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Classification and Birth Prevalence of Orofacial Clefts

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To determine the proportion and birth prevalence of "typical" orofacial clefts (cleft lip (CL), cleft palate (CP), cleft lip and palate (CLP)) and "atypical" clefts (median, transversal, or oblique facial clefts) and the conditions in which they occur, we analyzed a population-based sample of 4,433 cases ascertained from 2,509,881 California births. We classified cases into: isolated cleft anomalies, sequences of the primary defect, chromosomal aberrations, monogenic syndromes, results of known teratogens, associations, multiple congenital anomaly (MCA) of unknown etiology, or conjoined twins. The birth prevalence of isolated CL±P was 0.77 per 1,000 births (CL 0.29/1,000, CLP 0.48/1,000) and of isolated CP, 0.31 per 1,000 births. Non-Hispanic Whites had the greatest prevalence of isolated clefts, Asians slightly lower prevalences, and Blacks the lowest. Asians had the lowest prevalence of Robin sequence and non-Hispanic Whites the highest, twice that of Hispanics. Hispanics, followed by Asians, had the highest prevalence of CL±P with MCA; non-Hispanic Whites had the lowest. Asians had the lowest prevalence of CP; in Whites and Hispanics it was almost twice as high. Blacks had the highest CL:CLP ratio, followed by non-Hispanic Whites and Asians; Hispanics had the lowest. Isolated anomalies constituted 61.67% of clefts. In the total sample there were 3.9% sequences, 8.79% chromosomal aberrations, 6.02% monogenic syndromes, 0.2% known teratogens, 0.79% associations, 18.55% MCA of unknown etiology, and 0.1% in conjoined twins. This study supports evaluation of each child on a "case" level, and provides a framework for genetic counseling and other studies focused on causes and prevention of these serious anomalies. Am. J. Med. Genet. 75:126–137, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS: cleft lip; cleft lip and palate; cleft palate; atypical clefts; classification; multiple malformations; prevalence; epidemiology

INTRODUCTION

Orofacial clefts are one of the most common congenital anomalies. One case of orofacial cleft occurs in approximately every 500 to 550 births. On an average day in the United States, 20 infants are born with orofacial cleft; 7,500 are born with cleft in the U.S. every year. Each of these children requires several surgical procedures and complex medical treatments and together with his or her family often suffers serious psychological problems. The estimated average lifetime medical cost per orofacial cleft is $100,000 per child [Waitzman et al., 1994], amounting to $750 million for all such children born within one year.

This group of anomalies comprising clefting of facial structures and/or clefting of oral structures (e.g., palate) is heterogeneous. It comprises "typical" orofacial clefts (cleft lip, CL; cleft lip and palate, CLP; and cleft palate only, CP) and "atypical" clefts (median, transversal, oblique and other Tessier's types of facial clefts [Tessier, 1976]). Both typical and atypical clefts can occur as an isolated anomaly, as part of a sequence of the primary defect, or as a multiple congenital anomaly (MCA). In MCA, the cleft anomaly could be part of a known monogenic syndrome, part of a chromosomal aberration, part of an association, or part of a complex of multiple congenital anomalies of unknown etiology. For the classification of MCAs in which orofacial cleft

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was a part of the entity, we used a similar classification which we developed for the study of MCAs in California [Tolarová et al., 1994, 1995].

With rapidly progressing new knowledge in medical genetics and with new DNA diagnostic technologies, more and more cases of orofacial clefts are identified as syndromic. Thus, although the basic rate of clefting (1:500–550) has not changed since Fogh-Andersen [1942] did his pioneering genetic study, we can now clarify these clefts more accurately. The correct diagnosis of a cleft anomaly is fundamental to further genetic and etiopathological studies, as well as for preventive measures, targeting correctly the class of orofacial clefts that are preventable.

This study was done on a large and unique population-based sample of 4,433 cases of orofacial clefts from the California population. With the implementation of our present knowledge, the cases were carefully classified into homogenous groups and the birth prevalence was calculated within each separate group.

Previously reported epidemiological studies have had many weaknesses and biases, including small sample size, data from birth certificates only, surgical samples, or data from registries that were not "cleaned." These problems, which led to extreme differences in rates as well as in the proportion of cases with associated anomalies that were not always satisfactorily explained by differences in populations, were eliminated in our study.

MATERIALS AND METHODS

The sample studied consisted of 4,433 cases with any type of isolated or multiple orofacial cleft anomaly registered by California Birth Defects Monitoring Program (CBDMP) registry from 1983 through 1993; detailed review and classification of these cases took almost four years. The CBDMP registry is a regional population-based registry of congenital anomalies currently based on approximately 300,000 annual births [Croen et al., 1991]. CBDMP staff visit all hospitals and outpatient genetic centers in California counties to abstract data about all children with congenital anomalies diagnosed up to the age of 1 year. For each specific diagnosed anomaly, CBDMP staff record: 1) the type of physical examination and/or medical procedure and/or confirmatory test used to establish the diagnosis, and 2) the specific subspecialty of the physician who made the diagnosis. In this way, the accuracy of a particular diagnosis can be evaluated. Data from 1983 through 1993 were used, representing a total of 2,509,881 births, of which 2,493,331 were live births and 16,550 stillbirths; the sample contained data previously partially analyzed by Shaw et al. [1991] covering the years 1983–1986 and by Robert et al. [1996] covering the years 1983–1990. Abstracts of all registered cases (n = 4,433) were reviewed and cases were classified by a medical geneticist (M.M.T.) by using the same classification developed for the study of multiple congenital anomalies in California [Tolarová et al., 1994, 1995]. If necessary, for clarification of the diagnosis additional information was obtained from medical facilities. For the study done by Shaw et al. [1991], the abstracts were reviewed by a medical geneticist as well, for the study done by Robert et al. [1996] the data were "cleaned" on electronic file only.

We calculated the percentage of newborns with orofacial cleft that had an isolated anomaly and the percentage that had any other condition in which orofacial cleft was involved. We calculated the birth prevalence of orofacial clefts per 1,000 births for each individual subgroup. The 95% upper and lower confidence intervals (CI) based on the Poisson distribution were calculated for each estimate and for the overall estimate.

RESULTS

Classification

All 4,433 cases in our sample were classified into one of the following nine major groups. Within each major group, subclassification was according to final individual diagnoses (for groups 1 through 6) or according to best estimate of etiological origin (for group 7).

Case Definitions

Cases were identified as all liveborn or stillborn (>20 weeks of gestation) infants affected with an orofacial cleft and diagnosed up to 1 year of age.

1. Isolated orofacial clefts.

(1) Typical orofacial clefts (*cleft lip*, CL), unilateral or bilateral *cleft lip and palate* (CLP), and *cleft palate* (CP). Typical orofacial clefts were diagnosed in cases affected with the cleft anomaly and no other major anomaly or anomalies. The presence of minor anomalies, such as low-set ears, clinodactyly, or Mongolian spot, did not change the eligibility of the case to be considered as isolated.

(2) Atypical orofacial clefts (*median cleft lip*, unilateral or bilateral *transversal, oblique* or other types of *Tessier's facial* cleft). Cases with only cleft but no other major defect unrelated to the primary cleft defect were classified as isolated atypical clefts

2. Orofacial clefts in sequences.

Those cases of CL, CLP, CP, and atypical clefts were classified as orofacial clefts in sequences when the cleft was a part of the sequence of anomalies etiopathogenetically related to a single defect that had occurred in early embryonic development.

3. Orofacial clefts in chromosomal aberrations.

Cases with clinically significant numerical and/or structural chromosomal aberration were included in this group.

4. Orofacial clefts in monogenic syndromes.

Included in this group were orofacial clefts that were part of the spectrum of recognized pattern autosomal dominant (AD), autosomal recessive (AR), X-linked dominant (XD) and X-linked recessive (XD) syndromes. Also, syndromes that are mostly sporadic which have been described in the literature as AD or AR were included in this group.

5. Orofacial clefts in known environmental syndromes.

Cases included in this group were those of so-called "environmental syndromes" in which the orofacial cleft was part of the spectrum of environmental embryopathy or fetopathy cased by a known teratogen, such as fetal alcohol syndrome or Dilantin syndrome.

6. Orofacial clefts in known associations.
Clefts associated with the complex of multiple malformations that form known associations like VATER or CHARGE were classified as orofacial clefts in known associations.
7. Orofacial clefts in multiple congenital anomaly of unknown etiology.

Into this group were classified all cases of MCA in which, in addition to CL, CLP, CP, or atypical cleft, at least one other major anomaly occurred in the child with either normal or unknown karyotype whenever such a combination did not qualify for any of groups 2 through 6 listed above. Implementing the classification of anomalies introduced by Spranger et al. [1982] and further developed by Cohen [1982], we further classified all cases in this category into six subgroups according to best estimation of the etiological origin of these anomalies. The subgroups were:

7.1—Orofacial clefts in MCA of a malformation origin.

7.2—Orofacial clefts in MCA of a deformation origin.

7.3—Orofacial clefts in MCA of a disruption origin.

7.4—Orofacial clefts in MCA of a malformation and deformation origin.

7.5—Orofacial clefts in MCA of a malformation and deformation and disruption origin.

7.6—Orofacial clefts in MCA of a malformation and disruption origin.

7.7—Orofacial clefts in MCA of a deformation and disruption origin.

7.8—Orofacial clefts in MCA of a combination other than 7.4–7.6.

8. Orofacial clefts in entities belonging to more than one of the categories defined.

The cases in which combinations of group 2 through 7 occurred.

9. Orofacial clefts in conjoined twins.
The cases in which orofacial clefts occurred in one or both conjoined twins.

Proportion of Different Groups of Orofacial Clefts

In our population-based sample of 4,433 cases of orofacial clefts, only 61.67% of orofacial clefts occurred as *isolated* anomalies (Table I). The largest proportion of isolated clefts (70.83%) were CL±P, of which 62.89% were CLP. Isolated atypical clefts were diagnosed in 13 cases (0.29%).

Sequences represented 3.9% and the remaining 34.47% were cases other than isolated or sequences. The group of sequences was formed mostly by two sequences: Robin sequence (n = 134) and holoprosencephaly sequence (n = 36). There were two cases of frontonasal dysplasia sequence and one case of amyoplasia congenita disruption sequence.

Clefts in chromosomal aberrations were observed in 390 cases (8.79%). The most frequent unique diagnosis was trisomy 13 (n-143), followed by trisomy 18 (n = 80). Among 267 cases (6.07%) of monogenic syndromes, the most frequent were autosomal dominant syndromes (n = 194). There were nine cases with a known environmental cause and 35 cases in which orofacial cleft occurred in known association.

TABLE I. Classification of Orofacial Clefts

Group	Type of anomaly	Live births	Still births	Unknown	Total	%
Isolated anomaly	Cleft lip (CL)	701	14	3	718	16.20
(n = 2,732, 61.63%)	Cleft lip and palate (CLP)	1,202	14	1	1,217	27.45
	Cleft palate (CP)	770	12	2	784	17.69
	Atypical facial cleft	13	0	0	13	0.29
Sequence	Robin sequence	134	0	0	134	3.02
(n = 173, 3.90%)	Holoprosencephaly sequence	33	2	1	36	0.81
	Frontonasal dysplasia sequence	2	0	0	2	0.05
	Amyoplasia congenita disruption sequence	1	0	0	1	0.02
Chromosomal aberrations	Trisomy 21	19	1	0	20	0.45
(n = 390, 8.79%)	Trisomy 13	128	14	1	143	3.23
	Trisomy 18	72	7	1	80	1.80
	Other trisomies	23	2	0	25	0.56
	Other chromosomal aberrations	114	3	5	122	2.75
Monogenic syndromes	Autosomal dominant (AD)	187	5	2	194	4.38
(n = 267, 6.02%)	Autosomal recessive (AR)	50	4	2	56	1.26
	X-Linked dominant	4	0	0	4	0.09
	Mostly sporadic but also AD or AR	13	0	0	13	0.29
Known environmental cause		9	0	0	9	0.20
Associations		35	0	0	35	0.79
Multiple congenital anomalies	MCA of malformation origin	480	92	9	581	13.11
(MCA) of unknown etiology	MCA of deformation origin	5	0	0	5	0.11
(N = 822, 18.55%)	MCA of malformation & deformation origin	140	12	3	155	3.50
	MCA of disruption origin	23	2	7	32	0.72
	MCA of disruption & malformation origin	35	10	1	46	1.04
	MCA of other combinations	2	1	0	3	0.07
Conjoined twins		3	2	0	5	0.11
Total		4,198	197	38	4,433	100.00

The largest proportion of nonisolated nonsequence cases (53.8%) were multiple congenital anomalies of unknown etiology (n = 822). In the vast majority of cases (n = 581; 70.68%), MCA were of a malformation origin. The second-largest group consisted of MCA of a malformation and deformation origin.

Conjoined twins with orofacial cleft were observed in five cases.

Analysis of the data according to type of cleft (CL, CLP, CP, or atypical cleft) showed the lowest proportion of isolated cases (8.8%) in the subgroup of atypical clefts. For typical clefts, the lowest proportion of isolated cases was in the subgroup of CP (47.5%). For CL±P, isolated cases represented 73.5%, with a higher proportion of isolated cases in the CL subgroup than in the CLP subgroup (85.8% and 67.7%, respectively) (Table II).

Birth Prevalence

The birth prevalence of *isolated* CL±P was 0.77 per 1,000 births, indicating that one child was born with this anomaly in approximately every 1,300 births (1: 1,297). When the prevalence was evaluated separately for CL and CLP, the rate for CL was 0.29 per 1,000 births (1:3,496) and for CLP 0.48 per 1,000 births (1: 2,062). For *isolated* CP, the prevalence was 0.31 per 1,000 births (1:3,201) (Table III).

Isolated atypical clefts were diagnosed in 13 cases, for a birth prevalence of 0.005 per 1,000 births.

TABLE II. Proportion of CL, CLP, CP and Atypical Orofacial Clefts in Different Etiological Subgroups

		Type of cleft									
		CL		CLP		CL ± P		CP		Atypical	
Group	Type of anomaly	No.	%	No.	%	No.	%	No.	%	No.	%
Isolated anomaly	Cleft lip (CL)	718	85.8	—	—	| 1,935	| 73.5	—	—	—	—
(n = 2,732, 61.63%)	Cleft lip and palate (CLP)	—	—	1,217	67.7	|	|	—	—	—	—
	Cleft palate (CP)	—	—	—	—	—	—	784	47.5	—	—
	Atypical facial cleft	—	—		—	—	—	—	—	13	8.8
Sequence	Robin sequence	—	—	—	—	—	—	134	8.1	—	—
(n = 173, 3.90%)	Holoprosencephaly sequence	1	0.1	4	0.2	5	0.2	8	0.5	23	15.5
	Frontonasal dysplasia sequence	0	0.0	0	0.0	0	0.0	1	0.1	1	0.7
	Amyoplasia congenita disruption sequence	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0
Chromosomal aberrations	Trisomy 21	0	0.0	2	0.1	2	0.1	16	1.0	2	1.4
(n = 390, 8.79%)	Trisomy 13	2	0.2	92	5.1	94	3.6	36	2.2	13	8.8
	Trisomy 18	10	1.2	44	2.4	54	2.1	25	1.5	1	0.7
	Other trisomies	1	0.1	7	0.4	8	0.3	17	1.0	0	0.0
	Other chromosomal aberrations	8	1.0	41	2.3	49	1.9	67	4.1	6	4.1
Monogenic syndromes	Autosomal dominant (AD)	5	0.6	42	2.3	47	1.8	129	7.8	18	12.2
(n = 267, 6.02%)	Autosomal recessive (AR)	6	0.7	4	0.2	10	0.4	42	2.5	4	2.7
	X-Linked dominant	0	0.0	0	0.0	0	0.0	2	0.1	2	1.4
	Mostly sporadic but also AD or AR	1	0.1	0	0.0	1	0.0	11	0.7	1	0.7
Known environmental cause (n = 9, 0.20%)		1	0.1	2	0.1	3	0.1	6	0.4	0	0.0
Associations (n = 35, 0.79%)		2	0.2	19	1.1	21	0.8	13	0.8	1	0.7
Multiple congenital anomalies (MCA) of unknown etiology (n = 822, 18.55%)	MCA of malformation origin	57	6.8	252	14.0	309	11.7	225	13.6	47	31.8
	MCA of deformation origin	0	0.0	0	0.0	0	0.0	5	0.3	0	0.0
	MCA of malformation and deformation origin	9	1.1	35	1.9	44	1.7	104	6.3	7	4.7
	MCA of disruption origin	8	1.0	12	0.7	20	0.8	7	0.4	5	3.4
	MCA of disruption and malformation origin	7	0.8	22	1.2	29	1.1	13	0.8	4	2.7
	MCA of other combinations	0	0.0	0	0.0	0	0.0	3	0.2	0	0.0
Conjoined twins (n = 5, 0.11%)		1	0.1	2	0.1	3	0.1	2	0.1	0	0.0
Total (n = 4,433, 100%)		837	100.0	1,797	100.0	2,634	100.0	1,651	100.0	148	100.0

TABLE III. Prevalence of Nonsyndromic, Nonmultiple Orofacial Clefts, Robin Sequence, and Clefts in Holoprosencephaly Sequence in 2,509,881 California Births (Years 1983–1993)

	Prevalence per 1,000 births		
Type of cleft	No.	Rate	95% CI
Cleft lip (CL)	718	0.29	0.27, 0.31
Cleft lip and palate (CLP)	1,217	0.48	0.46, 0.51
Cleft lip with or without cleft palate (CL±P)	1,935	0.77	0.74, 0.81
Cleft palate only (CP)	784	0.31	0.29, 0.34
Atypical facial cleft	13	0.005	0.003, 0.009
Robin sequence	134	0.05	0.04, 0.06
Orofacial cleft in holoprosencephaly sequence*	36	0.014	0.01, 0.02

*Included only cases of holoprosencephaly sequence without major anomaly (unrelated to the sequence) and with normal or unknown karyotype.

As expected, the most common *sequence* was the Robin sequence, which was diagnosed as an isolated, nonsyndromic condition in 134 cases for a birth prevalence of 0.05 per 1,000 births. Therefore, approximately 1 in every 5 nonsyndromic, nonchromosomal CP cases had Robin sequence. The second most common sequence was the holoprosencephaly sequence–cases with no other major anomaly related to the sequence and with normal or unknown karyotype–which was observed in 36 cases (prevalence 0.014 per 1,000 births).

Orofacial clefts in *chromosomal aberration* occurred with a birth prevalence of 0.155 per 1,000 births (Table IV). The most common was trisomy 13, with a birth prevalence of 0.57 per 1,000 births.

Monogenic syndromes with orofacial clefts (Table V) were found in 267 cases (0.106 per 1,000 births) (Table V). The most common were autosomal dominant (AD) syndromes (n = 194, prevalence 0.077 per 1,000 births). Autosomal recessive syndromes were observed in 56 cases (0.022 per 1,000 births). Among the most common syndromes were hereditary progressive arthroophthalmopathy (Stickler syndrome; n = 29), craniosynostosis syndromes (n = 26; Apert in 18, Crouzon in 7, and Pfeiffer in 1), and lip pits (Van der Woude syndrome; n = 23).

Syndromes with orofacial clefts caused by *known environmental factors* (Table VI) were found in nine cases (six cases of fetal alcohol syndrome, two cases of Dilantin embryopathy, and one case of congenital syphilis). *Known associations* with orofacial clefts (Table VI) were observed in 35 cases (0.014 per 1,000 births). The most common were the CHARGE association (n = 19) and the VATER association (n = 13).

There were 822 cases of orofacial clefts with *MCA of unknown etiology* (0.328 per 1,000 births) (Table VI). Orofacial cleft in MCA of a malformation and/or deformation origin constitute the majority of cases in this group (n = 741, prevalence 0.295 per 1,000 births). In 78 MCA cases of unknown etiology, the origin of the malformation and/or disruption was classified.

California, with its diverse multiracial population, is an excellent background for the evaluation of the prevalence of birth defects in different ethnic groups. A detailed study of the prevalence of orofacial clefts in individual racial groups is in progress and will be published separately [Croen et al., in preparation]. In the present study, we focused our interest on four major ethnic groups in California: Whites who were not Hispanic, Hispanic Whites, Blacks, and Asians. Eligibility for these racial groups was assigned by mother's race. We evaluated separately isolated clefts (CL, CLP, CL±P, and CP) and clefts in other subgroups and also looked at the proportion of CL±P that were CL or CLP, and the ratio of CL over CLP (CL:CLP).

Table VII and Figure 1 show the prevalence per 1,000 births of isolated orofacial clefts by mother's race. The highest prevalence of all types of isolated clefts was found in non-Hispanic Whites: CL (0.34/1,000), CLP (0.47/1,000), CL±P (0.81/1,000), and CP (0.35/1,000). In Asians, the prevalences were slightly lower than in non-Hispanic Whites; however, CIs overlapped (Table VII). The lowest rates were found for all types of

TYPE IV. Prevalence of Orofacial Clefts in Chromosomal Aberrations

	Prevalence per 1,000 births		
Type of aberration	No.	Rate	95% CI
Trisomy 21	20	0.008	0.005, 0.013
Trisomy 13	143	0.057	0.048, 0.067
Trisomy 18	80	0.032	0.025, 0.04
Other trisomies	25	0.01	0.07, 0.015
Other chromosomal aberrations	122	0.049	0.041, 0.058
Total	390	0.156	0.141, 0.172

TABLE V. Prevalence of Orofacial Clefts in Monogenic Syndromes

	Prevalence per 1,000 births		
Type of syndrome	No.	Rate	95% CI
Autosomal dominant (AD)	194	0.077	0.067, 0.089
Stickler syndrome	29	—	—
Craniosynostosis syndromes (Apert, Crouzon, Pfeiffer)	26	—	—
Van der Woude	23	—	—
Other AD	116	—	—
Autosomal recessive (AR)	56	0.022	0.017, 0.029
Smith-Lemli-Opitz	7	—	—
Meckel	8	—	—
Other AR	41	—	—
X-Linked dominant	4	0.0016	0.005, 0.0044
Other	13	0.0052	0.003, 0.009
Total	267	0.104	0.094, 0.120

TABLE VI. Prevalence of Orofacial Clefts in Multiple Congenital Anomalies (MCA)

Type of anomaly	Prevalence per 1,000 births		
	No.	Rate	95% CI
Known environmental cause	9	0.004	0.0017, 0.007
Associations	35	0.014	0.01, 0.02
CHARGE	19	—	—
VATER	13	—	—
Other	3	—	—
MCA of unknown etiology	822	0.328	0.306, 0.351
MCA combination of malformations and/or deformations	741	0.2952	0.276, 0.318
MCA combination of malformations and/or disruptions	78	0.0311	0.025, 0.04
Other MCA	3	—	—

isolated clefts in Blacks (CL 0.19/1,000; CLP 0.22/1,000; CL±P 0.41/1,000; and CP 0.32/1,000). The highest prevalence of Robin sequence occurred in non-Hispanic Whites (0.08/1,000), twice as often as in Hispanics (0.04/1,000). The lowest prevalence (three cases per 179,473 births) was found in Asians. However, Asians had the highest prevalence of atypical clefts (0.09/1,000).

Typical orofacial clefts (CL, CLP, and CP) in nonsyndromic, nonchromosomal MCAs did not follow the racial pattern found in isolated cases (Table VIII). The highest prevalence of CL±P with MCAs was found in Hispanics (0.18/1,000), followed by Asians (0.17/1,000), and the lowest in non-Hispanic Whites (0.14/1,000). However, for CP the lowest prevalence was found for Asians (0.08/1,000), and for Whites and Hispanics it was almost twice as high (0.15/1,000). A comparison of prevalences of isolated and MCA cases is shown in Figure 2.

When the ratio of CL:CLP cases was evaluated by maternal race (Table IX), it was found that, while in non-Hispanic Whites approximately 60% were CLP and the CL:CLP ratio was 0.719, in Hispanics 70% were CLP cases and only 30% were CL cases (CL:CLP ratio 0.419). A similar ratio as in non-Hispanic Whites was found in Asians (0.651). The highest proportion (44.7%) of CL (CL:CLP ratio 0.841) was found in Blacks.

In nonsyndromic, nonchromosomal multiples, the CL:CLP ratio was the same (0.2) for Hispanics and Asians and was just a little higher (0.27) for Whites, but was twice as high (0.45) in Blacks, in whom 2/3 of clefts were CLP.

Rates for CL in Hispanics and Blacks were significantly lower than in Whites (the CI did not overlap). Also, the rate for CLP in Blacks was significantly lower than in the other three ethnic groups. In Hispanics, the rate for CP was significantly lower than the rate in Whites.

DISCUSSION

The fact that orofacial clefts are readily diagnosed in the newborn makes their registry relatively reliable, as compared to some other congenital birth defects. However, the variety of different types of clefts, as well as the variety of conditions in which orofacial clefts occur, require careful classification as to the individual groups with regard to their origin.

There have been many attempts to classify clefts, starting with the morphological classifications by Davis and Ritchie [1922], Brophy [1923], Veau [1931], Fogh-Andersen [1942], and Pruzansky [1953]–mostly made from the point of view of plastic surgeons. Embryological aspects of clefts were used in classification by Stark and Ehrmann [1953], Kernhan and Stark [1958], Vilar-Sancho [1962], Pfeiffer [1966], Kriens [1990], and Kernhan [1990]. Superb reviews of classification systems have been done by Millard [1976] and Berlin [1971], and finally in 1981 by the American Cleft Palate Association Ad Hoc Committee for Reclassification of Craniofacial Anomalies [Whitaker et al., 1981]. Fogh-Andersen [1965], Karfik [1966], and especially Tessier [1976] classified "rare," atypical facial clefts. Both typical and atypical clefts may be syndromic or nonsyndromic or may occur in a complex of multiple anomalies and this aspect is always considered when classification is done by a geneticist [Jones, 1988; Hanson and Murray, 1990]. The classification that we have introduced is also from a genetic point of view and is mainly focused on orofacial clefts at the case level. We consider the same anatomical cleft to be "different" if it occurs only as an anomaly, an isolated birth defect, or if it occurs as a part of the well-recognized syndrome, chromosomal aberration, or as a part of the complex of multiple congenital anomalies of unknown etiology. We strongly believe that this type of classification is fundamental to any kind of further analysis of the cleft data, both for correct genetic counseling and for further research toward defining the etiopathogeneses of these anomalies.

By using our classification, isolated cases were found in 63.67% of all cases. For CL±P, isolated cases represented 73.5%. A higher proportion of isolated cases was found for CL as compared to CLP (85.8% and 67.7%, respectively). For CP, isolated cases were found in

TABLE VII. Prevalence of Isolated CL, CLP, CL±P, and CP by Maternal Race

Maternal race	Prevalence per 1,000 births, 95% Confidence Interval (CI)											
	CL			CLP			CL±P			CP		
	No.	Rate	CI	No.	Rate	CI	No.	Rate	CI	No.	Rate	CI
White	366	0.34	0.32, 0.37	509	0.47	0.43, 0.51	875	0.81	0.76, 0.86	379	0.35	0.32, 0.39
Hispanic	203	0.22	0.19, 0.25	486	0.53	0.48, 0.57	688	0.74	0.69, 0.80	215	0.23	0.20, 0.27
Black	37	0.19	0.13, 0.26	44	0.22	0.16, 0.30	81	0.41	0.33, 0.51	58	0.29	0.22, 0.38
Asian	54	0.30	0.23, 0.39	83	0.46	0.37, 0.57	137	0.76	0.64, 0.90	57	0.32	0.24, 0.41

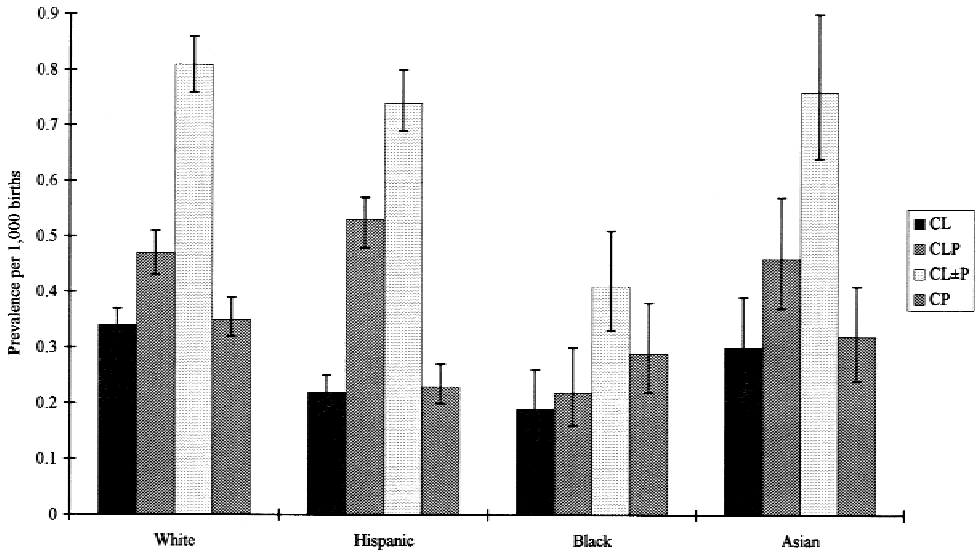

Fig. 1. Prevalence of CL, CLP, CL±P and CP by maternal race.

47.5%; for atypical clefts in 8.8%. Jones [1988], evaluating a clinical sample of 428 patients with orofacial clefts and velopharyngeal insufficiency from the Cleft Palate Program in San Diego, found 71% of isolated cases. Among 259 CL±P cases, 85.7% were isolated, and among 139 CP cases 45.3% were isolated. Even if we consider that the San Diego sample is not population-based but is a clinical sample, the proportions are similar to those in our sample. In CP, the proportions of isolated cases are practically the same. In CL±P cases, a higher proportion of isolated cases in the San Diego sample could be explained at first by a larger proportion of chromosomal aberrations (8% in our sample, 1.9% in the San Diego sample) and MCA of unknown etiology (21.6% in our sample, 5.4% in San Diego sample)–that is, the subgroups in which a certain proportion of cases did not survive and therefore did not reached the Cleft Palate Program clinic. Another consideration is that the criteria for MCA were different. In the San Diego study by Jones [1988], an anomaly was considered an MCA when cleft plus two additional major anomalies or cleft plus three additional minor anomalies occurred. In our study, an anomaly was considered an MCA when cleft plus one major anomaly occurred. In our sample, when cleft was reported with three or more minor anomalies, and if their combination did not resemble any recognizable pattern or familial features, we asked for additional information through follow-up visits and, together with new information, were able to classify the majority of those cases. Some cases, however, remained unclarified and, for the present study, we included them in the group of isolated cases. However, we did classify them as cleft+minors and will analyze them in detail in a future report. In our sample, syndromes represented 6.02%–a percentage a little lower than in the San Diego sample (7.2%). The difference, again, could be explained by a different ascertainment of cases in the population-based and clinical samples. A distribution of syndromes similar to that seen by Jones [1988] was observed in the recent study of orofacial clefts in a Filipino population by Murray et al. [1997].

The population-based sample of 4,362 cases from Czechoslovakia [Tolarová, 1990] combines the advantages of a population-based and a clinical sample. Cases were ascertained from a population of 2,153,221 live births from 1964 through 1986. All living probands affected with orofacial cleft were seen and followed up at a genetics department. Affected children and their first-degree relatives had a physical examination and a genetic evaluation, most performed by one of us (M.M.T.); all autopsies of stillborn children and children who died were also reviewed at the same department. The proportion of isolated cases of orofacial clefts to those classified as being other than isolated was found to be much higher in the California population (63.45% of isolated cases, atypical clefts excluded) than in the Caucasian Czech population (89.68% of isolated

TABLE VIII. Prevalence of CL, CLP, CL±P, and CP in Nonsyndromic, Nonchromosomal Multiples by Maternal Race

	Prevalence per 1,000 births, 95% Confidence Interval (CI)											
Maternal race	CL			CLP			CL±P			CP		
	No.	Rate	CI	No.	Rate	CI	No.	Rate	CI	No.	Rate	CI
White	33	0.34	0.32, 0.37	121	0.47	0.43, 0.51	154	0.81	0.76, 0.86	163	0.35	0.32, 0.39
Hispanic	29	0.22	0.19, 0.25	141	0.53	0.48, 0.57	170	0.74	0.69, 0.80	140	0.23	0.20, 0.27
Black	10	0.19	0.13, 0.26	22	0.22	0.16, 0.30	32	0.41	0.33, 0.51	20	0.29	0.22, 0.38
Asian	5	0.30	0.23, 0.39	25	0.46	0.37, 0.57	30	0.76	0.64, 0.90	15	0.32	0.24, 0.41

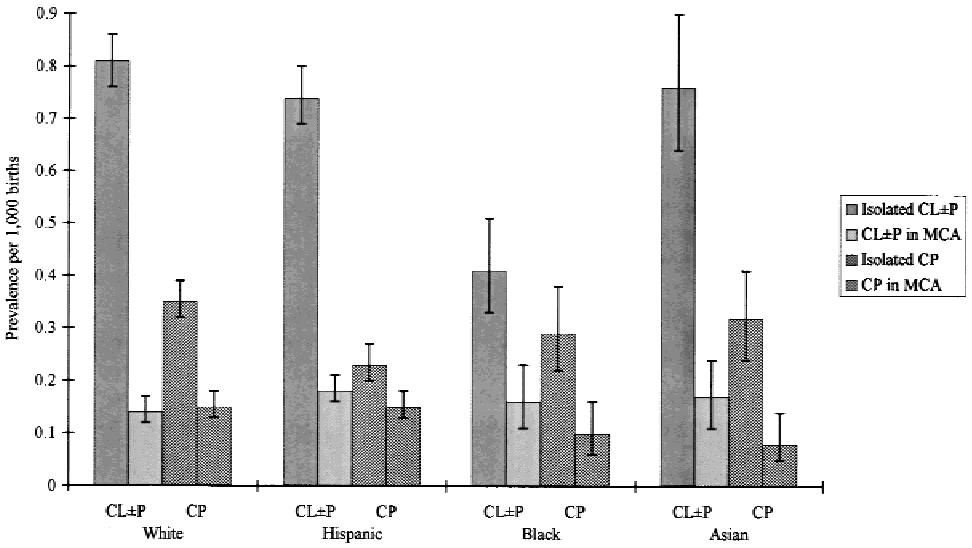

Fig. 2. Prevalence of isolated CL±P and CP in nonsyndromic nonchromosomal MCA by maternal race.

cases; atypical clefts excluded). Syndromes were diagnosed in 5% of cases in the Czech population.

Data on the prevalence of orofacial clefts reported in the literature vary according to the investigator and the country (Table X). In general, in White populations all types of typical orofacial clefts combined occur with a frequency of 1 per 500–550 liveborn children. Even though the total combined incidence of CL, CLP, and CP is often still used, it is necessary to point out that combining the two etiologically different groups (CL±P and CP) represents the same bias as there would be if either CL±P or CP with and without other congenital malformation were combined.

It has been well recognized that there is a considerable difference in the incidence of clefts in different racial groups, the lowest being found in Blacks [Stevenson et al., 1966; Chung and Myrianthopoulos, 1968]. The data from Nigeria [Iregbulem, 1982] confirm the early data on African Americans of the U.S. In Nigeria, an incidence for CL±P as low as 0.4/1000 was found by Lesi [1969], with CP at 0.06/1000 by the same author.

A high incidence of CL±P was found for Japanese (2.1/1000) [Neel, 1958], and the highest incidence was found in North American Indian populations [Niswander and Adams, 1967; Lowry and Trimble, 1977]. Trestven [1963] found the frequency of all facial clefts in newborn Indians in Montana to be 1:275, which contrasted markedly with 1:571 in newborn Whites of the same state. For CP, the highest incidence was described in Finland [Saxén and Lahti, 1974]. An even higher incidence (1.1/1000) was found by Morton et al. [1969] in a small series from Hawaii. The indication that the Japanese have a higher incidence of clefts [Tsukamoto, 1956; Fujino et al., 1963; Kobayashi, 1958; Neel, 1958] has been disputed by Kogushi [1980], who has combined the findings of ten Japanese authors from 1953–1972.

TABLE IX. Proportion of Isolated CL±P Cases That are Either CL or CLP and CL/CLP Ratio of Cases by Maternal Race

Maternal race	CL±P No.	CL		CLP		CL/CLP Ratio
		No.	%	No.	%	
White	875	366	41.8	509	58.2	0.719
Hispanic	688	203	29.5	485	70.5	0.419
Black	81	37	45.7	44	54.3	0.841
Asian	137	54	39.4	83	60.6	0.651

Interesting studies of racial differences have been reported from Hawaii, where several races coexist in similar environmental conditions. It appeared that genetic (racial) background is a more important variable than the environment in the frequency of clefts [Chung et al., 1974, 1980, 1987; Tyan, 1982].

The general discussion of the differences in prevalence was presented by Leck [1984], who combined 29 series from 19 countries; we prefer the term "prevalence" to "incidence" for use in this discussion. Leck's conclusions are as follows: most of the geographical variations of CL±P seem to be secondary to ethnic differences–prevalence is high in Asians, low in Blacks, and intermediate in Whites.

In 1920, the U.S. War Department issued a report on "Defects Found in Drafted Men," which was prepared under the direction of the Surgeon General of the U.S. Army, Major General M.W. Ireland. The study, which until now is probably the largest population survey, involved the analysis of anomalies and diseases found in about 500,000 men rejected by the medical examiners and two groups of about 1,000,000 men each who were examined at mobilization camps. The highest prevalence of clefts was found among the White agricultural workers of the North (0.88). It was low among Blacks (0.35). A high prevalence was found in Finns (1.1), with low prevalence in Germans (0.47–0.67) [Brophy, 1923].

In contrast to these findings, no remarkable variation among races was found in isolated CP. In particular, its prevalence did not vary significantly between Black and White infants in one British study and two done in the U.S. [Heinonen, 1977; Leck, 1972; Erick-

TABLE X. Prevalence of Orofacial Clefts Per 1,000 Newborns

Date	Author	Population	CL	CLP	CL±P	CP	All types
1864	Frobelius[a]	Petersburg—Leningrad	—	—	—	—	0.66
1929	Peron[a]	France—Paris	—	—	—	—	1.06
1934	Grothkopp[a]	Germany—Hamburg	—	—	—	—	1.57
1939	Edgerb[b]	Sweden	—	—	—	—	1.00
1939	Rubaskina[b]	USSR	—	—	—	—	1.00
1940	Conway[b]	USA—New York	—	—	—	—	1.40
1940	Faltin[b]	Finland	—	—	—	—	1.00
1940	Sanvenero Rosseli[b]	Italy	—	—	—	—	1.00
1940	Vaughan[b]	USA—Philadelphia	—	—	—	—	0.80
1942	Fogh-Anderson	Denmark (1934–1941)	—	—	1.10	—	—
1942	Lindswoop[b]	USA–Pennsylvania	—	—	—	—	1.20
1943	Grace	USA—Pennsylvania	—	—	—	—	1.20
1944	Mueller et al.[b]	USA—Wisconsin	—	—	—	—	1.30
1949	Litmanovic[b]	USSR	—	—	—	—	1.20
1949	Oldfield[b]	England	—	—	—	—	1.60
1950	Ivy[b]	USA—Pennsylvania	—	—	—	—	1.30
1951	Wallace et al.[b]	USA—New York	—	—	—	—	0.80
1953	Wallace et al.[b]	USA—New York	—	—	—	—	0.80
1954	Douglas[b]	USA—Tennessee	—	—	—	—	0.60
1955	Haym[b]	West Germany	—	—	—	—	1.00
1955	Lending et al.[b]	USA—New York	—	—	—	—	0.70
1955	Loretz et al.[b]	USA—California	—	—	—	—	1.20
1958	Neel	Japan (1948–1954)	—	—	2.14	0.57	2.71
1960	Ivy[b]	USA—Pennsylvania	—	—	—	—	1.10
1960	Seagin et al.[b]	USA—New York	—	—	—	—	0.80
1961	Curtis et al.	Canada	—	—	1.0	—	—
1961	Fogh-Anderson	Denmark	—	—	—	—	1.75
1961	Soivio et al.[b]	Finland	—	—	—	—	1.80
1962	Januszewska	Poland—Lodz	—	—	—	—	2.00
1963	Knox and Braithwaite	England	—	—	—	—	1.40
1963	Woolf et al.	USA—Utah	—	—	1.24	0.27	—
1965	Altemus	USA—African Americans	—	—	0.24	0.21	—
1967	Morton et al.	Hawaii—Caucasians	—	—	0.62	0.50	1.12
1967	Morton et al.	Hawaii—Japanese	—	—	1.71	0.71	2.42
1967	Niswander and Adams	USA—American Indians	—	—	1.38	0.59	—
1968	Chung et al.	USA—African Americans, 14 Hospitals (1961–1966)	—	—	0.41	0.41	0.82
1968	Chung et al.	USA—Caucasians, 14 Hospitals (1961–1966)	—	—	1.34	0.48	1.82
1968	Källén	Sweden (1964–1966)	—	—	1.24	0.55	1.79
1968	Leck	England—Birmingham	—	—	1.37	0.61	1.98
1968	Smitheles	England—Liverpool	—	—	1.05	0.49	1.54
1968	State registry	British Columbia (1966–1967)	—	—	—	—	2.25
1969	Newcombe	Nova Scotia (1964)	—	—	—	—	2.46
1969	State registry	USA—Atlanta, African Americans (1967–1968)	—	—	0.42	—	—
1969	State registry	USA—Atlanta, Caucasians (1967–1968)	—	—	1.11	—	—
1969	Tanaka et al.	Japan	—	—	1.7	—	—
1970	Chi and Godfrey	Australia	—	—	0.9	—	—
1971	Hay	USA—Iowa	—	—	1.60	0.61	2.22
1971	Henriksson	Sweden (1962–1967)	—	—	1.18	0.51	—
1973	Emanuel et al.	USA—Washington (1956–1965):					
		African American	—	—	0.80	0.46	1.26
		American Indian	—	—	2.83	0.57	3.40
		Caucasian	—	—	1.17	0.58	1.75
		Chinese	—	—	3.23	0.81	4.04
		Japanese	—	—	0.39	1.58	1.97
1974	Grochowski	Poland (1970–1972)	—	—	—	—	2.11
1974	Saxén (1974, 1975)	Finland (1967–1973)	0.22	—	0.78	0.88	1.66
1975	Chung and Myrianthopoulos	USA—African Americans	—	—	0.73	0.44	—
1975	Chung and Myrianthopoulos	USA—Caucasian	—	—	1.45	0.68	—
1976	Bear	England	—	—	1.0	—	—
1980	Bonaïti	France	—	—	0.82	0.35	—
1980	Czeizel	Hungary—Budapest (1962–1967)	—	—	1.03	0.27	—
1980	Czeizel	Hungary (1970–1976)	0.34	0.57	1.16[c]	0.48[d]	—
1980	Koguchi	Japan (1953–1972)	0.58	0.63	1.21	0.30	—
1980	Melnick et al.	Denmark (1941–1968)	—	—	1.30	—	—
1980	Melnick et al.	Denmark (1941–1970)	—	—	—	0.47	—
1981	Kromberg et al.	South Africa—Blacks (1976–1977)	—	—	—	—	0.30
1981	Padron-Caseres et al.	USSR—Moscow (1970–1976)	—	—	0.75	0.48	—
1982	Hu et al.	China—Shanghai (1970–1980)	—	—	1.33	—	—

(Continued)

TABLE X. (Continued)

Date	Author	Population	CL	CLP	CL±P	CP	All types
1982	Iregbulem	Nigeria (1976–1980)	0/18	0/14	—	0.05	0.37
1982	Rintala et al.	Finland (1943–1952)	—	—	0.53	0.78	1.31
1982	Rintala et al.	Finland (1948–1975)	—	—	—	—	1.74
1982	Rintala et al.	Finland (1969–1975)	—	—	0.95	1.21	2.16
1983	Chapman	New Zealand—Maori—Auckland	—	—	0.40	1.87	—
1983	Chapman	New Zealand (1960–1976)	—	—	1.20	0.64	—
1990	Tolarová	Czechoslovakia (1964–1986)	0.45	0.76	1.21	0.6	1.81
1991	International Clearinghouse for Birth Defects Monitoring Systems:	Atlanta (1974–1988)	—	—	1.05	0.56	1.61
		Australia (1981–1988)	—	—	0.92	0.55	1.47
		Canada (1974–1988)	—	—	1.17	0.66	1.83
		Central-East France (1976–1988)	—	—	0.68	0.46	1.14
		Denmark (1983–1988)	—	—	1.47	0.59	2.06
		Emilia-Romagna (1978–1988)	—	—	0.72	0.54	1.26
		England-Wales (1974–1988)	—	—	0.92	0.92	1.84
		Finland (1974–1988)	—	—	0.81	1.01	1.82
		Hungary (1974–1988)	—	—	1.07	0.40	1.47
		Israel (1974–1988)	—	—	0.52	0.45	0.97
		Italy (1978–1988)	—	—	0.68	0.49	1.17
		Japan (1979–1988)	—	—	1.45	0.87	2.32
		Mexico (1980–1988)	—	—	1.28	0.34	1.62
		New Zealand (1980–1988)	—	—	0.87	0.70	1.57
		Northern Ireland (1980–1988)	—	—	0.91	0.85	1.76
		Norway (1974–1988)	—	—	1.42	0.50	1.92
		Paris (1981–1988)	—	—	0.67	0.36	1.03
		Sichuan (1985–1988)	—	—	1.63	0.26	1.89
		South America (1974–1988)	—	—	1.02	3.6	1.38
		Spain (1976–1988)	—	—	0.54	0.45	0.99
		Strasbourgh (1982–1988)	—	—	0.89	0.87	1.76
		Sweden (1974–1988)	—	—	1.33	0.66	1.99
		Tokyo (1980–1988)	—	—	1.21	0.59	1.80
		United States (1974–1988)	—	—	0.88	0.52	1.40
1991	Shaw et al.	California (1983–1986)	—	—	0.74	0.38	1.12
1996	Robert et al.	Central-East France	—	—	0.59	0.44	—
1996	Robert et al.	Sweden	—	—	1.29	0.66	—
1997	Tolarová and Cervenka (present study)	California (1983–1993)	0.29	0.48	0.77	0.31	1.08

[a]From Kučra [1964].
[b]From Cervenka [1965].
[c]Including 0.25 for CL ± P with associated anomalies.
[d]Including 0.05 for Robin sequence and 0.12 for CP with associated anomalies.

son, 1976], or between infants of Japanese and European origin in Hawaii [Morton et al., 1967]. Leck [1984] considered that such findings may be a reflection of a greater etiological heterogeneity of CP than of CL±P. There is no doubt that the method of ascertainment and classification criteria have a major influence on the prevalence values.

The preferable manner for gathering such data is from a population-based sample in which a physical examination of each proband has been performed by an examiner equipped with well-defined criteria for diagnosis, by the selection of probands from a defined geographical region and within certain time periods, and by use of more than one source of information or registration. Those criteria have been applied in several studies [Owens et al., 1985; Shin et al., 1985; Czeizel and Nagy, 1986; Oliver-Padilla and Martinez-Gonzalez, 1986; Rintala, 1986; Coupland et al., 1988; Lowry et al., 1989a,b; Natsume et al., 1989; Tolarová, 1990]. Table X shows the prevalence in selected large studies. Several recently published studies have contributed to the epidemiology of clefts in different populations and races [Amaratunga, 1986; Chen and Wang, 1986; Kromberg and Jenkins, 1986; Natsume and Kawai, 1986; Usui et al., 1986; Gregg et al., 1987; Natsume et al., 1987, 1988, 1989; Tan, 1988; Datubo-Brown and Kejeh, 1989, 1990; Boo and Arshad, 1990; Srivastava and Bang, 1990].

In our study, one case of any type of orofacial cleft (typical, i.e., CL, CLP, CP, or atypical either isolated or multiple) was found in every 566 births, which corresponded to the prevalence of 1.77. This figure is generally in agreement with those in several published studies [Leck et al., 1968; Källén and Winberg, 1968; Chung and Myrianthopoulos, 1968; Emanuel et al., 1973; Fogh-Andersen, 1961; Soivio, 1961; Hu et al., 1982; Tolarová, 1990] (Table X). However, as mentioned earlier we must look at the prevalence of orofacial cleft for isolated cases and for all other types separately. Thus, the prevalence of all types of typical isolated orofacial clefts (CL, CLP, and CP) in our population-based sample of births in California is 1.08 per 1,000 births, or 1 case in every 923 births. The differences in prevalence in earlier studies may be explained by different

methods of ascertainment and also by a different case definition: it is likely that many cases that are now diagnosed without doubt as syndromic, and are therefore excluded, were included in previous studies. Also, cases of multiple congenital anomalies including orofacial cleft should not be mixed with isolated cases. However, there seem to be still more factors involved than those mentioned. The population-based and clinically examined cases that formed the sample of 4,362 cases from Czechoslovakia [Tolarová, 1990] demonstrated an overall prevalence for any type of cleft as 2.03 per 1,000 births, but the prevalence of isolated cases only as 1.81 per 1,000 (CL: 0.46, CLP: 0.76, CP: 0.6). The Czechoslovakian population was Caucasian only, but even when the results for only Whites from the present study are used in comparison (Table VII), the rates are much lower (CL: 0.34, CLP: 0.43, CP: 0.35). These findings suggest an influence of differences in both genetic and environmental factors that very probably exist between populations of the same race, and even between populations of the same ethnic group. Therefore, until it is possible to determine the etiology of nonsyndromic orofacial clefts definitively, detailed genetic studies–including genealogical studies as well as DNA studies based on precisely classified cases–are still needed.

We believe the classification and population-based study of the birth prevalence of different types of orofacial clefts and their associated conditions that are detailed in this report can provide a framework for other genetic studies, for genetic counseling, and for studies to determine the causes of the defect and approaches to the prevention of these serious anomalies.

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