

Associated Malformations in Children with Orofacial Clefts in Portugal: A 31-Year Study

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Background: Orofacial clefts are among the most common congenital craniofacial malformations and may be associated with other birth defects. However, the proportion and type of additional anomalies vary greatly between studies. This study assessed the prevalence and type of associated congenital malformations in children with orofacial clefts, who attended the largest cleft lip and palate tertiary referral center in Portugal.

Methods: Consecutive children with orofacial clefts who attended at least 1 consultation in our Clefts Unit between 1981 and 2012 were studied. Demographic and clinical data regarding the number and type of associated malformations were retrospectively collected and analyzed.

Results: Of the 701 patients studied, 219 (31.2%) had associated congenital malformations. These malformations were more frequent in children with cleft palate (43.4%) than in children with cleft lip and palate (27.5%) or with cleft lip only (19.4%). Within the group with associated anomalies, 73 cases (33.3%) had conditions related with known chromosomal defects, monogenic syndromes or sequences, and 146 cases (66.7%) had multiple congenital anomalies of unknown origin. From those, head and neck malformations were the most common (60.3%), followed by malformations in the cardiovascular (28.3%) and musculoskeletal systems (26%).

Conclusions: The overall prevalence of associated malformations of nearly 1 in 3 children with orofacial clefts stressed the need for a comprehensive evaluation of these patients by a multidisciplinary cleft team. Moreover, one-third of the children had multiple congenital anomalies of known origins. Thus, early routine screening for other malformations and genetic counseling might be valuable for orofacial clefts management. (*Plast Reconstr Surg Glob Open* 2018;6:e1635; doi: 10.1097/GOX.0000000000001635; Published online 9 February 2018.)

INTRODUCTION

Orofacial clefts are among the most common congenital malformations of the craniofacial region,¹⁻⁴ which include cleft palate only (CP) and cleft lip with or without palate (CL/P). Their estimated incidence worldwide is about 1 in 1,500–2,000 births for CP and 1 in 700–1,000 births for CL/P, showing a considerable sex, ethnic, and geographic variation.^{1-3,5,6} For instance, the highest

incidence rates for CL/P were reported in Native Americans and Asians (China, Japan), and the lowest in Africans and Southern Europeans. On the other hand, incidence rates for CP seem similar in Europeans, Africans, Native Americans, and Asians.^{3,5-7}

Although orofacial clefts most commonly appear as isolated conditions, with a generally favorable outcome for the patients, it has long been known that they may

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Ethical standards: This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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be frequently associated with other congenital malformations.⁸⁻¹¹ In these cases, the outcome depends primarily on the presence and type of associated malformations.¹² However, the proportions of patients with orofacial clefts with additional abnormalities varies greatly between studies, from 1.5% to 64.2%.^{8-11,13-22} Also, there is no consensus on the type of malformations that are most commonly associated with orofacial clefts.^{8,10,14,21,22}

The interplay of different environmental and genetic risk factors has been proposed as an underlying mechanism for orofacial clefts. However, a single major risk factor for these congenital malformations has not been identified yet, suggesting a more complex etiology than the oligogenic model originally proposed.²³⁻²⁷ Moreover, consanguinity and a positive family history for orofacial clefts also play a role. Those whose parents have a close degree consanguinity and those with a positive family history for clefts are subject to higher risks for congenital malformations.^{25,28,29} Hence, the identification of specific co-occurring congenital malformations with orofacial clefts is important for improving the definition of the etiology of this pathology.^{1,27,30}

A combination of epidemiological and clinical approaches may enhance our understanding of the causes and pathogenesis of congenital malformations with implications for the prevention, diagnosis, prognosis, treatment, and counseling as well in the development of public health policies. Portugal has several advantages for epidemiological studies on orofacial clefts and associated congenital malformations. Indeed, it has a relatively homogenous population, and the treatment is centralized in few centers. According to the European Network for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) report, the prevalence of cleft lip with or without cleft palate was 7.8 per 10,000 births between 1980 and 2015 in Southern Portugal.³¹ Approximately half of the patients in this country is or has been at some point referred to our cleft lip and palate tertiary care center. Therefore, the aim of this study was to assess the prevalence and type of associated congenital malformations in patients with orofacial clefts who attended our tertiary referral center in Portugal.

PATIENTS AND METHODS

Study Design

This was a retrospective study carried out at the Clefts Unit of the Paediatric Surgery Department at *Dona Estefânia* Hospital - Central Lisbon Hospital Centre in Lisbon, Portugal. This unit comprises a tertiary referral center for the multidisciplinary care of orofacial clefts patients in Southern Portugal and the Portuguese Islands being the largest in the country. It also receives some patients referred from the Portuguese-speaking African countries.

Data were collected retrospectively from the medical records on all consecutive pediatric patients with orofacial clefts, who had at least 1 appointment at the Clefts Unit between January 1, 1981, and December 31, 2012.

Patients

Eligible study participants were children (< 18 years old) with typical orofacial clefts, ie, CP, cleft lip only (CL), and cleft lip and palate (CLP). Orofacial clefts were defined as failures in developing embryonic facial and palatal processes to either completely merge or fuse, which results in a predictable series of postnatal deformities. Patients were excluded if they had atypical clefts, including median, transverse, oblique, and other Tessier types of orofacial clefts³² or those whose clinical files did not explicitly refer to the presence or absence of associated malformations.

Data Collection and Variables

Data were collected from the Cleft Patient Data Sheet, usually completed by the physician in the first appointment by direct interview of the patient or parents and by physical examination. Data were also collected from all available patients' medical records (electronic and paper), including prenatal consultation, maternity, neonatal unit, outpatient clinic, pediatrics, and pediatric surgery files.

Variables under study included the following: date of birth, sex, follow-up period, occurrence and laterality of the orofacial cleft, associated malformations and respective molecular diagnosis, family history of orofacial clefts, consanguinity between the parents, and prenatal ultrasound diagnosis.

Orofacial clefts were described according to Tessier's anatomical classification.³² Their occurrence was categorized as unilateral or bilateral, and complete, incomplete, or microform (eg, submucous cleft palate). Cases of orofacial clefts were categorized as: without associated malformations, whenever no other congenital abnormalities were identified; or with associated malformations, whether 1 or more congenital abnormalities, unrelated to orofacial clefts, were also present. Dental anomalies were excluded from this study as associated malformations because most of these anomalies are closely related to orofacial clefts.

Cases of orofacial clefts with associated malformations were further divided into 4 categories according to their etiology: recognized causes, such as chromosomal syndromes (ie, involving clinically significant structural and/or numerical chromosomal abnormalities), monogenic syndromes (ie, related to a single gene), or sequence (ie, occurrence of associated anomalies due to a single known structural defect), or multiple congenital anomalies (MCAs) of unknown origin. For this study, MCA cases were defined as cases with 2 or more structural malformations (other than the cleft) that could not be explained by an underlying syndrome or sequence. The MCA were grouped according to the organ system or the anatomic region primarily affected.

Each case of orofacial cleft was referred to a consultation with a geneticist, and the following diagnostic genetic tests were performed as appropriate: until 2009, karyotype and fluorescence in situ hybridization for the 22q11.2 region; from 2009, karyotype and multiplex ligation-dependent probe amplification for the main microdeletion/microduplication syndromes, including the 22q11.2

Table 1. Prevalence and Characteristics of Orofacial Clefts in the Study Population

	Total (n = 701, 100%)	CLP (n = 287, 40.9%)	CL (n = 165, 23.5%)	CP (n = 249, 35.5%)
Laterality, n (%)*				
Left	226 (50.0)	126 (43.9)	100 (60.6)	—
Right	117 (25.9)	67 (23.3)	50 (30.3)	—
Bilateral	109 (24.1)	94 (32.8)	15 (9.1)	—
Total, n	452	287	165	—
Occurrence, n (%)				
Complete	490 (69.9)	248 (86.4)	101 (61.2)	141 (56.6)
Incomplete	211 (30.1)	39 (13.6)	64 (38.8)	108 (43.4)
Total, n	701	287	165	249
Family history of clefting, n (%)†				
Yes	117 (24.6)	53 (27.0)	25 (24.3)	39 (22.2)
No	358 (75.4)	143 (73.0)	78 (75.7)	137 (77.8)
Total, n	475	196	103	176
Prenatal ultrasound diagnosis, n (%)†				
Yes	119 (24.0)	80 (39.0)	37 (35.2)	2 (1.1)
No	377 (76.0)	125 (61.0)	68 (64.8)	184 (98.9)
Total, n	496	205	105	186
Associated malformations, n (%)				
Without	482 (68.8)	208 (72.5)	133 (80.6)	141 (56.6)
With	219 (31.2)	79 (27.5)	32 (19.4)	108 (43.4)
Total, n	701	287	165	249
Etiology of associated malformations, n (%)				
Chromosomal syndromes	12 (5.5)	4 (5.1)	0 (0.0)	8 (7.4)
Monogenic syndromes	18 (8.2)	5 (6.3)	3 (9.4)	10 (9.3)
Sequence	43 (19.6)	0 (0.0)	0 (0.0)	43 (39.8)
MCA of unknown causes	146 (66.7)	70 (88.6)	29 (90.6)	47 (43.5)
Total, n	219	79	32	108

*Considering that cleft palate does not exhibit laterality.

†There were cases in which these variables were not documented in the medical record.

region; from 2011, comparative genomic hybridization array; and gene-targeted sequencing, as the molecular causes for specific monogenic syndromes have been identified.

Statistical Methods

The collected data were analyzed using the SPSS software (version 20.0). Continuous variables were summarized by mean and minimum-maximum. Categorical variables were expressed as number and percentage of cases in each group (ie, with and without associated malformations) and compared using the Chi-square test or Fisher's exact test, as appropriate. Due to the study design, no sample calculation was performed. The statistical significance was concluded at the 5% level.

RESULTS

A total of 1,059 patients with orofacial clefts has had at least 1 appointment at the tertiary referral center during the study period of 31 years. After applying the eligibility criteria, 8 subjects were excluded because they had atypical clefts, and 350 subjects were excluded because they had incomplete medical records (not referring explicitly to the presence or absence of associated malformations). Only the data of the remaining 701 patients were included in our analysis. Of those patients, 393 (56.1%) were males and 308 (43.9%) were females. Patients were followed up until a mean age of 15 years old (minimum 1 year and 2 months; maximum 33 years).

The prevalence and characteristics of the orofacial clefts and associated malformations are shown in Tables 1 and 2. Overall, the most frequent orofacial cleft was CLP, recorded in 287 (40.9%) patients, followed by CP and

CL, recorded in 249 (35.5%) and 165 (23.5%) patients, respectively.

In the 452 children with CL/P, 50.0% (n = 226) had left-sided cleft, 25.9% (n = 117) had right-sided cleft, and 24.1% (n = 109) had bilateral cleft. About 17.3% (n = 78) of the children with CL/P had a family history of clefting, compared with 15.7% (n = 39) of the 249 children with CP. In addition, a prenatal ultrasound diagnosis of cleft was obtained in 24.0% of our study population, comprising mostly cases with CL/P (Table 1).

As shown in Table 1, the prevalence of orofacial clefts without associated malformations was 482 (68.8%), whereas 219 (31.2%) cases were found to have an associated malformation that required follow-up or treatment. Moreover, associated malformations were more frequent in children who had CP (in 43.4% of those) than in children with CLP (27.5%) or CL (19.4%). Of the 219 children with associated malformations, 108 (49.3%) had CP, 79 (36.1%) had CLP, and 32 (14.6%) had CL (Table 2).

Regarding gender, the group without associated malformations had 280 males (58.1%) and 202 females (41.9%), whereas the group with associated malformations had 105 males (47.9%) and 114 females (52.1%) (Table 2).

As shown in Table 2, family history of clefting was present in 13.9% of the children without associated malformations and in 22.8% of the children with associated malformations. Cases with associated malformations had a statistically significant lower proportion of prenatal ultrasound diagnosis when comparing with the group without associated malformations (13.2% versus 18.7%; $P < 0.001$). Finally, parental consanguinity was present in 1.2% of the children without associated malformations and in 2.3% of children with associated malformations (Table 2).

Table 2. Prevalence and Characteristics of Associated Malformations in Children with Orofacial Clefts

	Associated Malformations		P
	Without (n = 482)	With (n = 219)	
Gender, n (%)			
Male	280 (58.1)	105 (47.9)	0.182
Female	202 (41.9)	114 (52.1)	
Orofacial cleft, n (%)			
CP	141 (29.3)	108 (49.3)	< 0.001
CL	133 (27.6)	32 (14.6)	
CLP	208 (43.2)	79 (36.1)	
Laterality, n (%)			
Left	115 (23.9)	43 (19.6)	< 0.001
Right	53 (11.0)	29 (13.2)	
Bilateral	42 (8.7)	34 (15.5)	
Family history of clefting	67 (13.9)	50 (22.8)	0.384
Prenatal ultrasound diagnosis	90 (18.7)	29 (13.2)	< 0.001
Parental consanguinity	6 (1.2)	5 (2.3)	0.765
Etiology			
Chromosomal syndromes		12 (5.5)	
Monogenic syndromes		18 (8.2)	
Sequence		43 (19.6)	
MCA of unknown origin		146 (66.7)	

In both groups of patients, isolated cleft or with associated malformations, the left side was the most affected. However, the group with associated malformations had a significantly lower proportion of left side involvement (19.6% versus 23.9%) and a higher proportion of right side (13.2% versus 11.0%) and bilateral involvement (15.5% versus 8.7%), compared with the group without associated malformations ($P < 0.001$).

Regarding the etiology of the associated malformations, 146 (66.7%) patients had MCA of unknown origin and 73 (33.3%) patients had recognized conditions. Among these, 12 patients (16.4%) had identified chromosomal syndromes, 18 patients (24.7%) had monogenic

syndromes, and 43 patients (58.9%) had sequences. The most frequent chromosomal anomaly was the 22q11.2 deletion syndrome, also known as the velocardiofacial or Di-George syndrome, occurring in 8 CP patients, followed by trisomy 13, trisomy 21, 21q deletion, and Klinefelter syndrome, in 1 patient each. The most frequently identified monogenic syndrome was the Van der Woude syndrome ($n = 6$), followed by Treacher-Collins syndrome ($n = 5$), Goldenhar syndrome ($n = 2$), orofacial digital syndrome type 1 ($n = 2$), Apert syndrome ($n = 1$), Gorlin syndrome ($n = 1$), and Kabuki syndrome ($n = 1$). Finally, the Pierre Robin sequence was identified in 43 patients.

Among the 219 patients with associated malformations, 90 cases (41.1%) had 1 unrelated associated malformation, whereas 2 associated malformations were found in 62 cases (28.3%), and 3 or more associated malformations were recorded in 67 cases (30.6%).

The number of individuals with a certain organ system affected among those with associated malformations is shown in Figure 1. Head and neck anomalies were the most frequent associated malformations, in 60.3% ($n = 132$) of the patients with associated malformations, and among them, eye and ear were the most affected organs. Cardiovascular malformations were the second most common anomalies, accounting for recorded malformations in 28.3% ($n = 62$) of the patients with associated malformations, of which atrial and ventricular septal defects, followed by patent ductus arteriosus, were the most prevalent. Musculoskeletal anomalies were the third most common malformations, occurring in 26.0% ($n = 57$) of patients, and among them, most were cases of polydactyly and limb reductions. In 11.4% ($n = 25$) of patients, urologic anomalies were also found, being cryptorchidism the most common. In 9.6% ($n = 21$) of the associated malformations cases, malformations of the digestive system and abdominal wall occurred, mostly inguinal and umbilical

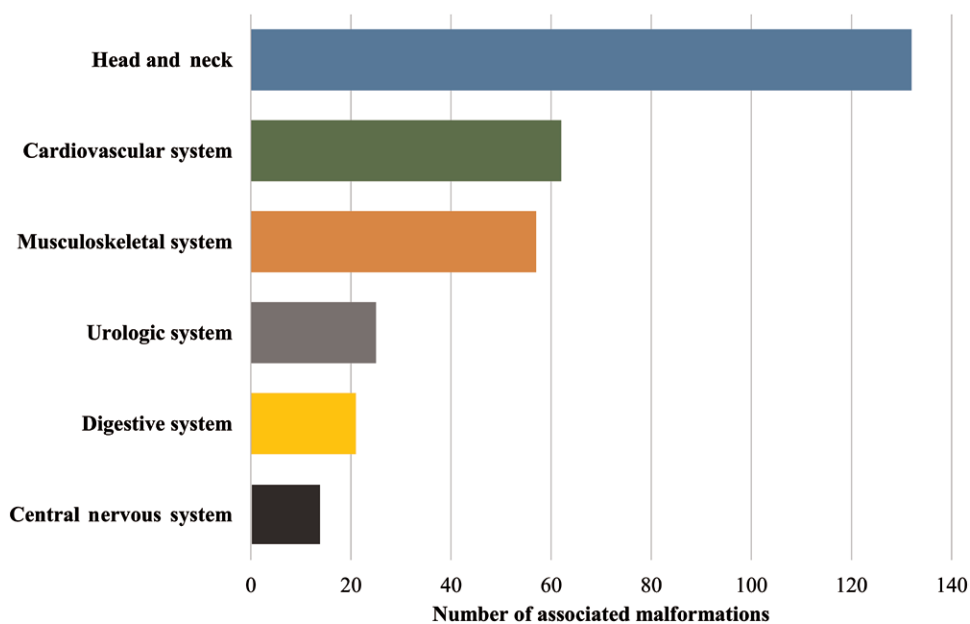


Fig. 1. Number of patients with associated malformations by organ system.

hernias. Finally, malformations of the central nervous system appeared in 6.4% (n = 14) of the associated malformations, of which the majority were reduction deformities of the brain.

DISCUSSION

We investigated the prevalence and type of associated congenital malformations in 701 children with CP and CL/P who attended a tertiary referral center during a 31-year period. These patients represented most of the cases of orofacial clefts born in Southern Portugal and the Portuguese Islands between 1981 and 2012. During this period, the overall incidence of clefts was around 5.5 per 10,000 total births in Southern Portugal, according to the literature.⁸ In our study, we found a higher prevalence of orofacial clefts in males, which is in agreement with published data,^{1-3,15,33} with a 1.3:1 ratio of affected boys to girls.

A prenatal diagnosis of orofacial cleft was obtained in only 24.6% of the study sample, and most of these cases correspond to CL/P. In fact, not all the subjects had an ultrasound performed, particularly the older ones, as routine obstetric ultrasound examinations were implemented in Portugal in the early 90s. In addition, although the diagnostic accuracy of ultrasound examinations has been improving over the past years, routine screening for the palate is technically more difficult than for the lip and is not included in most centers' protocols.³⁴ Therefore, prospective parents should be advised that palatal involvement might be underdiagnosed prenatally.

The frequency of associated congenital malformations in children with orofacial clefts was 31.2%, which was slightly above the 25.5% and 27.5% previously reported by 2 Portuguese studies,^{14,35} but in agreement with the international literature that reports a range from 1.5% to 64.2%.^{8,10,11,13,16-22,36-42} This wide variation might be in part attributed to the fact that most studies do not report all infants born within a certain geographical area, but only those referred to a specific unit (frequently tertiary). Another possible explanation for this variation is the lack of agreement on what should be regarded as a congenital defect. In our study, we have included abnormalities that could lead to function impairment and, in this sense, require either continual medical follow-up or treatment.

Similar to the results of our study, previous studies indicated that the orofacial cleft type most frequently associated with other malformations was CP.^{1,8,10,11,13,14,16-22,37-42} Moreover, we found a significantly higher proportion of bilateral involvement in the cases with associated malformations than in the cases without associated malformations, in agreement with several studies suggesting that more extensive clefts are associated with a higher risk of occurrence of other congenital malformations.⁸⁻¹⁰

In our study, most associated MCA were recorded in the head and neck region, accounting for 60.3% of the patients with malformations. The second most common MCA associated with orofacial clefts were those affecting the cardiovascular system, followed by the musculoskeletal, the urologic, the digestive, and the central nervous systems. From embryological studies, we know that the

development of facial structures is intimately related and interdependent with the development of other structures, and we also know that several components may be affected by the same etiopathogenic factors in pathological conditions. Also, failure in the adequate development of 1 anatomic structure may compromise the normal development of several dependent ones, as well illustrated by the Pierre Robin sequence.⁴³ Thus, associated malformations in children with orofacial clefts may involve several anatomic systems, even in areas far from the cleft. Indeed, in agreement with our study, the head and neck region, the musculoskeletal, cardiovascular, and central nervous systems are the most cited in the literature. However, there are divergent reports regarding which system and which congenital malformation is exactly the most common in orofacial cleft infants.^{8-11,13,14,16,18,19,21,39}

Once again, different results between studies may be due to different sampling methods, how long after birth the orofacial clefts cases were examined, differences in case definition and inclusion/exclusion criteria, or differences between the populations analyzed, which could themselves have different incidences of clefts and other congenital malformations. For instance, our long follow-up period (until patients were 15 years old on average) may have increased the proportion of minor or non-life-threatening conditions over serious life-threatening ones, which lead to death early in life. We believe that this may be responsible for the relatively low proportion of the recorded central nervous system malformations in our study. In addition, more recent studies may be influenced by the fact that several formerly regarded MCA of unknown origin are now recognized as part of a specific syndrome, sequence or chromosomal abnormality. On the other hand, we have been increasing our ability to diagnose morphologic anomalies with the development of more accurate imaging, genetic and molecular tests.

Potential limitations of this study arise from its retrospective observational nature, as our analysis was based on the available medical records over a long period of 31 years, which might have led to variations in case investigation, genetic diagnostic procedures, and completeness of reporting. Orofacial cleft patients were excluded from this study due to missing data on the presence or absence of associated malformations. Nevertheless, we found a significant homogeneity among registries and most patients had a complete Cleft Patient Data Sheet with all the variables under study. Another limitation might be the study setting, which was hospital-based. However, clefting is a condition that requires hospital treatment, and therefore, we considered that our study population was representative of the Portuguese orofacial cleft patients.

The main strengths of this study include a well-defined geographical area (South of Portugal and the Islands), a large sample size (n = 701), a long follow-up period, the classification into without associated malformations, chromosomal syndromes, monogenic syndromes, sequences or MCA of unknown origin, and the examinations by a clinical geneticist of the orofacial clefts cases with associated malformations.

CONCLUSIONS

This study provides a basis for research of the etiology of orofacial clefts. The presence and nature of different synchronous malformations might indicate different mechanisms of abnormal prenatal development. Identification of smaller subgroups or clusters may be important in etiological studies to elucidate the environmental and genetic risk factors and the interaction between them.

The overall prevalence of associated malformations (nearly 1 in 3 infants) emphasizes the need for a more comprehensive evaluation of children with orofacial clefts. An early screening routine for other congenital malformations, particularly those of the head and neck, cardiovascular, skeletal, and central nervous systems, should be considered in all orofacial clefts patients, especially when considering lip surgery within the first days of life, as many severe defects may not be diagnosed during the neonatal period by clinical examination alone. Genetic counseling might be also valuable, particularly in the orofacial cleft cases with associated malformations. Strict cooperation between cleft team members is essential to comprehensively cover all aspects of the management of the patient with orofacial clefts.

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REFERENCES

- Calzolari E, Bianchi F, Rubini M, et al; EUROCAT Working Group. Epidemiology of cleft palate in Europe: implications for genetic research. *Cleft Palate Craniofac J*. 2004;41:244-249.
- Derijcke A, Eerens A, Carels C. The incidence of oral clefts: a review. *Br J Oral Maxillofac Surg*. 1996;34:488-494.
- Mossey P, Castilla E, eds. *Global Registry and Database on Craniofacial Anomalies: Report of a WHO Registry Meeting on Craniofacial Anomalies, Baurú, Brazil, 4-6 December 2001*. Geneva, Switzerland: World Health Organization; 2001.
- Schutte BC, Murray JC. The many faces and factors of orofacial clefts. *Hum Mol Genet*. 1999;8:1853-1859.
- Butali A, Mossey PA. Epidemiology of orofacial clefts in Africa: methodological challenges in ascertainment. *Pan Afr Med J*. 2009;2:5.
- Natsume N. Incidence of cleft lip and palate among Japanese newborns, 1982 to 1984. *Plast Reconstr Surg*. 1987;79:499-501.
- Yi NN, Yeow VK, Lee ST. Epidemiology of cleft lip and palate in Singapore—a 10-year hospital-based study. *Ann Acad Med Singapore*. 1999;28:655-659.
- Calzolari E, Pierini A, Astolfi G, et al. Associated anomalies in multi-malformed infants with cleft lip and palate: an epidemiologic study of nearly 6 million births in 23 EUROCAT registries. *Am J Med Genet A*. 2007;143A:528-537.
- Hagberg C, Larson O, Milerad J. Incidence of cleft lip and palate and risks of additional malformations. *Cleft Palate Craniofac J*. 1998;35:40-45.
- Milerad J, Larson O, Haqberg C, et al. Associated malformations in infants with cleft lip and palate: a prospective, population-based study. *Pediatrics*. 1997;100:180-186.
- Stoll C, Alembik Y, Dott B, et al. Associated malformations in cases with oral clefts. *Cleft Palate Craniofac J*. 2000;37:41-47.
- Jones MC. Facial clefting. Etiology and developmental pathogenesis. *Clin Plast Surg*. 1993;20:599-606.
- Beriaghi S, Myers SL, Jensen SA, et al. Cleft lip and palate: association with other congenital malformations. *J Clin Pediatr Dent*. 2009;33:207-210.
- Duarte R, Leal MJ. [The range of congenital malformations associated with cleft lip and palate]. *Acta Med Port*. 1999;12:147-154.
- Ipdtoc Working Group. Prevalence at birth of cleft lip with or without cleft palate: data from the International Perinatal Database of Typical Oral Clefts (IPDTC). *Cleft Palate Craniofac J*. 2011;48:66-81.
- Jhawar D, Prasad B, Sharma S, et al. Congenital anomalies associated with cleft lip and/or palate (CL/P): an epidemiological study. *Int J Oral Maxillofac Surg*. 2007;36:988-989.
- Jones MC. The risk that an apparently isolated cleft lip with or without cleft palate will be associated with anomalies that impact outcome: follow up of 32 cases ascertained through prenatal diagnosis. *Proc Greenwood Genetic Center*. 2000;19:122-123.
- Lilii GP. Clefts with associated anomalies and syndromes in Finland. *Scand J Plast Reconstr Surg Hand Surg*. 1992;26:185-196.
- Perrotin F, de Poncheville LM, Marret H, et al. Chromosomal defects and associated malformations in fetal cleft lip with or without cleft palate. *Eur J Obstet Gynecol Reprod Biol*. 2001;99:19-24.
- Shaw GM, Carmichael SL, Yang W, et al. Congenital malformations in births with orofacial clefts among 3.6 million California births, 1983-1997. *Am J Med Genet A*. 2004;125A:250-256.
- Shprintzen RJ, Siegel-Sadewitz VL, Amato J, et al. Anomalies associated with cleft lip, cleft palate, or both. *Am J Med Genet*. 1985;20:585-595.
- Wyszynski DF, Sárközi A, Czeizel AE. Oral clefts with associated anomalies: methodological issues. *Cleft Palate Craniofac J*. 2006;43:1-6.
- Aylsworth AS. Genetic considerations in clefts of the lip and palate. *Clin Plast Surg*. 1985;12:533-542.
- Murray JC. Gene/environment causes of cleft lip and/or palate. *Clin Genet*. 2002;61:248-256.
- Murthy J, Bhaskar L. Current concepts in genetics of nonsyndromic clefts. *Indian J Plast Surg*. 2009;42:68-81.
- Shi M, Wehby GL, Murray JC. Review on genetic variants and maternal smoking in the etiology of oral clefts and other birth defects. *Birth Defects Res C Embryo Today*. 2008;84:16-29.
- Stanier P, Moore GE. Genetics of cleft lip and palate: syndromic genes contribute to the incidence of non-syndromic clefts. *Hum Mol Genet*. 2004;13 Spec No 1:R73-R81.
- Aquino SN, Paranaíba LM, Martelli DR, et al. [Study of patients with cleft lip and palate with consanguineous parents]. *Braz J Otorhinolaryngol*. 2011;77:19-23.
- Rittler M, Liasovich R, López-Camelo J, et al. Parental consanguinity in specific types of congenital anomalies. *Am J Med Genet*. 2001;102:36-43.
- Lidral AC, Murray JC. Genetic approaches to identify disease genes for birth defects with cleft lip/palate as a model. *Birth Defects Res A Clin Mol Teratol*. 2004;70:893-901.
- European Surveillance of Congenital Anomalies. EUROCAT prevalence data tables. A1 - cases and prevalence (per 10,000 births) for the following registries: S Portugal, from 1980 - 2015. Available at <http://www.eurocat-network.eu/prevdata/resultsPdf.aspx?title=A1&datefrom=1980&dateto=2015&allanom=&allreg=false&allrega=false&anomalies=®istries=28®istriesa=&winx=1256&winy=894>. Accessed May 8, 2017.
- Tessier P. Anatomical classification facial, cranio-facial and latero-facial clefts. *J Maxillofac Surg*. 1976;4:69-92.
- Lisi A, Botto LD, Rittler M, et al. Sex and congenital malformations: an international perspective. *Am J Med Genet A*. 2005;134A:49-57.
- Knox G, Braithwaite F. Cleft lips and palates in Northumberland and Durham. *Arch Dis Child*. 1963;38:66-70.
- Fino D, Almeida JMR. [Congenital malformations: retrospective study in 184282 newborns]. *Arquivo Clínico da Maternidade Alfredo da Costa*. 1980;8:57-71.

36. Croen LA, Shaw GM, Wasserman CR, et al. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. *Am J Med Genet.* 1998;79:42-47.
37. Magdalenić-Mestrović M, Bagatin M. An epidemiological study of orofacial clefts in Croatia 1988-1998. *J Craniomaxillofac Surg.* 2005;33:85-90.
38. Matthews MS, Cohen M, Viglione M, et al. Prenatal counseling for cleft lip and palate. *Plast Reconstr Surg.* 1998;101:1-5.
39. Sárközi A, Wyszynski DF, Czeizel AE. Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. *BMC Oral Health.* 2005;5:4.
40. Shafi T, Khan MR, Atiq M. Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. *Br J Plast Surg.* 2003;56:106-109.
41. Vallino-Napoli LD, Riley MM, Halliday J. An epidemiologic study of isolated cleft lip, palate, or both in Victoria, Australia from 1983 to 2000. *Cleft Palate Craniofac J.* 2004;41:185-194.
42. Wyse RK, Mars M, al-Mahdawi S, et al. Congenital heart anomalies in patients with clefts of the lip and/or palate. *Cleft Palate J.* 1990;27:258-264; discussion 264.
43. Sperber GH. First year of life: prenatal craniofacial development. *Cleft Palate Craniofac J.* 1992;29:109-111.