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Craniofacial anomalies and associated birth defects

2.1 Global distribution of craniofacial anomalies

Congenital anomalies (CA) are a major cause of infant mortality and childhood morbidity, affecting 2-3% of all babies. Approximately 1% of these newborns have syndromes or multiple anomalies; CFA are often a component part. Syndromes are composed of multiple malformations thought to be etiologically and/or pathogenetically related. Syndromes that have cleft lip and/or cleft palate as one of the features are of interest in the quest for etiologic and pathogenetic factors, and it is estimated that 30% of cleft cases are syndromic. Conversely, therefore, approximately 70% are non-syndromic.

Studies suggest that associated anomalies occur with a frequency of 44 % to 64 % in patients with clefts (Cohen, 1978). Isolated cleft palate (CP) is more frequently associated with congenital malformations (up to 50%), than CL/P (approximately 5 to 10%). There is however considerable variation in these figures in different populations.

Oral clefts (OC) therefore are among the most widely known and common CFA, occurring in approximately 1 in every 700 live births. CFA, other than cleft lip and palate, occur in 1 in every 1600 newborns in the United States of America (USA) and include jaw deformities, malformed or missing teeth, defects in the ossification of facial or cranial bones, and facial asymmetries. Clefts occur proportionately more often among the Asian populations than among African populations. Many factors contribute to cleft conditions, among them being heredity, pre-natal nutrition, drug exposure, and other environmental factors (WHO, 2002).

2.1.1 Global data for oral clefts

Coincidental findings reported from partially independent data bases – ICBDMs (Rosano & Mastroiacovo, 2001), EUROCAT (Bianchi, 2001), and NBDPN (2000) – as well as from the recent literature review by Mossey & Little (2002) are here summarized as representing non-spurious observations:

- **Cleft lip, with or without cleft palate (CL/P):** The highest reported prevalence rate (2.28 per 10 000) in the world is that of Bolivia (Rosano & Mastroiacovo, 2001; Mossey and Little, 2002). Known data comes mainly from the city of La Paz, at 4000 meters above sea level, with a large proportion of its population being of Amerindian ethnic background. The role of both environmental (chronic hypobaric hypoxia from altitude) and genetic (Mongolic Amerindian ethnicity) etiologic factors and their interactions are still unknown (Castilla, Lopez-Camelo & Campana, 1999). Interestingly, a similarly high-prevalence rate for CL/P seems to exist in the ethnic Mongolian population of Tibet at an almost equally high altitude (Zhang, 2001).
- **Cleft palate (CP):** The highest reported prevalence rate (10.0 to 14.0 per 10 000) in the world is that of Finland, where CP frequency is higher than that expected for northern Europe, followed by Scotland (8.0 per 10 000).

The prevalence for both OC main types, CL/P and CP, seems to depend largely on the same macro ethnicity, with maximum values among Mongols, lowest among Africans, and intermediate in Caucasians. The populations of two Asian countries, Japan (Neel, 1958) and the Philippines (Murray et al., 1997), as well as the mixed-race populations such as the American Indians of British Columbia (Lowry, Thunem & Uh, 1989) and California (Croen et al., 1998), and the mestizo populations in countries such as Argentina, Bolivia and Chile (Mossey and Little, 2002), fit into the Mongolian category. Likewise, low frequency of OC among Africans is reflected among African countries, Nigeria (Iregbulem, 1982), as well as North America's African Americans (Conway & Wagner, 1966) and Latin American countries with a substantial African ancestral background, namely, Venezuela (Mossey and Little, 2002) and Santo Domingo (Garcia-Godoy, 1980).

For CL/P in Europe, higher prevalence rates are reported from northern than from southern countries (Mossey and Little, 2002). Nevertheless, as expected, some inconsistencies to this general set of rules can be found, such as the low prevalence of CL/P in Japan reported by Kondo (1987) and of CP in China reported by Xiao (1989), as well as the high frequency for CL/P in Nairobi reported by Khan (1965). Such exceptional situations

may be reflecting operational differences in ascertainment or case definition, or “micro” ethnic situations such as geographical clusters.

2.1.2 Study on prevalence of non-syndromic oral clefts (OC)

A study on CL/P and CP occurrence was based on information collected from 1993-1998 by 57 registries worldwide (14 from the Americas, 5 from Asia, 2 from Oceania, 36 from Europe), all of which were members of either the ICBDMs or the EUROCAT. This data comprised the frequency of infants registered with a diagnosis of CL or CP, isolated or associated with other defects, from a total of 16 923 870 live births and stillbirths.

Rates were calculated by dividing the relevant cases by the number of live birth and stillbirths; a 95% confidence interval (CI) was calculated for each rate, using the Poisson distribution or the normal approximation when the number of cases exceeded 30. Heterogeneity within and among registries was tested using the chi square test.

Cleft palate without cleft lip (CP) prevalence at birth ranged from 1.3-25.3 per 10 000 births. The overall rate was 5.0 per 10 000 births, but the rate of distribution varied significantly among registries ($p < 0.001$). Considering the 5th and 95th centile of the rate distribution, the rates varied from a low of 2.2 to a high of 8.1, with the registries of Canada and Finland showing the highest rate and those of Cuba, Colombia and South Africa showing the lowest.

Cleft lip with or without cleft palate (CL/P) prevalence at birth varied from 3.4-22.9 per 10 000 births. The overall rate was 7.9 per 10 000. The rate distribution was not homogeneous among registries ($p < 0.001$). Higher values were found in Asian (China, Japan) and South American (Bolivia, Paraguay) countries, while Israel, South Africa and Southern European countries showed the lower values.

The proportion between infants with CL/P and CP was higher among Asian registries (from 4 to 6 times) and lower among Canadian and Finnish registries (from half to two thirds).

Findings in the study confirmed the low prevalence of CP observed among Africans. Caucasians and particular peoples from Canada and Northern European countries showed the highest prevalence rate for CP, i.e., twice as high as that in other countries. The prevalence of CL/P is also lower among Africans, and higher among Amerindians, Chinese and Japanese compared with Caucasians. By comparison with other countries CL/P prevalence, i.e. 7.4 (CI 95%: 7.3-7.6), the rate among Chinese and Japanese is double, 14.8 (CI 95%: 14.2-15.5). These differences might be explained by different methods of ascertainment. However, a high level of ascertainment has been broadly reported for facial clefts so different

Differences in rates in this study could be due to different methods of ascertainment ...

levels of ascertainment are unlikely to explain the differences reported. The level of the rate of CL/P was not correlated with that of CP, however Asian registries, which showed the highest rates for CL/P, showed low rates for CP.

2.1.3 Study on the sex ratio

A study on the sex ratio (SR) was based on information provided by 17 registries of congenital anomalies, also members of the ICBDMs, collected from 1974-1997. For the purpose of the study, 23 954 cases with CL/P (19 191 isolated and 4763 associated) and 14 000 cases with CP (9978 isolated and 4022 associated) were selected (EUROCAT, 1997; ICBDMs, 2001).

The SR was 0.93 (CI 95%: 0.89-0.96) among isolated cases with CP, and 1.81 (CI 95%: 1.75-1.86) among isolated cases with CL/P. An excess of prenatal mortality risk was found among females with cleft lip (CL). Among orofacial clefts associated with other defects, the sex ratios shrank towards the normal value, i.e. 1.01 (CI 95%: 0.96-1.07) for CP and 1.33 (CI 95%: 1.27-1.34) for CL/P.

Findings of this study confirm the known predominance of females among infants with CP and the known predominance of males among infants with CL/P. The sex ratio of CP was not significantly different from normal values when associated non-facial malformations existed, and was much lower than that for CL/P. The findings of previous studies that a male excess was less marked in races where CL/P is more common was not confirmed in this study in which Latin-American countries, with a higher prevalence of CL/P, had a lower sex ratio for males than the estimated common sex ratio.

CL/P, which is predominant among males, showed a greater intra-uterine mortality for females. The fact that liveborn infants with isolated CL usually have a good survival rate suggests that stillborn infants with an apparently isolated CL may, in fact, have other – unnoticed – anomalies, such as holoprosencephaly which, because of its female predominance, could explain the excess of females among stillborn cases.

2.2 Congenital anomalies associated with craniofacial anomalies

Cleft lip, with or without cleft palate, (CL/P) and isolated cleft palate (CP) are frequently associated with other major congenital malformations. It has been reported that about 20% of liveborn infants with facial clefts have associated malformations, and the figure is much higher among

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stillbirths. The study of associated anomalies is useful in identifying pathogenetically homogeneous patterns of malformations and hence contributes to more powerful etiologic studies and better public health monitoring.

2.2.1 *Study on multi-malformed infants*

This study was based on data collected from 15 registries that are members of the ICBDMS and participate in the collaborative project on monitoring multi-malformed infants. Data were collected from 1992-1999 in the 15 registries as case records of infants registered with a diagnosis of CL or CP, associated with other defects, from 7 180 511 live births, stillbirths and terminated pregnancies (ICBDMS, 2001).

Out of 6454 cases of multi-malformed infants, the study found 739 cases (11.4%) of CL/P and 544 cases (8.4%) of CP. The most frequently associated anomalies with CL were congenital heart defects (28.6%), polydactyly (16.2 %), deformation/s (14.6%), hydrocephaly (11.4%), and a-microphthalmia (8.3%). The proportional analysis showed anencephaly, encephalocele, a-microphthalmia and polydactyly to be the preferential patterns associated with CL/P.

CP was more frequently associated with congenital heart defects (31.1 %), deformation/s (22.4%), hydrocephaly (11.2%), urinary tract defects (9.7%) and polydactyly (9.2%). CP was preferentially associated with neck anomalies.

To distinguish between isolated and associated cases in birth-defect epidemiology it is useful to provide clues for the etiology of the defect. The definitions of associated anomalies may vary among researchers, and the completeness of the identification and registration of such anomalies will depend on the data-collection method and the length of follow-up time. The ICBDMS collaborative project on monitoring multi-malformed infants allows comparable and reliable data – in terms of data collection, coding and analysis – to be gathered.

Findings in literature show that the most frequent defects associated with facial clefts are malformation of the limbs, followed by cardiovascular and other facial anomalies. The collaborative effort of the 15 registries participating in the ICBDMS project for monitoring multi-malformed infants has made it possible to obtain these findings. This is a significant research project, unique for the extent of its coverage of collected cases and the variety of races and ethnic groups represented.

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2.3 Hungarian population-based data set of multi-malformed cases including orofacial clefts

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Multiple congenital abnormalities (MCA) – the occurrence of two or more different congenital abnormalities (CA) in the same person (Czeizel et al., 1988a) – represent about 10% of the recorded CA in the Hungarian Congenital Abnormality Registry (Czeizel, 1997). The birth prevalence of recorded cases affected by MCA was 4.0 per 1000 total births (range: 3.7-4.5) in Hungary for 1973-1982. The stillbirth and infant death rates for the MCA category were 8.67% and 23.8%, respectively, that is, about 10 times higher than the corresponding national figures for the study period (Czeizel et al., 1988b).

Cases with MCA, including CL/P and posterior CP were evaluated in the population-based, almost-complete data set of the Hungarian Congenital Abnormality Registry. For the evaluation, the clinically recognized and notified syndromes and associations were included; the proportion of unspecified, multi-malformed cases being reduced when new or supplemental information was requested from clinicians. Furthermore, an attempt was made to classify unidentified, multi-malformed cases as syndromes or associations. This was done by referring them either to the regional multiple congenital abnormality examination centres or the so-called registry diagnoses in well-defined multiple-congenital abnormality entities. Finally, the remaining unidentified multi-malformed cases were evaluated on the basis of their component abnormalities. Of 651 cases with multiple congenital abnormalities, including OC, 58 (8.9%) had identified syndromes:

- Mendelian 23 (3.5%),
- chromosomal 31 (4.8%),
- teratogenic factors (hydantoin) 4 (0.6%).

The majority of the previously delineated syndromes were not identified. 78 (12.0 %) cases were affected with the so-called schisis association. The rest of the multi-malformed cases (351 [53.9 %] and 169 [26.0 %], including those with CL/P or posterior cleft palate, had unidentified multiple congenital abnormalities with mention of component abnormalities, respectively. These cases, all with two to eight component abnormalities, were evaluated together on the basis of different pairs of component abnormalities in the hope that this approach might help to identify and/or delineate syndromes or associations, thus reducing the proportion of random combinations of congenital abnormalities. Of 31 cases with ADAM sequence, 8 had CL; of 31 cases with holoprosencephaly, 7 had CL and 2 had CP. (See Box 10 below.)

BOX 10

Definitions of some isolated CA entities that include CL and/or CP

- **Robin sequence (or Pierre Robin syndrome)** includes a U-shaped cleft palate, micrognathia and/or glossoptosis without other major CA.
- **ADAM sequence** comprises asymmetric limb deficiencies caused by an amniotic band with atypical anencephaly/encephalocele and/or orofacial cleft and/or ectopic cordis-thoracoschisis and/or abdominal wall defect.
- **Holoprosencephaly** is the consequence of a prechordial mesoderm defect with varying degrees of deficit of midline facial development (from cyclopia to hypotelorism), especially the median nasal process and incomplete morphogenesis of the forebrain. This CA-entity frequently includes CL and CP.

In the past, the classification of CA was based on anatomic localization. In the future, an etiologic classification will be established. At present, the cause in several CA and MCA groups is still unknown so a pathogenetically oriented classification, as outlined below, would be a reasonable compromise:

- 1) Differentiate isolated and multiple CA (Czeizel et al., 1988a).
- 2) Separate subclasses within the above two categories (Spranger et al, 1982; Opitz et al, 1987), e.g., delineate MCA association as a schisis association (Czeizel, 1981).
- 3) Separately evaluate the known etiologic MCA entities, i.e., syndromes and associations.

BOX 11

Definitions of MCA patterns

- **MCA syndromes** are recognized patterns of component CA presumably having the same etiology, e.g. mutant autosomal or X-linked dominant or recessive genes, chromosomal aberrations or teratogenic factors.
- **MCA associations** are recognized patterns of non-random associations of two or more different component CA that do not have the same etiology; they are currently not considered to constitute MCA syndromes.

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After the delineation of new MCA syndromes and MCA associations, and the identification of previously delineated and recognizable MCA syndromes and MCA associations, the balance corresponds to the so-called random combination of CA which are a chance concurrence of two or more different CA.

Of the 651 multi-malformed cases, 58 (8.9%) were identified as previously delineated MCA syndromes. Among 23 (3.5%) Mendelian CA entities, the majority were EEC, OFD II, Meckel and Roberts syndromes. Of 31 (4.8%) chromosomal syndromes, 29 cases were affected with trisomy 13. All four (0.6%) MCA caused by teratogens were identified as fetal hydantoin syndrome. CL and CP were not differentiated among these MCA entities because they occurred alternatively among the cases. Only one delineated MCA association had CL or CP. Of 130 MCA cases with schisis association, 73 (11.2%) had either CL (55) or CP (18).

The numbers of unidentified MCA cases including CL or CP were 351 (53.9%) and 169 (26.0%) respectively. The majority of MCA cases were not identified; on the contrary, that random combination may explain only 12.1% of the study material. Clearly, the proportion depends on the number of component CA:

2 = 16.7% (1 in 6);
3 = 0.4% (1 in 225), and
4 or more = 0.0% (1 in 14 000).

It is an important task to decrease the proportion of unidentified MCA entities and delineate further MCA entities including CL and/or CP. The hope is that this population-based data set will stimulate experts to attempt to identify either previously delineated or new MCA entities.

Finally, it is necessary to obtain the family histories of MCA cases and consanguinity data of the parents as this information may help to identify Mendelian MCA entities. The advances made in CFA research have given medical doctors greater understanding and expertise in identifying previously delineated MCA entities. "Diagnosis" of MCA entities is the task of the clinicians who see and examine the cases so it is helpful to adopt registry diagnoses to identify well-defined, previously delineated MCA entities. The validity of these diagnoses will, however, need to be further checked. The progress in gene mapping will drastically facilitate identification of newly recognizable MCA entities.

Table 2: Diagnostic criteria of MCA entities (MCA syndromes): registry diagnosis

CA syndromes	Obligatory CA	Additional CA
Acrocephalosyndactyly type I	Craniosynostosis	*
Apert syndrome	Syndactyly	-
Asplenia with cardiovascular CA	Asplenia-polysplenia	*
Ivemark syndrome	Cardiovascular CA	-
Congenital rubella	Cataract; Cardiovascular CA	Microcephaly supports the diagnosis
Cryptophthalmos with other CA	Cryptophthalmos	*
Fraser syndrome	Syndactyly	-
EEC	Split hand and/or foot; Orofacial clefts	Ectodermal dysplasia confirms the diagnosis
Ellis-van Creveld	Achondroplasia; Polydactyly	Cardiovascular CA confirms the diagnosis
Wiedemann-Beckwith syndrome	Omphalocele; Macrosomia-macroglossia	*
Holt-Oram	Septal heart CA; Radial-type limb reduction	Vertebral CA, analatresia-stenosis, oesophageal atresia-stenosis and renal agenesis exclude the diagnosis
Klippel-Trenaunay-Weber	Unilateral limb hemihypertrophia ; Haemangioma	*
Meckel	Occipital encephalocele; Cystic kidney	Orofacial clefts, polydactyly and hypo-genitalism confirm the diagnosis
Mohr (OFD II)	Cleft palate; Polydactyly	*
Poland	Syndactyly; Pectoral muscle hypoplasia	In general unilateral
Roberts	Orofacial clefts; Phocomelia	*
Ullrich-Turner	Congenital lymphoedema ; Pterygium colli	*

* With or without some other characteristic CA; however, the occurrence of other non-characteristic CA excludes the diagnosis.

Table 3: Diagnostic criteria of MCA entities (MCA associations): registry diagnosis

CA-associations	Obligatory CA	Additional CA
Postural	Two or more postural type CA (club-foot, dislocation of the hip and torticollis)	*
Schisis	Two or more schisis-type CA (neural-tube defect, orofacial cleft, omphalocele and/or diaphragmatic CA)	*
Vacterl	Three or more VACTERL-type CA from the following six: specified vertebral CA, anal atresia-stenosis, cardiovascular CA, tracheo-oesophageal atresia-stenosis, renal agenesis or dysplasia, radial type limb reduction or polydactyly	*

* Other major CA exclude the diagnosis.

2.4 Example of epidemiology of hereditary syndromes with CFA in the former Soviet Union

The prevalence of Mendelian hereditary diseases was studied among the populations of the former Soviet Union over the last 20 years, as follows:

- **Step 1:** A special form that included the symptoms of different hereditary disorders (neurological, ophthalmological, dermatological, skeletal, etc.) was distributed to local medical professionals for them to enter information on all families they had encountered with such symptoms. The form allowed for the recording of at least 500 different hereditary diseases, autosomal dominant, autosomal recessive and X-linked recessive, in approximately the same proportion as they are presented in Victor McKusick's *Catalogue for Mendelian Phenotypes in Man* (McKusick, 1998).
- **Step 2:** A professional team personally investigated the data submitted by the local medical staff and also collected from other sources. Team members visited every family, excluding those where cases were evidently nonhereditary; the team subsequently compiled the genealogical trees of the affected families.
- **Step 3:** Specialists from Moscow's medical institutes investigated the most recently recorded cases. Finally, the study revealed the prevalence rates for autosomal dominant, autosomal recessive and X-linked recessive disorders, as well as the spectrum of hereditary diseases in the population that had been investigated.

In 1976-1984, a similar study was conducted on a population of almost one million people in the Central Asian Republics of the former Soviet Union. The same methodology was used and more than 420 families, with 1114 people affected with different hereditary disorders, were revealed in the course of the study.

In 1985, further studies were conducted in Northern, Central and Southern regions of the European part of the former Soviet Union. A study that included other ethnic groups, namely Adigean, Chuvashian and Mari, investigated a population of more than 1.5 million people. During the course of this study the following statistics were revealed:

- 1723 patients from 884 families with 111 different autosomal dominant disorders;
- 942 patients from 707 families with 111 different autosomal recessive disorders; and

The diversity of hereditary syndromes with CFA in the population of the former Soviet Union was broad ...

- 223 patients from 169 families with 36 different X-linked recessive disorders.

The prevalence rates for autosomal dominant, as well as for recessive disorders, were approximately two times higher in rural populations than they were in the urban populations of all the territories investigated, except for Krasnodar Province. Prevalence rates for X-linked pathology were approximately equal in both urban and rural populations. It should be mentioned that values of prevalence rates for hereditary pathology of rural populations in the study were close to the values of the frequencies of Mendelian disorders in the highly respected Register for Handicapped Individuals of British Columbia.

The spectrum of hereditary syndromes and diseases, including CFA, detected during the medical genetic study of populations of the former Soviet Union is shown in the Tables 4 and 5. There were more than 30 autosomal dominant syndromes with CFA. Only four of them had a relatively high prevalence rate ($p > 1:100000$). Among those, Marfan syndrome and trichorhinophalangeal syndrome type 1, showed local accumulation, the latter among the Adigean population. Three syndromes, namely Noonan syndrome, EEC syndrome and Waardenburg syndrome, had a prevalence rate of approximately 1:150 000; EEC syndrome showed local accumulation in the Mari population. All other autosomal dominant (AD) syndromes had a low, or extremely low, prevalence rate but, in spite of this, Moebius syndrome, Saethre-Chotzen syndrome and frontonasal dysplasia showed local accumulation. Eleven autosomal recessive syndromes with CFA were detected during the study; prevalence rates for most of them were extremely low. There were no cases of local accumulation for autosomal recessive syndromes. Several X-linked recessive syndromes and one X-linked dominant syndrome with CFA were registered, such as oto-palato-digital syndrome, type II, Coffin-Lowry syndrome and Aarskoga syndrome.

Conclusions based on the study:

- 1) The diversity of hereditary syndromes with CFA in the population of the former Soviet Union is broad.
- 2) On the contrary, the proportion of common hereditary syndromes with CFA is low.
- 3) The prevalence of hereditary disorders in populations of the former Soviet Union depended on genetic structure.
- 4) Some ethnic characteristics in the distribution of hereditary pathology should be expected in the population of the former Soviet Union.

Table 4: Spectrum and prevalence rates ($\times 10^{-5}$) of autosomal dominant syndromes with orofacial anomalies in the population of the former Soviet Union

Syndrome	Populations							Prevalence rate
	Mari	Russians in Mari EI	Adigi	Kostroma	Krasnodar	Kirov	Briansk	
1. Achondroplasia	1.16±1.82	-	1.66±1.66	1.57±0.59	0.93±0.46	1.88±0.84	-	1:82 161
2. Multiple osteochondromatosis	3.49±1.42	2.25±1.59	1.66±1.66	0.44±0.31	2.81±0.81	1.13±0.65	-	1:82 161
3. Marfan syndrome	0.58±0.58	(5.63±2.51)	1.66±1.66	0.67±0.38	1.40±0.57	0.75±0.53	-	1:67 872
4. Trichorhinophalangeal syndrome, type 1	0.58±0.58	-	(13.33±4.71)	0.44±0.31	0.23±0.23	1.13±0.65	3.40±1.96	1:86 725
5. Noonan syndrome	1.74±1.00	-	-	-	0.70±0.40	1.51±0.75	1.13±1.13	1:141 914
6. EEC syndrome	(4.66±1.64)	-	-	-	0.23±0.23	0.37±0.37	-	1:156 105
7. Waardenburg syndrome	1.74±1.00	-	-	1.57±0.59	-	-	-	1:156 105
8. Pseudoachondroplastic dysplasia	0.58±0.58	-	-	0.44±0.31	0.23±0.23	-	-	1:390 026
9. Goldenhar syndrome	-	-	-	-	0.93±0.46	-	-	1:390 026
10. Cleidocranial dysplasia	-	-	-	0.89±0.44	-	-	-	1:390 026
11. Williams syndrome	0.58±0.58	1.12±1.12	-	-	0.46±0.32	-	-	1:390 026
12. Crouson craniofacial dysostosis	-	-	-	0.22±0.22	0.46±0.32	0.75±0.53	-	1:312 211
13. Moebius syndrome	1.74±1.00	(2.25±1.59)	-	-	-	-	-	1:312 211
14. Saethre-Chotzen syndrome	-	1.12±1.12	-	-	0.23±0.23	0.37±0.37	(2.26±1.60)	1:312 211
15. Treacher-Collins syndrome	-	-	-	0.89±0.44	-	-	-	1:390 026
16. Acrodysostosis	-	-	-	-	0.46±0.32	-	-	1:780 529
17. Frontonasal dysplasia	-	(2.25±1.59)	-	-	-	-	-	1:780 529
18. Chondrodysplasia punctata	-	-	-	-	0.23±0.23	-	-	1:1561058

(continued)

Table 4 (continued)

Syndrome	Populations								Prevalence rate
	Mari	Russians in Mari EI	Adigi	Kostroma	Krasnodar	Kirov	Briansk	Briansk	
19. Cornelia de Lange syndrome	0.58±0.58	-	-	-	-	0.37±0.37	-	-	1: 780 529
20. Apert syndrome	-	-	-	0.22±0.22	-	-	-	-	1:1 561 058
21. Van der Woude syndrome	-	-	-	-	-	1.13±0.65	-	-	1: 520 353
22. Coffin-Siris syndrome	0.58±0.58	-	-	-	-	-	-	-	1:1 561 058
23. Langer-Giedion syndrome	-	-	-	-	-	0.37±0.37	-	-	1:1 561 058
24. Marshall syndrome	-	-	-	-	0.46±0.32	-	-	-	1:0 780 529
25. Acrocephalosyndactyly, type V	-	-	-	-	0.23±0.23	-	-	-	1:1 561 058
26. Cloverleaf skull syndrome	0.58±0.58	-	-	-	-	-	-	-	1:1 561 058
27. Femoral-facial syndrome	-	1.12±1.12	-	-	-	-	-	-	1:1 561 058
28. Goldenhar syndrome	1.16±0.82	-	-	0.22±0.22	0.23±0.23	-	-	-	1:0 312 500
29. Beckwith-Wiedemann syndrome	-	1.12±1.12	-	-	-	0.38±0.38	-	-	1: 769 230
30. Townes-Brocks syndrome	-	-	-	0.89±0.44	-	-	-	-	1:0 375 000

Legend:

- = no information exists.

(italics) = not included in calculation of overall prevalence rate.

Table 5: Spectrum and prevalence rates ($\times 10^{-5}$) of autosomal recessive syndromes with orofacial anomalies in the population of the former Soviet Union

Syndrome	Populations							Prevalence rate
	Mari	Russians in MariEI	Adigi	Kostroma	Krasnodar	Kirov	Briansk	
1. Cockayne syndrome	0.58±0.58	-	-	-	0.45±0.33	-	-	1: 526 315
2. Dubowitz syndrome	0.58±0.58	1.12±1.12	-	-	-	-	-	1: 526 315
3. Cohen syndrome	-	-	-	0.22±0.22	0.22±0.22	-	-	1: 769 230
4. Larsen syndrome	1.16±0.82	-	-	-	-	0.38±0.38	-	1: 526 315
5. C Trigoncephaly syndrome	0.58±0.58	-	-	-	-	-	-	1: 1 544 371
6. Oral-facial-digital syndrome, type III	-	-	-	-	0.22±0.22	-	-	1: 1 544 371
7. Russell-Silver syndrome	-	-	1.16±0.82	-	0.22±0.22	0.38±0.38	-	1: 526 315
8. Roberts syndrome	-	1.12±1.12	-	-	-	0.38±0.38	-	1: 769 230
9. Robinow syndrome	1.16±0.82	-	-	-	-	-	-	1: 769 230
10. Smith-Lemli-Opitz syndrome	-	-	-	-	0.22±0.22	-	-	1: 1 544 371
11. Ellis-van Creveld syndrome	-	-	-	-	0.22±0.22	-	-	1: 1 544 371

Legend:

- No information exists.

2.5 Example of ascertainment and registration of birth defects: Atlanta, USA

Surveillance systems in the USA collect information on the race and ethnicity of yearly births ...

Birth defects are the leading cause of infant mortality and contribute substantially to illness and long-term disability. Given the public health importance of birth defects, it is necessary for birth-defect surveillance systems to monitor and detect trends in birth defects, provide data for etiologic studies of birth defects, and provide the basis to plan and evaluate the effects of prevention activities. These purposes are best accomplished through surveillance systems that use multiple data sources, possess accurate and precise diagnostic criteria, perform timely data analysis, provide timely dissemination of the data, and use personal identifiers for follow-up and data linkage.

The population covered by the surveillance system needs to be specified in terms of the geographical area, number of yearly live births and stillbirths to area residents and the hospitals in the study area where births are delivered and children undergo medical evaluations. Surveillance systems in the USA also collect information on the race and ethnicity of the yearly births. It is important to collect this information given the variation in these characteristics and in the prevalence of some birth defects (e.g., the prevalence of oral clefts varies by race/ethnicity). One example of a population-based, intense birth-defect surveillance system is the Metropolitan Atlanta Congenital Defects Program (MACDP) sponsored by the CDC. The MACDP serves as a case registry for epidemiological studies, a prototype for other birth-defect surveillance systems, and a “laboratory” for testing new surveillance methodologies. The CDC also established eight Centers for Birth Defects Research and Prevention. The major activities of these centres are to participate in the National Birth Defects Prevention Study and expand and improve the birth-defect surveillance systems in their respective states.

The CDC is also actively engaged in efforts to improve birth defect surveillance across the USA. For example, 36 cooperative agreements have been awarded to enhance state-based birth-defect surveillance activities. These cooperative agreements provide the opportunity for state-based birth-defect surveillance systems to share data and increase the information on rare birth defects and geographical variation. The state birth-defect surveillance programmes that provide data on oral clefts vary in several respects, including:

- case ascertainment methods,
- definition of birth defects,
- coding systems,

- the inclusion of stillbirths and pregnancy terminations in counts of the occurrence birth defects, and
- the population coverage.

Hence, state surveillance data on the prevalence of OC cannot be combined to give a reliable overall national rate for the USA or used to make meaningful comparisons between states. Although differences between each state's approach for birth-defect surveillance systems sometimes creates such limitations, the diversity of approaches serves as a useful resource for guiding the development of surveillance systems for other childhood conditions.

2.6 Frequencies for oral clefts: global literature review

After a thorough critical revision and discussion of more than 150 published sets of data on the frequency of OC, Peter Mossey and Julian Little (2002), reached the following conclusions:

- 1) Cleft lip with or without cleft palate (CL/P), and cleft palate only (CP) are two different nosological entities. Furthermore, distinct subgroups within these conditions seem to exist according to severity, sidedness, and associated anomalies.
- 2) There is a large geographical variation in the birth prevalence rates of OC, which is more marked for CL/P than CP.
- 3) The proportion of OC cases with additional CA and syndromes is quite variable.
- 4) Migrant groups seem to retain rates of CL/P similar to those of their area of origin.
- 5) There is no consistent evidence of time trends, variation by socioeconomic status or seasonality, but adequate studies are still lacking.
- 6) There is large international variation in the reported birth prevalence rates of OCs, but part of that variation seems to be based on differences in source population (hospital versus population), time period, method of ascertainment, inclusion/exclusion criteria and sampling fluctuation.
- 7) Data on OC frequency are still lacking for many parts of the world, in particular parts of Africa, Asia and Eastern Europe.

2.6.1 Basis for the differences

Registries involved in birth-defect monitoring and other forms of surveillance know well that OC seldom produce an alarm or a suspected epidemic (ICBDMS, 1991) and do not experience cyclic periodical variations (Saxén & Lathi, 1974; Castilla et al., 1990) or changing secular trends (ICBDMS, 2000; EUROCAT, 1996). The only exception to the latter is the increasing trend reported by the Finnish national registry for both CL/P and CP (ICBDMS, 2000).

It is clear that, when very large time periods are considered, time increases or decreases can be found (Mossey and Little, 2002) – time increases are due to better reporting and survival; time decreases are due to prenatal diagnosis followed by unregistered terminated pregnancies, mainly in the syndromic forms of OC.

As can be seen in the following table (extracted from ICBDMMS, 2001), OC seldom present an alarm during quarterly or yearly monitoring of prevalence rates, if compared with the four other frequent and well-known congenital anomaly types.

Table 6: Summary of the results of observed to expected ratios in 1999 births

Malformation	Observed to expected ratio *	
	Number	Statistically significant
CP	27	2
CL/P	27	3
Anencephaly	28	3
Spina bifida	27	4
Down syndrome	27	6
Hypospadias	25	7

* The total number of ratios was 1078. The reasons the number of ratios was different, malformation by malformation, were that several registries did not contribute data for a few malformations and some expected ratios were not computable. The number of computed ratios was very high so a certain number (about 5%) of significant ratios can be expected by chance.

There is no clear evidence that under-ascertainment of CP is greater than that of CL/P ...

- **Differences:** Differences in ascertainment rate do not seem to play a major role. In comparison with other congenital anomalies, OC are rather conspicuous, severe anomalies, rarely overlooked at birth because they are external and obvious and cause typical changes in crying pitch and sucking ability. CL/P is more obvious than CP and severe forms, such as complete bilateral cleft of the lip and palate, are more obvious than mild forms, such as incomplete cleft of the soft palate. However, in spite of this clinical logic, there is no clear evidence for a greater under-ascertainment of CP than of CL/P.

Obvious under-reporting exists for the microforms such as “healed” or “fruste” CL (Castilla & Martínez Frías, 1995), sub-mucous CP, and notched gums (clefts of the alveolar ridge). However, except for sub-mucous CP, these forms are too rare to be reflected in the total registered number of cases (Christensen & Fogh-Andersen, 1994).

- **Variability:** The largest source of variability among populations seems to be genetic predisposition rather than environmental differences or differences in ascertainment. This statement is mainly supported by the above-mentioned inter-ethnic differences and stable time trends.

Ethnicity must be considered in its macro as well as its micro components. Macro-ethnicity was already summarized as having maximal OC frequencies in the Mongoloid races, minimal in Africans, and intermediate in Caucasians. Furthermore, micro-ethnicity could be responsible for reported geographical clusters, such as the Cumaná cluster on the Caribbean coast of Venezuela, apparently due to a single mutation-producing, non-syndromic CL/P (Sözen et al., 2001).

Some situations could even be intermediate between the above-mentioned macro- and micro- ethnicity, as for instance those of Finland (Saxén and Lathi, 1974) or the Philippines (Murray et al., 1997).

The major role of genetic factors in the etiology of OC was recently updated by Calzolari (2001) with EUROCAT data.

BOX 12

ICBDMS experience

When summarizing 15 years of experience in the book *Congenital malformations worldwide* (ICBDMS, 1991), the ICBDMS made the following statements:

“Cleft lip with or without cleft palate: This is one of the most stable malformations among those studied, probably because it is a condition easily observed and described. Some temporal changes can be noted, however. Up to 1982, the rates of Canada-National and Atlanta were virtually identical, but since that time the Canadian rate increased and the Atlanta rate decreased slightly. A slightly increasing trend is seen in the Tokyo programme. More remarkable is the difference among programmes. Programmes in southern Europe and Israel have rates around 6 per 10 000, while the Scandinavian, and the Asian programmes, as well as Canada have rates twice as high. The rate of total cleft lip apparently differs in different populations, and it is likely that genetic factors play a decisive role for this difference.

“Cleft palate: In most programmes, the rate is around 5 per 10 000 births, and remains reasonably constant during the observation period. Some remarkable exceptions can be seen. In England-Wales, Japan, and Atlanta very high rates existed at the beginning of the observation period followed by a marked decrease down to the approximate level of most other programmes. High and increasing rates are seen in Finland. A tendency to an increase is seen in Sweden, France-Strasbourg, and perhaps to a lesser extent in some other programmes. Although such changes might have arisen by an increased inclusion of mild cases, a special study made at ICBDMS on this problem yielded no convincing evidence that this was a major cause of the observed changes.”