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Patterns of Co-Occurring Birth Defects in Children with Anotia and Microtia

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Abstract

INTRODUCTION: Many infants with anotia or microtia (A/M) have co-occurring birth defects, although few receive syndromic diagnoses in the perinatal period. Evaluation of co-occurring

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CONFLICT OF INTEREST STATEMENT: The authors have no conflict of interest to declare.

ETHICS APPROVAL STATEMENT: The protocol for this study was approved by the Institutional Review Boards of the Texas Department of State Health Services, University of Texas Health Science Center at Houston, and Baylor College of Medicine. The requirement for informed consent was waived as the study involved analysis of de-identified data from a public health surveillance program.

birth defects in children with A/M could identify patterns indicative of undiagnosed/unrecognized syndromes.

METHODS: We obtained information on co-occurring birth defects among infants with A/M for delivery years 1999-2014 from the Texas Birth Defects Registry. We calculated observed-to-expected ratios (OER) to identify birth defect combinations that occurred more often than expected by chance. We excluded children diagnosed with genetic or chromosomal syndromes from analyses. Birth defects and syndromes/associations diagnosed ≤1 year of age were considered.

RESULTS: We identified 1,310 infants with non-syndromic A/M, of whom 38% (N=492) were diagnosed with co-occurring major defects. Top combinations included: hydrocephalus, ventricular septal defect, and spinal anomalies (OER 58.4); microphthalmia and anomalies of the aorta (OER 55.4); and cleft lip with or without cleft palate and rib or sternum anomalies (OER 32.8).

CONCLUSIONS: Some combinations observed in our study may represent undiagnosed/atypical presentations of known A/M associations or syndromes, or novel syndromes yet to be described in the literature. Careful evaluation of infants with multiple birth defects including A/M is warranted to identify individuals with potential genetic or chromosomal syndromes.

Keywords

anotia; microtia; epidemiology; co-occurring defects

INTRODUCTION

Anotia/microtia is a birth defect in which the outer ear is absent or underdeveloped. In the United States, the condition has an estimated birth prevalence of approximately 3 cases per 10,000 livebirths (Canfield et al., 2009; Shaw et al., 2004; Stallings et al., 2018). However, there is variation by sex and race/ethnicity (Canfield et al., 2014; Luquetti et al., 2011), with higher rates observed in males and Hispanic and Asian individuals compared to non-Hispanic Whites. There is likewise considerable phenotypic variability among infants with anotia/microtia (Hunter et al., 2009; Marx, 1926). In grade one microtia, the least severe form, the ear is small but normal structures are present. In grades two and three (also termed conchal and lobular, respectively) microtia, more extensive hypoplasia is apparent and there is often stenosis or atresia of the ear canal (Suutarla et al., 2007; van Nunen et al., 2014). In anotia, the most severe form, the external ear and external auditory canal are absent. Because of the high frequency of hearing loss and potential for facial nerve weakness or paralysis (Luquetti et al., 2012; Suutarla et al., 2007; van Nunen et al., 2014), as well as adverse psychosocial outcomes across the life course (Mandelbaum et al., 2017; Volpicelli et al., 2017), anotia/microtia has an enduring impact on the overall health of affected individuals and on the public health.

Genetic or chromosomal syndromes involving anotia/microtia have been well described, although they are diagnosed in fewer than 20% of all individuals with anotia/microtia (Cabrejo et al., 2019; Canfield et al., 2009; Stallings et al., 2018; van Nunen et al., 2014). Anotia/microtia is a cardinal feature of oculo-auriculo-vertebral spectrum

(OAVS, which includes Goldenhar syndrome, hemifacial macrosomia, and oculo-auriculo-vertebral disorder) (Tasse et al., 2005); affected individuals frequently also present with cardiac (5-40%), nervous system (5-40%), and genitourinary anomalies (10-30%) (Tingaud-Sequeira et al., 2022). Ear anomalies are likewise a key feature of CHARGE (Coloboma, Heart defects, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) syndrome (Blake & Prasad, 2006); in one cohort of patients with CHARGE syndrome (N=254), ear anomalies were reported in >90% of individuals (Zentner et al., 2010). Botto et al. reported severe ear defects in 2.1% of infants with VACTERL association. However, this definition excluded milder forms of microtia (Botto et al., 1997; Rittler et al., 1996). Anotia/microtia may also be a feature of trisomies 13, 18, and 21, Treacher Collins syndrome, and Townes-Brock syndrome (Cabrejo et al., 2019; Kallen et al., 2004; Rittler et al., 1996; Stoll et al., 2016; van Nunen et al., 2014).

Even among infants without a known syndrome or association, co-occurring birth defects are frequent. Multiple population-based assessments report that >50% of infants with anotia/microtia are diagnosed with additional malformations, most commonly involving the heart (10-50%), musculoskeletal (3-25%) or genitourinary systems (10-30%) (Cabrejo et al., 2019; Canfield et al., 2009; Stallings et al., 2018; Stoll et al., 2016). These recurrent, apparently non-random constellations of birth defects may well be the consequence of undiagnosed or even previously unrecognized anotia/microtia syndromes (Paput et al., 2011). A recent study of 40 patients with isolated, non-syndromic grade III microtia reported that 27 (67.5%) carried rare heterozygous variants in one of 42 genes involved in external ear formation (Wang et al., 2019), suggesting that careful clinical and molecular investigation may reveal distinct etiologies in many such cases.

Historically, syndromes and associations involving anotia/microtia were defined and characterized by “astute clinicians”, who carefully described phenotypic features in series of patients and recognized recurrent patterns of malformations that reflected possible shared etiologies (Gorlin et al., 1963; Hall, 1979). However, this approach is challenging when identifying very rare patterns or attempting to accurately estimate birth prevalence. More recently, we and others have demonstrated that data from population-based birth defects registries can be highly useful for identifying, characterizing, and refining the definitions of birth defect syndromes and associations (Benjamin et al., 2022; Kallen et al., 2004; Paput et al., 2011; Schraw et al., 2020; van de Putte et al., 2020). These resources are critical to overcoming the historical barriers to identifying multiple birth defect patterns, although population-based descriptions of these patterns among infants with anotia/microtia are largely confined to reports on the prevalence of individual co-occurring defects (Bennun et al., 1985; Cabrejo et al., 2019; Stallings et al., 2018; Stoll et al., 2016; van Nunen et al., 2014). These studies have left unanswered questions about co-occurring birth defects among infants with anotia/microtia, because higher-order combinations were generally not evaluated and reports of individual co-occurring defects are not adjusted for the generalized, non-specific clustering of birth defects (Khoury et al., 1990). Therefore, our objective was to describe two-through five-way birth defect combinations occurring in the setting of non-syndromic anotia/microtia, using data from a large, population-based birth defects registry.

METHODS

The protocol for this study was approved by the Institutional Review Boards of the Texas Department of State Health Services, University of Texas Health Science Center at Houston, and Baylor College of Medicine, and conforms to the principles of the Declaration of Helsinki. The requirement for informed consent was waived as the study involved analysis of de-identified data from a public health surveillance program. Information on birth defect diagnoses was obtained from the Texas Birth Defects Registry (TBDR) for all deliveries to Texas residents between 1999 and 2014, regardless of pregnancy outcome. TBDR is a population-based, active birth defects surveillance system; registry staff routinely review records from hospitals, pediatrics clinics, and birthing centers throughout the state to ascertain cases diagnosed with monitored structural birth defects and chromosomal abnormalities up to one year of age (Miller, 2006). Records for eligible individuals are abstracted into an electronic database where they undergo extensive quality control checks, including frequent manual review by clinical geneticists.

TBDR classifies birth defects using the six-digit Centers for Disease Control modified-British Paediatric Association codes, referred to as BPA codes ("Appendix A: ICD-9 and CDC/BPA codes," 2002), and retrieves demographic information from birth and fetal death records. To facilitate the analysis of distinct groups of related defects, we collapsed these codes to their four-digit prefixes and excluded sex-specific defects or unspecified congenital anomalies. We included data from singleton pregnancies that resulted in a livebirth, stillbirth, fetal death, or termination, and were affected by anotia or microtia (BPA codes 744.01 and 744.21, respectively) and one or more additional defects. Possible or probable diagnoses (those that could not be verified by TBDR) were not included in our analysis. Because our objective was to describe multiple birth defect patterns of unknown etiology, we excluded subjects diagnosed with chromosomal abnormalities (e.g., trisomy 13, 18, or 21), genetic syndromes (e.g., Treacher Collins or CHARGE syndromes) or birth defect sequences/associations (e.g., Pierre Robin sequence, VACTERL association) in the pre-or peri-natal period.

For comparison with the published literature, we summarized demographic information using counts and percentages and generated an UpSet plot (Conway et al., 2017; Lex et al., 2014) to visualize the number of individuals with co-occurring defects in the five most common categories (heart, musculoskeletal, central nervous system, gastrointestinal, and circulatory). Then, we used our Co-Occurring Defects Analysis (CODA) software platform (Benjamin et al., 2019) to evaluate two-through five-way combinations involving anotia/microtia. CODA estimates the ratio of the observed number of cases of a birth defect combination to the number that would be expected if the defects occurred independently, adjusted for the nonspecific tendency of birth defects to cluster (OER) (Benjamin et al., 2019; Khoury et al., 1990). We focused our reporting on combinations with OER >1 (that is, those that occurred more often than expected by chance) that were observed in five or more individuals and were not redundant with other, higher-order combinations that had a greater OER. In addition, we did not include the two-way combination of anotia/microtia with ear anomalies causing hearing impairment, as we felt that hearing loss alone did not

necessarily constitute a second, distinct birth defect when anotia/microtia was present. All statistical analyses were conducted in R version 4.0.5 (R Core Team, Vienna, Austria).

RESULTS

We identified 6,181,631 livebirths, 172,488 individuals with birth defects, and 1,322 individuals with anotia/microtia. Among these, we included 467 singleton births with multiple birth defect phenotypes involving anotia/microtia in further analyses (36.3% of singleton births with anotia/microtia). Included individuals were predominantly male. Mothers of cases were predominantly Hispanic. Relative to the reference population of all livebirths in Texas, cases were more often delivered by women who were overweight or obese, or who were diagnosed with diabetes (Table 1). Co-occurring defects most commonly involved the cardiac (137 individuals, 29.3%), musculoskeletal (114 individuals, 24.4%), nervous (50 individuals, 10.7%), or gastrointestinal systems (44 individuals, 9.4%) (Figure 1). Heart and musculoskeletal defects were observed alone (59 and 43 individuals, respectively), in combination with each other (25 individuals), as well as with anomalies of the central nervous (10 individuals) or gastrointestinal systems (8 individuals).

Using CODA, we identified 107 recurrent birth defect combinations involving anotia/microtia that occurred more often than expected by chance. Of these, 31 were two-way combinations, 65 were three-way combinations, and 11 were four-way combinations (no five-way combinations were observed in at least five individuals). We observed three combinations with OER>50 (Table 2), involving heart defects co-occurring with musculoskeletal anomalies, hydrocephalus, or microphthalmia. Other top combinations involved cardiovascular and rib/sternum/spine defects in combination with one another, orofacial clefts, eye/ear/face/neck anomalies, and renal anomalies (e.g., cleft lip +/− cleft palate, other anomalies of the ribs and sternum, OER=32.8; ostium secundum type atrial septal defect, spinal anomalies, other anomalies of the ribs and sternum, OER=31.3). Microcephalus was an additional feature of several top combinations.

DISCUSSION

A substantial proportion of children with anotia/microtia are diagnosed with co-occurring birth defects, but these patterns have not been evaluated systematically. We characterized the spectrum of multiple birth defect phenotypes involving anotia/microtia, using data from a large, population-based birth defects registry, to identify infants with patterns suggestive of undiagnosed or unrecognized anotia/microtia-related syndromes or associations. Top birth defect combinations identified by CODA most often involved the co-occurrence of cardiac, musculoskeletal, or nervous system defects in combination with one another, orofacial clefts, and microphthalmia. These combinations seem consistent with certain syndromes in which anotia/microtia is a common feature (described below), and our results suggest that careful evaluation of children with multiple birth defect phenotypes involving anotia/microtia is warranted to rule out such syndromes.

In the present study, 36% of singletons with anotia/microtia had co-occurring defects. This proportion is somewhat lower than in other assessments, which reported co-occurring

defects in 40-80% of individuals (Cabrejo et al., 2019; Guo et al., 2021; Stallings et al., 2018; Stoll et al., 2016). These included infants with known syndromes or associations, who are more likely to have co-occurring defects. In the National Birth Defects Prevention Study (NBDPS), which likewise excluded children with most known syndromes or associations, 31% of individuals with anotia/microtia were classified as having multiple defects (Howley et al., 2022). We most often observed co-occurring defects in the cardiac and musculoskeletal systems (~25% of individuals), followed by the nervous, circulatory, and gastrointestinal systems (~10% of individuals). While there is variability in the literature regarding the frequency of individual co-occurring defects, these estimates are consistent with a report from thirty population-based U.S. birth defects surveillance systems (Stallings et al., 2018).

The two studies most comparable to ours applied CODA to data from the TBDR and National Birth Defects Prevention Study (NBDPS) (Benjamin et al., 2022; Howley et al., 2022). The study utilizing TBDR data - which focused on the top 5% of combinations observed among at least five individuals that involved multiple organ systems and were not suggestive of known syndromes - did not report on combinations involving anotia/microtia (Benjamin et al., 2022). However, the large OERs previously observed for combinations involving co-occurring diaphragm and spine anomalies were also observed in this study with anotia/microtia. In the report from NBDPS, two multiple birth defect combinations involving anotia/microtia were seen among the top 20% of all combinations. These involved anotia/microtia with 1) sacral agenesis and anorectal atresia (OER=28.9) or 2) oral clefts, cardiac malformations, and limb deficiencies (OER=20.2) (Howley et al., 2022). These phenotypes partially overlap those observed in our study (cardiac malformations, oral clefts, spinal anomalies), and adjusted OERs were of a similar magnitude. Although we observed a wider spectrum of co-occurring defects overall, none of the top combinations in our study involved sacral agenesis or anorectal atresia.

Anotia/microtia is required for a diagnosis of OAVS (Cousley & Calvert, 1997; Tasse et al., 2005) and can be present in CHARGE syndrome (Hall, 1979; Hittner et al., 1979) and (less frequently) VACTERL association (Botto et al., 1997; Rittler et al., 1996). OAVS is characterized by eye, ear, craniofacial, and spinal defects. Infants with Goldenhar syndrome may also be diagnosed with orofacial clefts (particularly cleft palate), as well as cardiac, renal, and limb defects. CHARGE syndrome and VACTERL association overlap phenotypically with OAVS (Bergmann et al., 2003; Kallen et al., 2004), and many of the top combinations reported in this study are broadly consistent with these conditions. For example, the combination of anotia/microtia, congenital hydrocephalus, ventricular septal defect, and spinal anomalies includes features of OAVS (Castori et al., 2006; Tingaud-Sequeira et al., 2022), whereas infants with anotia/microtia, renal agenesis, and spinal anomalies, may not have met the clinical criteria for a diagnosis of VACTERL as they did not have three or more of the hallmark features. We note that the absence of birth defect combinations that involve hallmark features of CHARGE syndrome and VACTERL association is unsurprising, given that we excluded infants with syndromes/associations diagnosed prenatally or within the first year of life from our analyses.

We observed multiple combinations involving co-occurring anotia/microtia and cleft lip with or without cleft palate. The combination of these phenotypes was reported in three members of a consanguineous Iranian family with bilateral microtia, mixed symmetric severe to profound hearing impairment, and partial cleft palate who were homozygous for a missense variant in *HOXA2* that affects HOXA2's DNA binding activity (Alasti et al., 2008). This emphasizes the possible (perhaps probable) presence of individuals with undiagnosed single-gene syndromes in our study.

Alternatively, certain top combinations may represent developmental field defects (DFDs), such as those in which anotia/microtia co-occurred with other craniofacial defects, orofacial clefts, or heart defects. Duncan and Shapiro reported an association between hemifacial macrosomia and VACTERL (Duncan & Shapiro, 1993), which others have attributed to the fact that they are both primary field defects (Martínez-Frías et al., 1998). DFDs may be useful in explaining the co-occurrence of multiple birth defect phenotypes that do not appear consistent with known syndromes, such as the co-occurrence of anotia/microtia with spinal and diaphragm anomalies (the latter is also an occasional feature of CHARGE syndrome) (Stoll et al., 2008).

Some of the combinations observed in our study may be attributable to maternal exposures. In particular, maternal pre-gestational diabetes has been associated with multiple birth defect phenotypes including hemifacial macrosomia and VACTERL association. Diabetes has been linked to sacral agenesis (which, with anotia/microtia, was one of the combinations identified in the NBDPS report), and, separately, ear anomalies. Pre-gestational or gestational diabetes was diagnosed in 16% of women whose pregnancies resulted in a case with anotia/microtia compared to 4% of all pregnancies resulting in livebirths; diabetes is estimated to affect 6–7% of pregnant people in the U.S. population (Deputy et al., 2018).

Our study has several strengths. First, we used data from a large, population-based active surveillance registry. Our relatively large sample size enabled the evaluation of rare birth defect combinations (including some with estimated birth prevalence less than one case per million), which may be difficult or impossible in other settings. Secondly, the CODA platform can evaluate high-order birth defect combinations and accounts for the tendency of birth defects to cluster, which may otherwise bias estimates of birth defect co-occurrence. Thus, CODA produces robust estimates of co-occurrence and can identify complex combinations that may be especially helpful for characterizing syndromes or associations. Despite these, our study also has certain limitations. While we excluded infants with known syndromes or associations, it is possible that these were undiagnosed in some cases, as not all children undergo comprehensive clinical and molecular investigation. This may have led to the inclusion of some cases with previously described syndromes or associations in this cohort. We lacked information on developmental, behavioral, and neuropsychological outcomes, and on diagnoses made >1 year of age, as these data are not recorded by TBDR. Likewise, we could not distinguish microtia based on grade, and were unable to perform a separate analysis of anotia, which was diagnosed in <5% of individuals.

CONCLUSIONS

We identified 467 infants with multiple birth defect phenotypes involving anotia/microtia in Texas during the delivery years 1999-2014. Cardiac and musculoskeletal anomalies were frequent, and combinations with large adjusted observed-to-expected ratios in Co-Occurring Defects Analysis were generally consistent with patterns seen in OAVS, VACTERL association, or CHARGE syndrome. Our findings suggest that anotia/microtia-related syndromes or associations may be present in a substantial proportion of individuals who do not receive a diagnosis by one year of age. Careful evaluation of such infants is warranted to rule out syndromic disease, assess for additional features such as hearing loss and developmental delay, and optimize reproductive counseling approaches.

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DATA AVAILABILITY STATEMENT:

The investigators are prohibited by the terms of the data use agreement from sharing the underlying data publicly. Data may be obtained by application to the Texas Birth Defects Registry and Texas Department of State Health Services Institutional Review Board.

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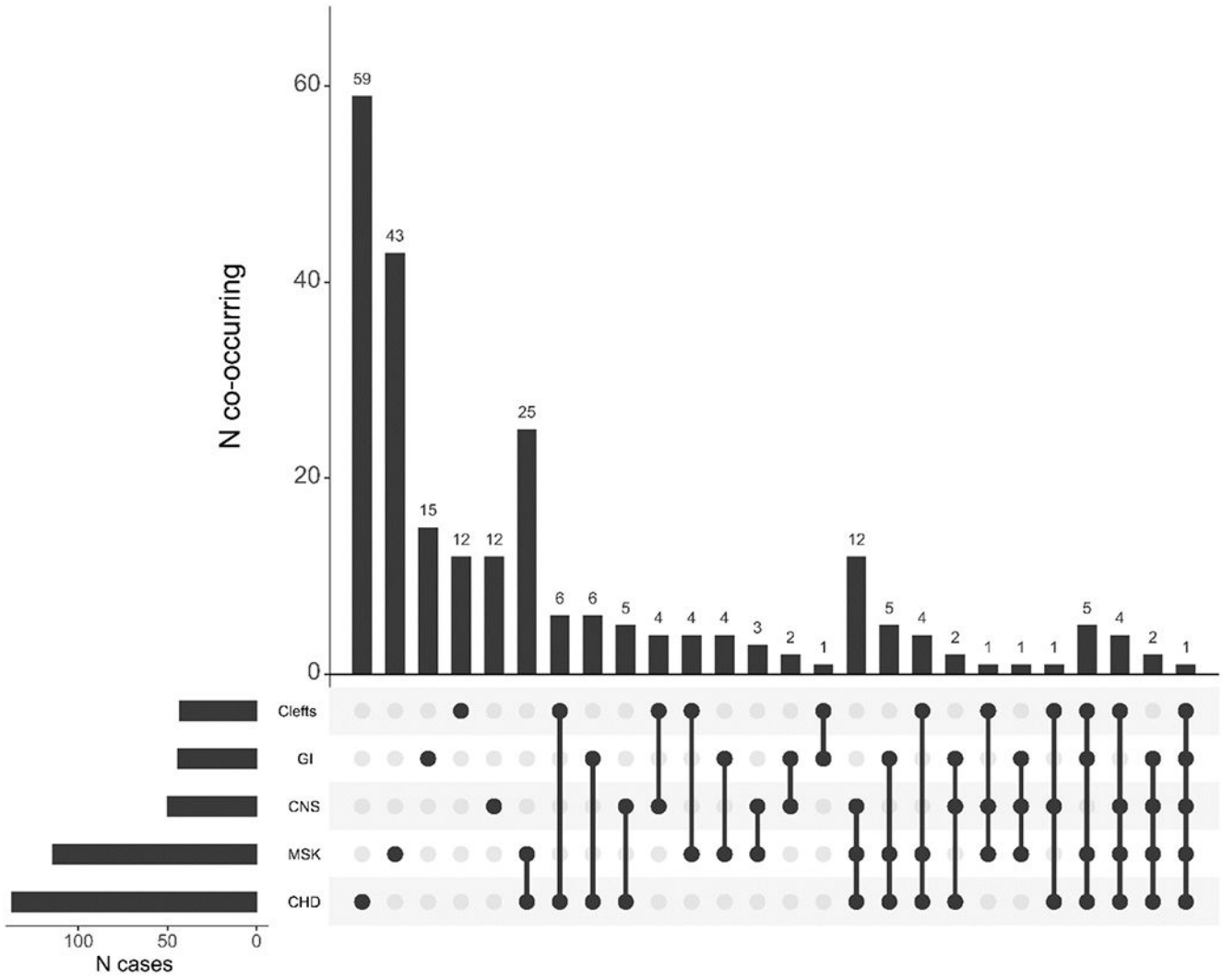

Figure 1. Co-occurring defects among individuals with multiple birth defect patterns involving anotia/microtia, Texas Birth Defects Registry, 1999-2014 (N=467).

Birth defects were grouped into broad categories of related defects, and information was presented for the five most commonly observed categories of co-occurring defects (heart [CHD], musculoskeletal system [MSK], central nervous system [CNS], gastrointestinal [GI] system, and orofacial clefts). Bottom left: histogram showing the number of individuals with co-occurring defects in each organ system. Bottom: legend describing evaluated birth defect combinations. Phenotypes involved are represented by black-shaded circles; combinations involving multiple co-occurring phenotypes are represented as multiple shaded circles connected by lines. Top: histogram showing the number of individuals with anotia/microtia and the index combination (e.g., among 133 individuals with anotia/microtia and heart defects, 59 were diagnosed with co-occurring CHD only, 25 with co-occurring CHD and MSK anomalies, six with co-occurring CHD and clefts, etc.).

TABLE 1.

Distributions of infant and maternal characteristics among included individuals with anotia/microtia and co-occurring defects, Texas, 1999-2014 (N=467).

	N (%)[†]	
	Livebirths	**Anotia/Microtia**
Live birth	6,181,631 (100.0)	454 (97.2)
Sex		
Male	3,159,950 (51.1)	264 (56.5)
Female	3,021,681 (48.9)	203 (43.5)
Maternal age (years)		
<20	759,054 (12.3)	62 (13.3)
20-24	1,672,253 (27.1)	119 (25.5)
25-29	1,678,322 (27.2)	119 (25.5)
30-34	1,318,102 (21.3)	101 (21.6)
35-39	613,552 (9.9)	49 (10.5)
≥40	139,824 (2.3)	17 (3.6)
Maternal race/ethnicity		
Hispanic	3,004,303 (48.6)	349 (74.7)
Non-Hispanic White	2,204,720 (35.7)	71 (15.2)
Non-Hispanic Black	698,954 (11.3)	20 (4.3)
Other non-Hispanic	266,324 (4.3)	19 (4.1)
Unknown	7330 (0.1)	8 (1.7)
Maternal education		
Less than high school	1,739,482 (28.1)	178 (39.1)
High school	1,742,822 (28.2)	132 (29.0)
Greater than high school	2,656,707 (43.0)	145 (31.9)
Maternal pre-pregnancy body mass index (kg/m^2) [‡]		
Underweight	151,217 (2.4)	7 (2.1)
Normal weight	1,756,582 (28.4)	147 (44.1)
Overweight	1,025,864 (16.6)	73 (21.9)
Obese	1,009,993 (16.3)	106 (31.8)
Maternal diabetes [‡]	246,821 (4.0)	56 (16.6)

[†]. Values may not sum to the total (N=467) due to missingness.

[‡]. Available for delivery years 2005-2014. Includes gestational and pre-gestational diabetes.

TABLE 2.

Co-occurring birth defect combinations among individuals with anotia/microtia in the Texas Birth Defects Registry, 1999-2014, ranked by adjusted observed-to-observed ratio.

Combination	OER	N
Congenital hydrocephalus, ventricular septal defect, anomalies of spine	58.4	5
Transposition of great vessels, other anomalies of ribs and sternum	55.6	6
Microphthalmia, other anomalies of aorta	55.4	6
Cleft lip +/− cleft palate, other anomalies of ribs and sternum	32.8	6
Anomalies of ear causing impairment of hearing, ventricular septal defect, ostium secundum type atrial septal defect	32.7	6
Other unspecified anomalies of face and neck, anomalies of spine	32.1	8
Ostium secundum type atrial septal defect, anomalies of spine, other anomalies of ribs and sternum	31.3	7
Anomalies of ear causing impairment of hearing, cleft lip +/− cleft palate	26.8	8
Anomalies of ear causing impairment of hearing, other specified anomalies of kidney	26.3	5
Anomalies of ear causing impairment of hearing, obstructive defects of renal pelvis and ureter	26.0	10
Anomalies of ear causing impairment of hearing, other unspecified anomalies of face and neck	21.7	5
Microphthalmia, ventricular septal defect	21.2	6
Microcephalus, anomalies of ear causing impairment of hearing	20.8	7
Anomalies of spine, anomalies of diaphragm	19.8	5
Microphthalmia, ostium secundum type atrial septal defect	19.4	6
Ventricular septal defect, ostium secundum type atrial septal defect, anomalies of spine	18.9	9
Cystic kidney disease, anomalies of spine	18.7	5
Renal agenesis and dysgenesis, anomalies of spine	17.9	9
Other unspecified anomalies of face and neck, ventricular septal defect	17.0	10
Anomalies of ear causing impairment of hearing, anomalies of spine	16.4	5
Other unspecified anomalies of face and neck, obstructive defects of renal pelvis and ureter	15.4	5
Cleft lip +/− cleft palate, anomalies of spine	15.0	5
Microcephalus, other unspecified anomalies of face and neck	14.1	5
Anomalies of pulmonary artery, anomalies of spine	13.7	6
Reduction deformities of brain, anomalies of spine	13.5	5
Ventricular septal defect, ostium secundum type atrial septal defect, renal agenesis and dysgenesis	12.6	5
Microcephalus, other anomalies of aorta	12.0	6

Includes combinations with OER > 10 and N≥5, which are not redundant with another higher order combination with a greater OER.