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Preferential Associated Anomalies in 818 Cases of Microtia in South America

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Abstract

The etiology of microtia remains unknown in most cases. The identification of patterns of associated anomalies (i.e., other anomalies that occur with a given congenital anomaly in a higher than expected frequency), is a methodology that has been used for research into the etiology of birth defects. We conducted a study based on cases of microtia that were diagnosed from more than 5 million live (LB)- and stillbirths (SB) examined in hospitals participating in ECLAMC (Latin American Collaborative Study of Congenital Malformations) between 1967 and 2009. We identified 818 LB and SB with microtia and at least one additional non-related major congenital anomaly (cases) and 15,969 LB and SB with two or more unrelated major congenital anomalies except microtia (controls). A logistic regression analysis was performed to identify the congenital anomalies preferentially associated with microtia. Preferential associations were observed for 10 congenital anomalies, most of them in the craniofacial region, including facial asymmetry, choanal atresia, and eyelid colobomata. The analysis by type of microtia showed that for anomalies such as cleft lip and palate, macrostomia, and limb reduction defects, the frequency increased with the severity of the microtia. In contrast, for other anomalies the frequency tended to be the same across all types of microtia. Based on these results we will integrate data on the developmental pathways related to preferentially associated congenital anomalies for future studies investigating the etiology of microtia.

Keywords

microtia; birth defects; multiple congenital anomalies; epidemiology

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INTRODUCTION

Microtia, a congenital malformation of the external ear, has a global prevalence of 2.06 per 10,000 (confidence interval [CI], 2.02–2.10) with a higher prevalence observed in Central and South America (2.58; CI, 2.43–2.74), and Asia (1.39; CI, 1.31–1.48) compared to other regions of the world [Luquetti et al., 2011]. It is believed to be a multifactorial complex congenital anomaly, i.e., genetic and non-genetic (environmental) factors contribute to its occurrence. For the non-genetic risk factors, there is strong evidence for association between the occurrence of microtia and the exposure to the teratogens retinoic acid, thalidomide [Carey et al., 2006], and mycophenolate mofetil [Anderka et al., 2009]; altitude [Castilla et al., 1999; Castilla and Orioli, 1986; González-Andrade et al., 2010]; and Hispanic, Asian and Native American ethnicity [Canfield et al., 2009; Castilla and Orioli, 1986; Forrester and Merz, 2005; Jaffe, 1969; Luquetti et al., 2011; Shaw et al., 2004].

For most cases of microtia the etiology remains unknown, whether occurring as an isolated defect or in association with other anomalies. The majority of the well-known syndromes that present with microtia, such as Treacher Collins, Miller and Meier-Gorlin syndromes, have had the causative genes identified, although the specific role of those genes during external ear development has not yet been elucidated. The current hypotheses for the pathogenesis of microtia are neural crest cell disturbance and vascular disruption. Given the clinical heterogeneity of this condition both hypotheses may be correct, the pathogenesis depending on the type of microtia. The lack of knowledge on the etiology for most individuals that present with microtia, except when a well-known syndrome is recognized, is a barrier for genetic counseling, as well as for the identification of ways to prevent microtia.

Specific or preferential association of congenital anomalies is defined as two or more congenital anomalies that tend to occur together more often than expected. In other words, the observed versus the expected ratio is greater than one. The expected frequency can be calculated from population rates of anomalies [Khoury et al., 1990] or by the currently more accepted method of proportional distribution of anomalies among infants with multiple anomalies (i.e. preferential associations) [Botto et al., 1997; Kallen et al., 1999b]. This methodology has been used to confirm already known associations between congenital anomalies, such as in VATER association and in CHARGE syndrome. However, it can also be used to identify new associations that may provide pathogenetic insight as certain malformations might form clinically recognizable associations that suggest a shared developmental origin or cause [Botto et al., 1997; Kallen et al., 1999a; Rittler et al., 2008; Rosano et al., 2000]. The identification of specific anomalies preferentially associated with microtia may therefore be a first step to help elucidate developmental mechanisms in the future.

Microtia is reportedly associated with one or more additional congenital anomalies in 30–60% of the cases [Canfield et al., 2009; Castilla and Orioli, 1986; Forrester and Merz, 2005; Harris et al., 1996; Mastroiacovo et al., 1995; Shaw et al., 2004; Suutarla et al., 2007]. The studies on the frequency of anomalies associated with microtia reported in the literature show a higher prevalence of congenital heart disease, cleft palate, esophageal atresia, vertebral anomalies, an/microphthalmia, and limb reduction defects. Previous studies were conducted in Europe and North America and most did not study preferential associations but simply the frequency of congenital anomalies that occurred together with microtia. The objective of this study is to describe the distribution of congenital anomalies associated with microtia and to identify specific associations between microtia and other major congenital anomalies in a South American population.

METHODS

The study population consisted of all live- or stillbirths with microtia and additional major congenital anomalies not involving the ear (cases) and all newborns with two or more major congenital anomalies except microtia ("controls") ascertained from 1967 to 2009 by the ECLAMC (Latin-American Collaborative Study of Congenital Malformations) participating hospitals. ECLAMC is an ongoing case-control study on birth defects in South America. Cases are actively ascertained at birth, through physical examination by trained physicians at participating hospitals. Data collection is standardized through the use of a comprehensive manual of operations and training during the annual meetings of ECLAMC. Cases are reviewed and coded centrally. If two or more anomalies are part of a sequence or have a known etiology they receive an additional code to indicate this. More detailed information about the network can be found in Castilla and Orioli [2004].

We considered an individual with associated congenital anomalies if s/he had two or more unrelated major anomalies that were not part of a sequence (i.e.: pattern of anomalies that results from a single primary anomaly or single mechanical factor [Jones and Smith, 1997]). Sequences were counted as one defect, for example, an individual affected with microtia and preauricular tag was counted as having one defect as were individuals with the combination of spina bifida, hydrocephalus and clubfoot. Cases with syndromes were included and cases with chromosomal anomalies (assessed by karyotype) were excluded. Minor congenital anomalies (e.g: umbilical and inguinal hernia) were excluded. A complete list of anomalies considered as minor for this study can be found in Appendix 1 (See Supporting Information online).

The ECLAMC database has detailed information on case characteristics. The following were included as part of the phenotypic description of cases: sex, plurality, still/live birth, maternal age, laterality (unilateral or bilateral), side affected, number of associated anomalies, and type of microtia. Information on the type of microtia was available from 1996–2009 in the database. Cases were classified according to that of Marx [1926] where all of the features of a normal auricle are present in grade I, but the pinna is smaller than normal. In grade II, some anatomical structures are still recognizable. In grade III (the peanut-shell type), only a rudiment of soft tissue is present. The extreme case where there is no external ear and auditory canal is called anotia or microtia grade IV.

We used observed versus expected ratio (O/E), where the expected frequency of a defect was the frequency of the selected defect among all multi-malformed infants and the strength of the association was measured by the odds ratio. We defined preferential associations as non-random association between two or more non-related major anomalies (O/E > 1). We performed a logistic regression analysis to calculate the odds ratios and adjusted by country, year, live-birth/stillbirth, sex, and number of associated malformations. Level of statistical significance was set at 0.05.

RESULTS

We identified 2,645 cases of microtia among 5,860,995 live and stillbirths delivered between 1967 and 2009 at the ECLAMC participating hospitals. In total, 1,747 cases of microtia were associated with one or more malformations. However, we excluded cases associated with only minor congenital anomalies, leaving 818 (30.9%) cases for the analysis. Using the same database, we identified 15,969 controls (live or stillbirths with two or more unrelated major congenital anomalies except microtia).

The proportions of males, twins and still-births was similar between cases and controls (Table I). The average number of associated anomalies per case was 3.5 ± 1.5 (standard

deviations (sd)). Microtia, when unilateral, more commonly involved the right side (59.5%). Microtia type I was the most frequent (40.4%) (Table II).

The frequency of each congenital anomaly and the associations found are summarized In Table III. Congenital heart disease was the most frequent associated anomaly, but its frequency was less than expected in cases than in controls. Preferential associations (O/E> 1) were observed for 10 congenital anomalies, most of them in the craniofacial region. For 16 congenital anomalies, including neural tube defects and gastroschisis, a negative association (O/E<1) was found.

The analysis by type of microtia showed that for some anomalies, such as cleft lip and palate, macrostomia, and limb reduction defects the frequency increased with the severity of the microtia, whereas for other anomalies the frequency tended to be the same across all types of microtia (Table IV).

DISCUSSION

Microtia associated with at least one major malformation occurred in 30.9% of the cases, slightly lower than reported in the majority of other studies in the literature (Table V). This difference could be related to the analytic method we followed in which sequences were counted as one defect and minor anomalies were excluded. It is also possible that internal organ malformations were potentially underreported in our study. However, we suggest some of this difference could be attributable to the fact that a considerable proportion (16.1%) of the cases with microtia reported here were born in the Andean highlands, a high birth prevalence area for microtia, although mainly based on its isolated (non-additional anomalies) forms [Castilla and Orioli, 1986].

The defects most frequently associated with microtia were congenital heart disease, limb reduction defects, hydrocephalus, an/microphthalmia, cleft lip and palate, cleft palate only, facial asymmetry, and clubfoot. However, among those, a high O/E ratio (indicative of a non-random preferential association) was only found for cleft palate, cleft lip and palate, and an/microphthalmia. Other preferential associations occurred between anomalies found in the oculo-auriculo-vertebral spectrum (OAVS) as well as with holoprosencephaly, choanal atresia and preaxial polydactyly. These latter preferential associations are intriguing as they are not usually reported in OAVS and therefore may represent an unappreciated developmental or genetic link. In this regard, co-presentation of microtia with preaxial polydactyly has been described in lacrimo-auriculo-dento-digital (LADD) and Townes-Brocks syndromes, and very rarely in branchio-oculo-facial syndrome [Stevenson, 2006]. Thus, some of the individuals with this association might represent unrecognized or variable presentations of these syndromes. Mastroiacovo et al [1995] also found a positive association between microtia and preaxial polydactyly in their study, supporting our finding and suggesting that it might not be specific to the South American population, but to a true association between these two malformations. It is tempting to speculate that these specific associations may reflect an underlying defect in a pathway(s) downstream of, or convergent with, that in which the *FGF10/FGFR2-3* (LADD) the *SALL1* (Townes-Brocks) genes participate.

An/microphthalmia, eyelid coloboma, facial asymmetry, and choanal atresia are common in CHARGE syndrome, whereas preaxial polydactyly, all found in this study as preferential associations, is part of VATER association. A study, including data from ECLAMC and another three birth defects registries in which associations between selected malformations, and pairs of malformations, were identified by multiple logistic regression analyses without any preanalytic delineation of any association, found a statistical relationship between

VATER association, OAVS, and CHARGE syndrome [Kallen et al., 2001]. Interestingly, the association of VATER and microtia did not reach significance in a previous study published with ECLAMC data (O/E 1.14; p= 0.53), although one potential reason being the number of cases of microtia were notably lower at that time [Rittler et al., 1996]. These recognized patterns of associations may indicate similarities in pathogenesis or in etiology. The connection between OAVS and CHARGE syndrome was proposed to be a common underlying disturbance of neural crest development.

When analyzing an individual with multiple anomalies the hypotheses are of one teratogenic event affecting two or more developing pathways, shared basic developmental process between the two structures, or structures developing at the same time. Only one non-craniofacial anomaly presented a preferential association with microtia (although not statistically significant): preaxial polydactyly. This would suggest that microtia is a more isolated craniofacial dysmorphologic event. A severe insult early in the embryological development of the craniofacial region could lead to cell death of multiple primordial structures in the craniofacial region. The retinoic acid, thalidomide and mycophenolate mofetil embryopathies all present with microtia, cleft lip and palate, and microphthalmia (among other features) supporting this mechanism [Anderka et al., 2009; Stevenson, 2006].

Mastroiacovo et al [1995] used the same methodology of observed versus expected ratios and found as preferential associations: holoprosencephaly, cleft palate, preaxial polydactyly, esophageal atresia, and vertebral defects; the only finding discordant with ours is vertebral defects. Their negative associations (see Table V) were concordant with our results. However, some of our findings were not reported in their study. That said, there are some differences between the two studies that could account for this: 1) sample size, their study had only 48 cases versus 818 in this study, 2) they excluded syndromic cases, and 3) only defects occurring in at least 3 infants were reported in their study. Given the frequency in our large cohort, it is feasible the frequency of association with, for example, an/microphthalmia and cleft lip, did not meet their third criterion for reporting. Notably, Forrester and Merz [2005] also found similar associations to most of those we report, although they also reported preferential association of limb reduction defects with microtia, a result we did not observe in our data.

Only the most severe type of microtia (anotia) was found to have a significant association with renal defects, specifically renal agenesis. A preferential association of renal and ear anomalies has been clinically recognized for many years, potentially due to the mistaken consideration of pinna deformities due to oligohydramnios secondary to renal agenesis or cystic conditions as a part of the Potter sequence. Notably, Hudgins et al [1991] and Wang et al [2001] reported an association between renal and ear malformations when the individual had other congenital anomalies or a positive family history for deafness and/or microtia which was attributed to the coexistence of syndromes and malformation patterns. Although in our cohort patients did not have routine post-natal ultrasound and were not usually followed for more than 3 days, our findings further suggest that the association between ear and renal abnormalities should only be suspected in more severe cases.

Overall there appears to be a continuous trend towards more congenital anomalies as the degree of severity of microtia increases. This observation suggests that anotia (or grade IV microtia) is not a congenital anomaly different from microtia, or at least not more different from grade-III than this is from grade-II, and grade-II from grade-I. Thus, the common nomenclature anotia-microtia, or an/microtia seems to be unjustified, with perhaps the only exception being absent pinna with the presence of hair in the lower temporal area, since this indicates agenesis of the part of the ear which is known to inhibit the hair growth in the covering skin [Hunter et al., 2009].

The proportion of males with isolated microtia is reported to be significantly elevated over that reported for females [Carey et al., 2006]. Indeed in our study, we observed a slightly higher proportion of males (54.4%; 95% CI: 50.9–57.8). However, in a previous study performed in this same cohort analyzing cases of isolated microtia, the male proportion was 56.9% (95% CI: 54.1–59.4) [Luquetti et al., 2010]. Although this difference is not statistically significant, it is interesting that a lower proportion of males with associated anomalies compared to isolated cases of microtia was also reported by Harris et al [1996].

In considering our results, it is important to appreciate some potential limitations of our study. The most important study limitation is that ascertainment occurred from birth to 3 days of age without further follow-up; therefore there is potentially an underreporting for detection rate of internal organ defects and defects that typically become more apparent with age, such as facial asymmetry. However, for all the external malformations we suggest there is minimal underreporting considering that trained physicians have examined each infant.

There are numerous strengths of our study compared to previous similar assessments. The homogeneous method of ascertainment across hospitals and the coding system used by ECLAMC, a six-digit code, which facilitates a refined classification of the anomalies allowed our analysis to be more robust. In addition, this is the largest sample size that has been used for the study of associated anomalies in microtia with more than double the number of cases of previous studies. This increased size allowed a sufficiently larger number for the analysis of each subgroup of anomalies. For example, neural tube and congenital heart disease were analyzed in separate groups, a very important aspect when we consider that they might have different pathogenetic mechanisms. Our finding of preferential associations mostly with anomalies found in the oculo-auriculo-vertebral spectrum and negative or neutral associations for anomalies that have different embryological origins and timing further supports the strength of the methodology used for our analysis.

Based on these results we plan on studying non-genetic maternal exposures and individual genotypes of sub-groups (e.g.: microtia-microphthalmia or microtia-cleft palate) in future research. In addition, collaboration with other birth defects surveillance systems may show differences and similarities related to the population structure and exposures, complementing our findings. The identification of mouse models with similar sub-groups will also help to elucidate developmental pathways and direct studies of the genetic causes of microtia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

General characteristics of the microtia cases and no microtia: multiple anomalies (controls) in the ECLAMC (1967–2009).

	Microtia (N=818)	No-microtia: multiple anomalies (controls) (N=15,969)
	% (95% CI)	% (95% CI)
Male	54.4 (50.9–57.8)	54.3 (53.4–55.1)
Twin	3.2 (2.1–4.6)	2.8 (2.6–3.1)
Still-birth	12.1 (9.9–14.5)	11.2 (10.7–11.7)
Maternal age, years (sd)	27.5 (7.5)	26.1 (7.1)
Mean number of anomalies (sd)	3.5 (1.5)	2.7 (1.1)

sd: standard deviation

Table II

Distribution of the 818 cases of microtia associated with congenital anomalies by type and side affected by microtia.

Side of microtia	N (%)
Bilateral	396 (49.7)
Unilateral -Right	116 (59.5)
Unilateral -Left	79 (40.5)
Unilateral NS	205
Side not specified	1
Type of microtia *	
I	129 (40.4)
II	83 (26.0)
III	70 (21.9)
IV	37 (11.6)
NS	27

* data from 1996–2009

NS: Not-Specified

Table III

Congenital anomalies associated with microtia, ECLAMC 1967–2009.

	Microtia (N=818)	No-microtia: multiple anomalies (controls) (N=15,969)		
	% Observed	% Expected	OR [a]	95% CI
PREFERENTIAL ASSOCIATIONS (O/E >1)				
An/microphthalmia	11.5	4.4	1.5	1.2–2.0
Eyelid coloboma	0.4	0.1	3.4	0.9–13.0
Epibulbar dermoid	1.7	0.1	18.9	8.7–40.8
Choanal atresia	1.6	0.6	2.1	1.1–3.9
Cleft lip and palate	11.5	6.3	1.2	1.0–1.6
Cleft palate	12.8	6.3	1.7	1.3–2.1
Macrostomia	6.4	0.4	13.6	9.0–20.5
Facial asymmetry	10.6	2.1	5.8	4.5–7.5
Pre-axial polydactyly	2.2	1.2	1.4	0.9–2.4
Holoprosencephaly	2.2	1.2	1.2	0.7–2.0
NEGATIVE ASSOCIATIONS (O/E <1)				
Anencephaly	2.1	4.5	0.4	0.3–0.7
Spina bifida	2.4	10.7	0.2	0.1–0.4
Encephalocele	3.2	3.1	0.6	0.4–1.2
Cleft lip	0.9	1.6	0.4	0.2–1.0 [c]
Congenital heart disease [b]	18.5	19.7	0.7	0.6–0.9
Diaphragmatic hernia	2.8	3.0	0.7	0.5–1.1
Omphalocele	4.2	4.4	0.7	0.5–1.0 [c]
Gastroschisis	0.1	1.3	0.1	0.0–0.7
Anal atresia	7.9	8.6	0.7	0.5–0.9
Small intestine atresia	0.7	1.9	0.2	0.1–0.6
Renal agenesis	3.3	3.8	0.6	0.4–0.9
Polycystic kidney	2.0	4.0	0.2	0.1–0.4
Hydronephrosis	2.1	5.0	0.3	0.2–0.5
Arthrogryposis	4.0	5.6	0.5	0.4–0.8
Limb reduction defects	12.7	12.3	0.7	0.5–0.8
Clubfoot	10.3	15.8	0.5	0.4–0.6
Post-axial polydactyly	1.6	3.4	0.4	0.2–0.6
Hypospadia	3.4	6.1	0.5	0.3–0.9
O/E ~=1				
Microcephaly	6.2	4.8	0.9	0.6–1.2
Hydrocephalus	11.9	11.3	1.0	0.8–1.2
Esophageal Atresia	6.0	4.5	1.0	0.7–1.3
Vertebral anomalies	6.9	4.6	1.0	0.7–1.4

OR: odds ratio; CI: confidence interval

O/E: observed vs expected ratio

[a] Adjusted by: country, year, livebirth/stillbirth, sex, number of malformations

[b] Congenital heart disease was analyzed by sub-groups (septal and conotruncal defects), however no specific differences among those sub-groups were observed.

[c] CI does not include 1.0, it was rounded to 1.0, thus result is statistically significant.

Table IV

Congenital anomalies associated with microtia by severity of microtia (1997–2009)[a]

	Type I (n=129)	Type II (n=83)	Type III (n=70)	Type IV (n=37)
	Ref	OR 95% CI	OR 95% CI	OR 95% CI
Neural tube defects [b]	1.0	0.5 (0.2–1.6)	0.6 (0.2–1.9)	1.5 (0.5–0.6)
Microcephaly	1.0	1.0 (0.3–3.1)	1.2 (0.4–3.7)	0.4 (0.1–3.5)
Holoprosencephaly	1.0	0.7 (0.2–2.6)	0.0	0.5 (0.1–4.1)
Hydrocephalus	1.0	1.0 (0.5–2.2)	0.4 (0.2–1.2)	0.3 (0.1–1.4)
An/microphthalmia	1.0	0.5 (0.2–1.3)	0.9 (0.4–2.1)	0.7 (0.2–2.4)
Epibulbar dermoid	1.0	0.0	3.8 (0.3–42.3)	3.6 (0.2–58.3)
Choanal atresia	1.0	0.8 (0.1–8.7)	0.9 (0.1–10.3)	0.0
Cleft lip and palate	1.0	0.0	0.9 (0.1–10.3)	0.0
Cleft lip	1.0	1.8 (0.8–4.3)	1.8 (0.7–4.4)	3.4 (1.3–9.1)
Clef palate	1.0	1.2 (0.5–3.0)	2.0 (0.9–4.8)	0.6 (0.1–2.6)
Macrostomia	1.0	4.5 (1.2–17.4)	6.2 (1.6–23.7)	3.7 (0.7–19.2)
Facial asymmetry	1.0	0.8 (0.3–2.0)	0.9 (0.4–2.4)	0.7 (0.2–2.7)
Esophageal atresia	1.0	0.9 (0.2–4.0)	2.8 (0.8–9.0)	3.0 (0.8–11.8)
Congenital heart disease [c]	1.0	1.0 (0.5–1.9)	0.8 (0.4–1.6)	1.3 (0.6–2.9)
Diaphragmatic hernia	1.0	1.6 (0.4–6.5)	0.9 (0.2–5.1)	0.8 (0.3–2.6)
Vertebral anomalies	1.0	0.8 (0.2–3.2)	0.9 (0.2–3.8)	0.6 (0.1–4.9)
Intestinal mal rotation	1.0	1.0 (0.4–3.0)	0.6 (0.2–2.3)	1.6 (0.5–5.6)
Anal atresia	1.0	3.9 (1.0–15.4)	0.6 (0.1–6.0)	0.0
Renal agenesis	1.0	1.0 (0.2–6.3)	0.0	5.1 (1.1–23.9)
Polycystic renal disease	1.0	1.2 (0.3–5.4)	2.4 (0.6–9.3)	1.8 (0.3–10.2)
Hydronephrosis	1.0	0.0	0.2 (0.0–1.8)	0.9 (0.2–4.3)
Pre axial polydactyly	1.0	0.8 (0.1–4.3)	0.9 (0.2–5.1)	0.0
Arthrogryposis	1.0	0.9 (0.3–2.6)	0.8 (0.2–2.7)	0.8 (0.2–3.8)
Limb reduction defects	1.0	0.6 (0.2–1.5)	0.7 (0.2–1.8)	2.3 (0.9–5.7)
Clubfoot	1.0	0.9 (0.4–2.1)	1.1 (0.5–2.5)	0.8 (0.3–2.5)
Hypospadia	1.0	0.0	1.4 (0.2–8.7)	0.0

[a] Eyelid coloboma, omphalocele, small Intestine atresia, and post axial polydactyly were not included because there were no cases with type specified

[b] Neural tube defects were analyzed by sub-groups (anencephaly, spina bifida and encephalocele), however no specific differences among sub-groups were observed.

[c] Congenital heart disease was analyzed by sub-groups (septal and conotruncal defects), however no specific differences among those sub-groups were observed.

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Table V

Frequency (%) of congenital anomalies associated with microtia reported in previous studies (Pubmed search: 1970–2011)

	Italy [a] (n=48)	California, East France, Sweden [b] (n=376)	California [c] (n=389)	Hawaii [d] (n=44)	Our study South America (n=818)
	%	%	%	%	%
Proportion of cases associated with other CAs	27.9	California: 49.6 East France: 31.8 Sweden: 32.8	61.2	36.7	30.9
Neural tube defects	-	5.0	-	0.0	7.7 [neg]
Microcephaly	-	6.1	7.5	6.8	6.2
Holoprosencephaly	8.3 [pos]	7.2	-	0.0	2.2[pos]
Hydrocephalus	6.3 [neg]	4.0	-	6.8	11.9
An/Microphthalmia	-	14.1	8.7	9.1 [pos]	11.5[pos]
Choanal atresia	-	-	5.7	0.0	1.6[pos]
Cleft lip with or w/out palate	-	-	5.9	11.4	12.4[pos]
Cleft Palate	16.7 [pos]	-	11.1	11.4	12.8[pos]
Esophageal atresia	14.6 [pos]	6.9	-	2.3	6.0
Congenital heart disease	31.3 [neg]	30.6	32.4	52.3 [neg]	18.5[neg]
Diaphragmatic hernia	-	2.1	-	2.3	2.8[neg]
Vertebral anomalies	12.5 [pos]	-	14.9	-	6.9
Omphalocele	-	-	-	4.5	4.2 [neg]
Anal atresia	6.3 [neg]	6.9	-	4.5	7.9 [neg]
Small Intestine atresia	-	2.7	-	2.3	0.7 [neg]
Renal agenesis	-	8.0	-	11.4 [pos]	3.3 [neg]
Preaxial Polydactyly	6.3 [pos]	3.7	-	-	2.2[pos]
Limb reduction	-	11.2	-	15.9 [pos]	12.7 [neg]
Clubfoot	-	6.1	-	-	10.3 [neg]
Hypospadias	6.3 [neg]	4.0	-	6.8	3.4 [neg]

"-": not reported

"neg": negative association, as reported by authors

"pos": positive (preferential) association, as reported by authors

[a] Mastroiacovo et al, 1995: hospital based registry, neonatal period, excluded syndromic and chromosomal anomalies, sequences counted as one defect.

[b] Harris et al, 1996: population-based registry, up to one year of age, included syndromic cases (excluded chromosomal anomalies), no information on how dealt with sequences

[c] Shaw et al, 2004: population-based registry, up to one year of age, included syndromic cases (excluded chromosomal anomalies), no information on how dealt with sequences

[d] Forrester & Merz et al, 2005: population-based registry, included syndromic cases (excluded chromosomal anomalies), no information on how dealt with sequences

Other studies, not in the table:

Suutarla et al, 2007 (Finland): population-based registry up to one year of age, include syndromic cases (excluded chromosomal anomalies), no information on how dealt with sequences. Based on a mail questionnaire responded by the parents: 32.8 % associated (n=109), 10.9% CHD, no other CAs reported

Canfield et al, 2009 (Texas): 38.4% had multiple anomalies (chromosomal and syndromic excluded)—did not specify which malformations.