1–5} Some of these infants have a syndromic condition with a known genetic, chromosomal, or teratogenic aetiology (e.g., trisomy 21, valproic acid) or an identifiable sequence of associated defects attributable to a single primary defect (e.g., Potter sequence). However, an estimated 50% of patients seen in medical genetics clinics do not receive a diagnosis encompassing the co-occurring birth defects.⁶ While co-occurrence of multiple defects in the same individual is common, the population-level landscape of different patterns of birth defect co-occurrence among infants without a syndromic diagnosis is not well understood. Describing patterns involving two or more defects may help researchers and clinicians better understand which combinations of defects co-occur more frequently than would be expected based on their prevalence in the population. This foundational work may also help to identify groups of cases with similar phenotypes, which could ultimately have implications related to shared etiologic mechanisms that could be further investigated.^{7,8}

To date, the characterization of new birth defect patterns (e.g., syndromes) has primarily relied on clinicians' recognition of phenotypic or genetic patterns within relatively small, clinical populations; however, some recurrent phenotypic patterns may be so uncommon that a single clinical practice will not see sufficient patients to identify those patterns. Therefore, our group has recently developed a software platform for analysing co-occurrence patterns that occur more frequently than expected in large data resources (i.e., birth defects registries), which could help identify new patterns.⁹

Our objective was to identify and characterize combinations of defects that co-occurred more frequently than expected in a large, population-based registry. To do so, we used statewide data from the Texas Birth Defects Registry (TBDR). For each combination of two to five co-occurring birth defects, we calculated an adjusted observed/expected ratio to identify the combinations that co-occurred more frequently than expected based on their population prevalence.

Methods

Data from the TBDR, which is managed by the Birth Defects Epidemiology and Surveillance Branch at the Texas Department of State Health Services, was obtained for deliveries to Texas residents occurring between 1999 and 2014. The TBDR conducts active surveillance for birth defects among live births, still births, terminations, and fetal deaths at relevant hospitals, clinics, and birthing centers throughout the state.¹⁰ To be included in the registry, infants must have at least one of the monitored structural birth defects or a chromosomal abnormality diagnosed by one year of age. This project was approved by the Institutional Review Board of the Texas Department of State Health Services and the UTHealth Committee for the Protection of Human Subjects.

Birth defects in the TBDR are recorded using modified six-digit British Pediatric Association (BPA) codes.^{11,12} As our objective was to identify potentially novel syndromes and associations, we excluded infants with a documented syndromic diagnosis. Excluded syndromic diagnoses included chromosomal anomalies (e.g., trisomy 21, 22q11.2 deletion syndrome), syndromes (e.g., Marfan syndrome, Goldenhar syndrome), and sequences/associations (e.g., VACTERL association, Potter sequence) recorded in the abstracted record. We restricted analyses to infants with major structural birth defects based on input from medical geneticists at the TBDR and criteria used to define minor defects in the National Birth Defects Prevention Study.¹³ To analyze distinct groups of defects, BPA codes were grouped by the first 4 digits, as detailed in the Supplemental Appendix.⁹ Singleton pregnancies resulting in live births, still births, fetal deaths, or terminations with two or more major birth defects were included in analyses.

Maternal and infant demographic characteristics were tabulated in order to describe the study cohort. We then used the R-based software platform, Co-Occurring Defect Analysis (CODA),⁹ to analyze two, three, four, and five-way combinations of defects observed in the TBDR. CODA calculates an adjusted observed-to-expected (O/E) ratio, based on the method developed by Khoury, et al.¹⁴ Briefly, the adjusted O/E ratio compares the observed prevalence of a birth defect combination to the prevalence that would be expected based

on the population prevalence of each defect in the combination. The adjustment method accounts for the tendency of the birth defects in a given combination to co-occur with any other defects. An O/E ratio greater than 1 indicates that the combination occurs more frequently than would be expected if the defects occurred independently of one another.

After calculating adjusted O/E ratios for all observed two to five-way combinations in the study population, we reviewed the top 5% of patterns of defects with the highest adjusted O/E ratios that had five or more cases observed. Among these, combinations that consisted of only defects within the same system (e.g., two or more eye defects only) or were suggestive of heterotaxy (e.g., heart defect with only lung, spleen, and/or intestinal fixation anomalies)^{15,16} were tabulated and removed from further consideration. Two medical geneticists (A.E.S. and D.A.S.) reviewed the remaining combinations, including individual-level detailed birth defects descriptions, to assess whether the combinations were suggestive of known syndromes or patterns. Thus, the remaining combinations represented the top patterns of interest, defined as the top 5% of combinations that 1) included defects in multiple systems and 2) were not suggestive of known syndromes or patterns. A Venn diagram was constructed *post hoc* to visualize organ system overlap among these top patterns of interest (e.g., the number of the top combinations that involved both heart and spine defects). Due to the large number of observed combinations with heart, spine, and rib defects, we also conducted a *post hoc* tabulation of the full six digit BPA codes present in these cases to determine if the vertebral defect level was spatially closer to the heart/ribs (i.e., thoracic level vertebral defects, BPA codes: 756.150–756.156) or at a different level among cases with these patterns.

Results

There were 40,771 infants with 2 major birth defects recorded in the TBDR delivered between 1999 and 2014 and there were 6,181,631 live births in Texas during the same time period. Maternal and infant demographic characteristics for the analytic sample are shown in Table 1. A majority of mothers of children with 2 defects were between 20–29 years old (53%). Fifty-one percent of mothers were Hispanic, 40% of mothers had at least some college education, and 50% of mothers were overweight or obese prior to pregnancy. After running CODA to analyze co-occurrence patterns for 138 major birth defects groups, there were 10,595 observed combinations of two to five defects with at least five individuals. We reviewed the 530 patterns with the highest adjusted O/E ratios (i.e., the top 5% of all eligible combinations).

Of the 530 patterns we evaluated, 352 patterns (66%) were comprised of only two to five defects in the same organ system (Figure 1). Of these same-system defect combinations, 312 of the combinations involved multiple heart defects. Eye and limb defect combinations were the second and third most frequent same-system patterns observed, with 17 and 9 combinations, respectively.

Of the remaining combinations, which consisted of defects in multiple systems, 94 combinations (18%) were suggestive of heterotaxy (Figure 1). The remaining 84 combinations were reviewed by two medical geneticists (A.E.S. and D.A.S.), and 57 (68%)

of these combinations also included defects that likely reflected known syndromes or patterns. Patterns associated with midline developmental defects affecting the brain, eye, and face (e.g., nose defects, cleft lip) were the most frequently observed (26 patterns) and 50% of the cases with those patterns of defects had holoprosencephaly recorded in the TBDR. Patterns reflective of spina bifida co-occurring with associated anomalies, including limb (e.g., clubfoot), spine, and renal defects, were also frequently observed (9 patterns). Patterns suggestive of OEIS (Omphalocele, Exstrophy, Imperforate anus, and Spinal defects) and Bladder-Exstrophy-Epispadias Complex (4 patterns), VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, TracheoEsophageal fistula, Renal, Limb; 3 patterns) and gastroschisis co-occurring with associated anomalies (gastroschisis with intestinal anomalies; 2 patterns) were also noted.

The remaining 27 top combinations that did not clearly represent an identifiable association or developmental sequence are shown in Table 2. The adjusted O/E ratios for these patterns ranged from 63.0 to 193.8 and the combination with the highest adjusted O/E ratio included atrial septal defects, spinal defects (e.g., vertebral defects), diaphragm defects (e.g., congenital diaphragmatic hernia), and spleen defects. This was one of only two top combinations involving diaphragm or spleen anomalies, with the other being combination 19 in Table 2, which included three of the same defect categories (spine, diaphragm, and spleen) and included five of the same infants, with one additional case.

Over half of the 27 top combinations included in Table 2 (n=14) comprised one or more heart defect with co-occurring spine defects. For example, pattern 13 included heart and spine defects only, while pattern 16 consisted of heart, lung, and spine defects. In fact, four of the five cases with pattern 16 had scimitar syndrome, a type of partial anomalous pulmonary venous return. The other twelve heart-spine patterns comprised only heart, spine, and rib defects with no other systems involved (patterns 2–4, 6–7, 9, 14–15, 20–22, 26). In *post hoc* analyses of cases with only heart, spine, and rib defects in the pattern, we looked at the six-digit BPA codes for the 23 unique cases in these patterns to examine vertebral defect level in order to determine if the defect was spatially close to the heart/ribs (thoracic level). All 23 cases had defects of the thoracic vertebrae recorded (more than one vertebral defect could be recorded per case); 10 had thoracic hemivertebrae (43%) and 17 had other anomalies of the thoracic vertebrae (74%).

Ten additional patterns involved combinations with two defects in the following systems: heart, spine, limbs, anal atresia/stenosis, or renal. Considering these and the 14 combinations with heart and spine defects described above, 24 combinations involved two hallmark features of VACTERL (25 with the inclusion of pattern 1), but none included tracheoesophageal fistula, a common hallmark VACTERL feature. We constructed a Venn diagram *post hoc* to visualize organ system overlap among the five VACTERL component organ systems represented among these results: anomalies of the spine, anal atresia (atresia and stenosis of large intestine, rectum, and anal canal), heart, renal, and limb defects (Figure 2). The count displayed in the Venn diagram represents the number of top combinations that included the indicated defects. For example, among the top 27 combinations, heart and spine defects were represented the most frequently (present in 15 patterns), followed by heart and limb defects (present in three patterns).

Finally, one additional combination involved reduction anomalies of the brain, congenital hydrocephalus, anomalies of spine, and anomalies of ribs and sternum. Our review of individual data did not reveal a consistent pattern among these cases; two of the seven individuals with this pattern of defects had holoprosencephaly recorded in the TBDR, while none of the individuals had spina bifida.

Discussion

We aimed to describe patterns of multiple birth defects observed much more frequently than expected and to identify unique patterns of co-occurring phenotypes, which may indicate a shared etiological basis for the observed pattern of defects. In this population-based analysis of birth defect co-occurrence patterns among infants without a syndromic diagnosis in the TBDR, we identified several interesting patterns, including birth defect combinations that may represent novel patterns.

The pattern with the highest adjusted O/E ratio consisted of heart, vertebral, diaphragmatic, and spleen anomalies. All of the infants with this pattern of defects had congenital diaphragmatic hernia (CDH). Non-isolated CDH can occur with chromosomal abnormalities (e.g., trisomy 18) and genetic syndromes (e.g., Fryns syndrome, Cornelia de Lange syndrome),^{17–19} however, co-occurring heart, spine, and spleen anomalies are not defining features of these syndromes. While the majority of instances of CDH have no identified etiological basis,^{19,20} recent genetic studies investigating infants with multiple malformations and CDH have reported genetic variants associated with specific patterns of co-occurring defects. For example, infants with pathogenic variants in *MYRF* commonly have CDH, heart defects (including scimitar syndrome) and genitourinary abnormalities.^{21,22} Similarly, *HLX* has been reported as a candidate gene for a pattern of anomalies that included CDH, short bowel, and asplenia.²³ While infants with patterns 1 and 19 had CDH with co-occurring heart and spleen defects, they were phenotypically different from the infants with shared genetic variants reported in these prior publications. More work is needed to better understand whether the co-occurrence of the defects observed in our data could reflect a shared etiological basis.

Another pattern of note involved heart (anomalies of great veins), lung, and vertebral defects (Table 2; pattern 16). Four of the five cases with this pattern of defects had scimitar syndrome, an anomaly involving partial anomalous pulmonary venous return directly to the systemic venous system.²⁴ While lung malformation, specifically hypoplasia, is a component of scimitar syndrome, co-occurring vertebral defects are less common. Masrani et al. examined co-occurring defects in a cohort of 16 scimitar syndrome patients and noted vertebral anomalies in only one patient.²⁵ There may be a shared etiological mechanism in this cluster of cases given the infrequency of co-occurring scimitar syndrome and vertebral defects reported previously. More work is needed to confirm and better understand this possible connection.

Many of the top observed patterns included combinations of heart, spine, and rib anomalies. Heart defects and vertebral anomalies can co-occur in syndromic conditions (e.g., Goldenhar syndrome)²⁶ and have been reported to co-occur among infants without an identified

syndrome. An estimated 10–37% of infants with vertebral malformations have cardiac anomalies.^{27–29} Rib defects also commonly co-occur with both. A study looking at co-occurring defects among infants with rib anomalies found that 72% of the infants without a syndromic diagnosis also had a vertebral anomaly and 40% had a heart defect.³⁰ Disruptions of development during vertebral fusion or segmentation, perhaps via mutations in notch signaling pathway genes (*DLL3*), alterations in genes involved in vertebral development (e.g., *PAX1*, *PAX9*), or environmental factors (e.g., maternal hyperglycemia), can result in vertebral and rib malformations.^{31–33} Martínez-Frías described segmentation anomalies of the vertebrae and ribs as developmental field defects arising from failure of segmentation of the preaxial mesoderm at 4–6 weeks of gestation.³⁴ Cardiac structures also arise from the mesoderm and these patterns of defects suggest that a disturbance during early development could contribute to a developmental field defect affecting these systems.³⁵ Given the high rates of co-occurring defects in these systems and heterogeneous presentation among our results, there were likely multiple causes involved, and future work may shed further light on potential developmental overlap.

Nearly all of the top observed patterns contained two features of VACTERL association, which represents a non-random group of defects known to co-occur.^{36,37} VACTERL, a heterogeneous spectrum, it is typically only diagnosed when three or more characteristic defects are present and other syndromic causes have been ruled out.^{36–40} There is some evidence for “caudal” VACTERL patterns, resulting in anal atresia, renal, and lower vertebral defects and “cranial” patterns involving tracheoesophageal fistula, upper vertebral, and preaxial limb defects.^{38,41} Moreover, some of our results may additionally support the possibility of a spectrum of VACTERL-like combinations. Despite exclusion of 517 cases with VACTERL recorded in the medical record, 25 patterns in our top results contained two of the component defects. Further, none of the cases in any of our top 27 combinations had tracheoesophageal fistula, which is estimated in some studies to be the most common VACTERL defect, present in up to 80% of VACTERL cases.^{37,40} It is unclear if some of these two-way combinations of VACTERL components that occurred much more frequently than expected might be etiologically related to VACTERL. Since this was a registry study, no further clinical examination or screening could be completed, and it is possible that additional VACTERL component defects were missed in some of these cases. Regardless, our findings support and reinforce the importance of screening patients with patterns suggestive of VACTERL for additional defects.

As expected, many of the top 530 patterns reflected known patterns. For example, multiple defects within the same organ (e.g. heart or eye) occurred much more frequently than expected. This may be a reflection of the known co-occurrence of defects in the same organ system⁴² and the likelihood of finding additional defects when one defect is present and additional evaluations of the affected system are undertaken. It may also be a consequence of TBDR procedures that lead to detailed recording of all reported defects. Midline developmental defects and known associations (e.g., spina bifida with associated defects) were also reflected in patterns with high adjusted O/E ratios. Several of the midline developmental patterns included orofacial clefts; though they are not presented in Table 2, defects co-occurring with orofacial clefts in the TBDR have been previously described.⁴³ Analyses that group infants with birth defects into isolated and non-isolated

cases without accounting for these established co-occurrence patterns may classify cases as multimalformed when they may more accurately be classified as isolated for some analyses. In our analyses, certain infants with one primary defect and additional secondary, related defects could have been reclassified as “isolated” cases. For example, an infant with spina bifida, clubfoot, and tethered cord could be considered as isolated spina bifida. However, classification of isolated-sequence cases should be done after careful review of the recorded defects and their descriptions and after developing objective criteria establishing which defects would be considered secondary for all defects of interest.⁴⁴ Many birth defects registries do not have resources for a manual clinical review for all cases (e.g., thousands of records) and criteria may vary from study to study. While this individual review and reclassification was beyond the scope of this study looking at all observed patterns for all defects, the large proportion of patterns with same-system defects and defects suggestive of sequences further reinforces the importance of considering the impact of etiologically related defects on classification of multiple versus isolated cases.

Several factors may have affected our analyses. First, at the time of study onset, data were only available through 2014. While it is not unusual for availability of registry data to lag for several years following birth due to ascertainment and quality control procedures, inclusion of additional recent cases may have changed our results. Secondly, the TBDR relies on abstracted medical records, including progress notes, genetic testing results, and operative reports, to classify defects and syndromic conditions. Our analyses could not account for potential differences in the type or number of clinical evaluations of the same infant, which may have generated additional recorded defects and more specific diagnoses, and some diagnoses may have been made after the first year of life, including genetic testing undertaken after the first year, or in settings that were not included in the Registry’s active surveillance. As a result, some infants with a syndrome may have been included in analyses of non-syndromic cases. Finally, no standard system exists for grouping defects and analyzing co-occurrence patterns. We grouped defects based on the first four digits of the BPA code, however, other more broad or specific groups could have been analyzed. Because these broad groupings have been given general names (e.g., anomalies of spine), additional details have been provided in the Supplemental Appendix. Differences in ascertainment procedures, coding of defects, and analytic grouping could affect the reproducibility of these results.

Strengths of this study included our utilization of a large, population-based birth defects registry with active surveillance to recognize rare birth defect patterns that could go undetected by clinical observation among individual clinicians, who might be unlikely to see enough cases to make the connection. Using data from a single registry ensured consistent ascertainment and classification protocols. Our approach also assessed patterns occurring much more frequently than would be expected given their observed prevalence in the population and adjusted for the frequency with which defects in a pattern tend to co-occur with other defects.

Conclusions

In this analysis of over 40,000 infants with multiple malformations, we found that the majority of patterns occurring more frequently than expected involved multiple defects within the same organ system and known associations. Nearly all of the top patterns (beyond same system and those suggestive of known associations) involved organ systems that are components of the VACTERL association, with heart, spine, and rib defect patterns being the most common. Several patterns of potential interest for further investigation were noted and future work could be undertaken to replicate our findings and further assess groups of infants with CDH, heart, spine, and/or spleen defects and scimitar syndrome with vertebral defects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact Statement:

- In this large-scale, population-based study of birth defect co-occurrence patterns, we found several birth defect combinations of potential interest that warrant further investigation: congenital diaphragmatic hernia, heart, spine, and spleen defects and scimitar syndrome with vertebral defects.
- The majority of patterns of co-occurring defects observed more frequently than expected involved multiple defects within the same system and combinations suggestive of known associations.
- Nearly all of the top patterns (beyond same system and those suggestive of known associations) involved organ systems that are components of the VACTERL association, with heart, spine, and rib defect patterns being the most common.

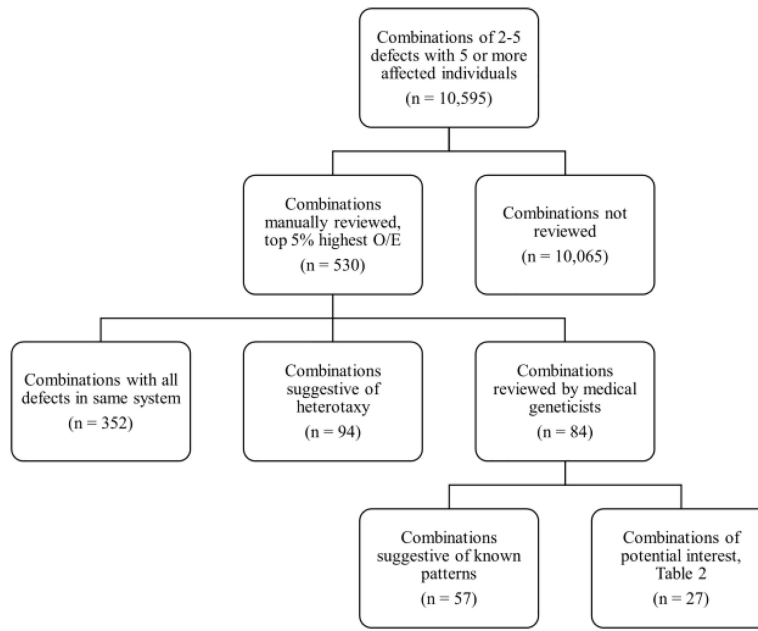


Figure 1. Flow chart of the review process of top birth defect combinations among non-syndromic cases, Texas Birth Defects Registry, 1999–2014

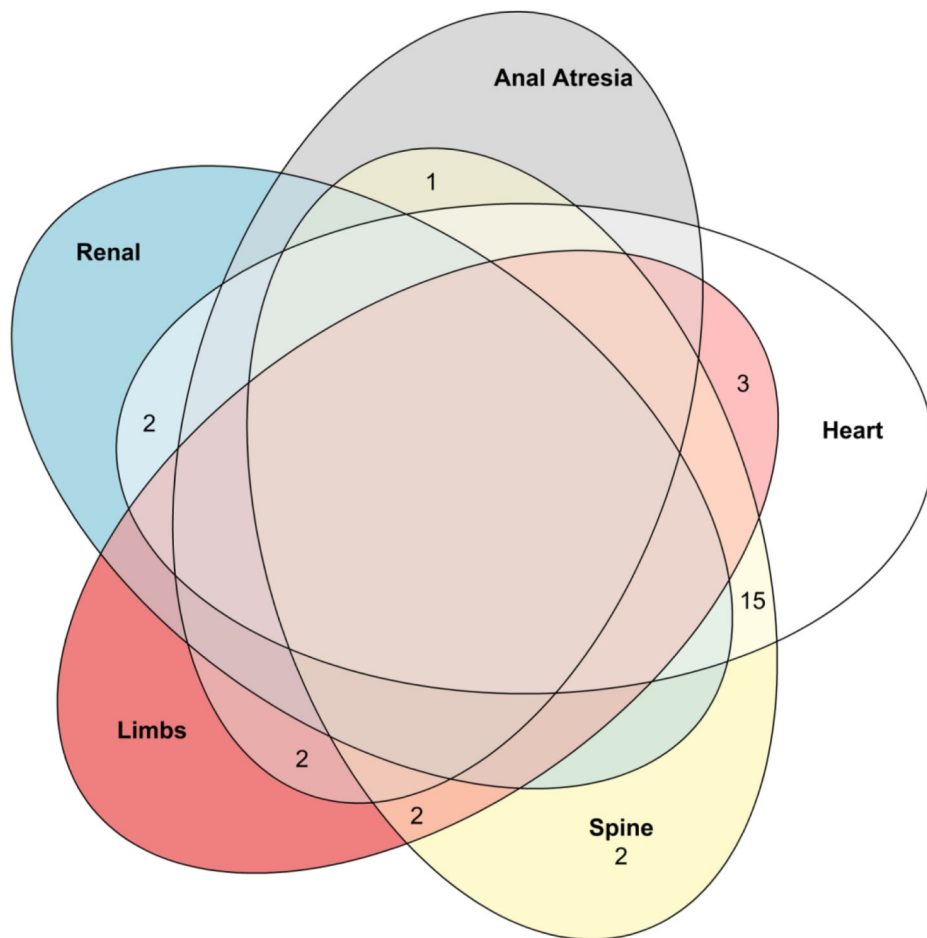


Figure 2. Venn diagram of the five VACTERL component organ systems represented in the top 27 birth defect patterns, where the count represents the number of combinations that include the indicated defects (e.g., 15 of the top 27 combinations include heart and spine defects), Texas Birth Defects Registry, 1999–2014

Table 1.

Maternal and infant demographic characteristics of infants with two or more major birth defects in the Texas Birth Defects Registry (n=40,771), 1999–2014

Demographic characteristic	N (%) ^a
Maternal age (years)	
<20	5416 (13.3)
20–29	21 505 (52.7)
30–39	12 778 (31.3)
40	1070 (2.6)
Maternal race/ethnicity	
White non-Hispanic	14 151 (34.7)
Black non-Hispanic	4278 (10.5)
Hispanic	20 799 (51.0)
Other	1519 (3.7)
Maternal education	
<High school	11 671 (28.6)
High school	12 071 (29.6)
>High school	16 101 (39.5)
Maternal prepregnancy body mass index (kg/m ²) ^b	
Underweight (<18.5)	1204 (4.3)
Normal (18.5 – <25)	12 889 (45.9)
Overweight (25 – <30)	6630 (23.6)
Obese (≥ 30)	7388 (26.3)
Infant sex	
Male	21 424 (52.5)
Female	19 210 (47.1)

^aPercentages may not sum to 100 due to missing values and/or rounding.

^bMaternal prepregnancy weight and height available beginning in 2005.

Table 2. Top defect patterns, ranked by adjusted observed-to-expected ratio (O/E), in the Texas Birth Defects Registry, 1999–2014

Rank	Defect 1	Defect 2	Defect 3	Defect 4	Defect 5	N ^a	O/E
1	Ostium secundum type atrial septal defect	Anomalies of spine	Anomalies of diaphragm	Anomalies of spleen		5	193.8
2	Ostium secundum type atrial septal defect	Coarctation of aorta	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum	6	112.9
3	Coarctation of aorta	Other anomalies of aorta	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum	6	105.7
4	Common truncus	Other anomalies of aorta	Anomalies of spine	Anomalies of ribs and sternum		5	98.4
5	Varus (inward) deformities of feet	Other specified anomalies of unspecified limb	Anomalies of spine	Anomalies of ribs and sternum		6	95.8
6	Ventricular septal defect	Other specified anomalies of the heart	Anomalies of great veins	Anomalies of spine	Anomalies of ribs and sternum	6	93.4
7 ^b	Coarctation of aorta	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum		9	87.5
8	Atresia and stenosis of large intestine, rectum, and anal canal	Indeterminate sex	Reduction defects of upper limb			7	84.2
9	Other specified anomalies of the heart	Other anomalies of aorta	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum	6	83.4
10	Other deformities of feet	Other specified anomalies of unspecified limb	Anomalies of spine	Anomalies of ribs and sternum		6	81.6
11	Ostium secundum type atrial septal defect	Other anomalies of aorta	Reduction defects of upper limb	Other anomalies of upper limb including shoulder girdle		6	80.8
12	Atresia and stenosis of large intestine, rectum, and anal canal	Indeterminate sex	Other specified anomalies of unspecified limb			5	76.4
13	Congenital stenosis of aortic valve	Congenital mitral stenosis	Other anomalies of aorta	Anomalies of pulmonary artery	Anomalies of spine	5	76.3
14	Congenital mitral stenosis	Other specified anomalies of the heart	Anomalies of spine	Anomalies of ribs and sternum		8	76.1
15	Ventricular septal defect	Ostium secundum type atrial septal defect	Other specified anomalies of the heart	Anomalies of spine	Anomalies of ribs and sternum	9	75.4
16	Anomalies of great veins	Other anomalies of lung	Anomalies of spine	Anomalies of ribs and sternum		5	74.8
17	Ostium secundum type atrial septal defect	Anomalies of pulmonary artery	Other anomalies of upper limb including shoulder girdle	Anomalies of ribs and sternum		6	74.5
18	Other unspecified anomalies of face and neck	Atresia and stenosis of large intestine, rectum, and anal canal	Anomalies of spine	Anomalies of ribs and sternum		6	74.5
19 ^b	Anomalies of spine	Anomalies of diaphragm	Anomalies of spleen			6	67.4

Rank	Defect 1	Defect 2	Defect 3	Defect 4	Defect 5	N ^a	O/E
20	Ventricular septal defect	Other specified anomalies of the heart	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum	5	67.4
21	Ostium secundum type atrial septal defect	Other specified anomalies of the heart	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum	6	67.0
22	Ostium secundum type atrial septal defect	Other specified anomalies of the heart	Anomalies of great veins	Anomalies of spine	Anomalies of ribs and sternum	6	66.4
23	Reduction deformities of brain	Congenital hydrocephalus	Anomalies of spine	Anomalies of ribs and sternum		7	65.7
24	Ostium secundum type atrial septal defect	Other anomalies of intestine	Renal agenesis and dysgenesis	Anomalies of ribs and sternum		5	64.2
25	Transposition of great vessels	Endocardial cushion defects	Anomalies of pulmonary valve	Other specified anomalies of the heart	Renal agenesis and dysgenesis	6	63.1
26 ^b	Other specified anomalies of the heart	Anomalies of pulmonary artery	Anomalies of spine	Anomalies of ribs and sternum		10	63.1
27	Other anomalies of aorta	Anomalies of pulmonary artery	Reduction defects of upper limb	Anomalies of ribs and sternum		5	63.0

O/E, adjusted observed-to-expected ratio

^aCombinations with 5 or more cases included in table.

^bCombination is represented in a higher-order pattern (e.g., combination with defects A, B, and C represented in combination A, B, C, and D).