Pediatric Cleft Lip and Palate

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Background

Orofacial clefts (ie, cleft lip [CL], cleft lip and palate [CLP], cleft palate [CP] alone, as well as median, lateral [transversal], oblique facial clefts) are among the most common congenital anomalies. Approximately 1 case of orofacial cleft occurs in every 500-550 births. In the United States, 20 infants are born with an orofacial cleft on an average day, or 7500 every year. Children who have an orofacial cleft require several surgical procedures and complex medical treatments; the estimated lifetime medical cost for each child with an orofacial cleft is $100,000, amounting to $750 million for all children with orofacial cleft born each year in the United States.[1] Also, these children and their families often experience serious psychological problems.

With rapidly advancing knowledge in medical genetics and with new DNA diagnostic technologies, more and more orofacial clefts are identified as syndromic. Although the basic rate of clefting (1:500 to 1:550) has not changed since Fogh-Andersen performed his pioneering 1942 genetic study distinguishing 2 basic categories of orofacial clefts (cleft lip with or without cleft palate [CL/P] and cleft palate alone), these clefts can now be more accurately classified. The correct diagnosis of a cleft anomaly is fundamental for treatment, for further genetic and etiopathological studies, and for preventive measures correctly targeting the category of preventable orofacial clefts.

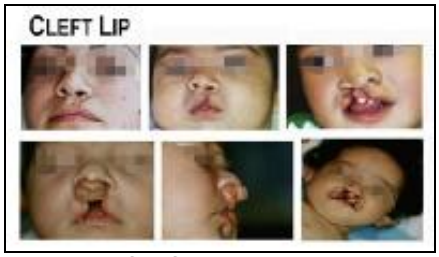
Problem

Classification and diagnostics

The group of orofacial cleft anomalies is heterogeneous. It comprises typical orofacial clefts (eg, cleft lip, cleft lip and palate, cleft palate) and atypical clefts, including median, transversal, oblique, and other Tessier types of facial clefts.[2, 3] Typical and atypical clefts can both occur as an isolated anomaly, as part of a sequence of a primary defect, or as a multiple congenital anomaly (MCA). In an 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 MCA of unknown etiology (see the image below).

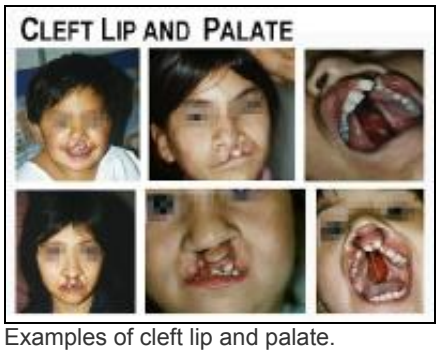
Classification of orofacial clefts.

Cleft lip can occur as a unilateral (on the left or right side) or as a bilateral anomaly. The line of cleft always starts on the lateral part of the upper lip and continues through the philtrum to the alveolus between the lateral incisor and the canine tooth, following the line of sutura incisiva up to the foramen incisivum. The clefting anterior to the incisive foramen (ie, lip and alveolus) is also defined as a cleft primary palate. Cleft lip may occur with a wide range of severity, from a notch located on the left or right side of the lip to the most severe form, bilateral cleft lip and alveolus that separates the philtrum of the upper lip and premaxilla from the rest of the maxillary arch (see the image below).



Examples of cleft lip.

When cleft lip continues from the foramen incisivum further through the sutura palatina in the middle of the palate, a cleft lip and palate (either unilateral or bilateral) is present (see the image below).

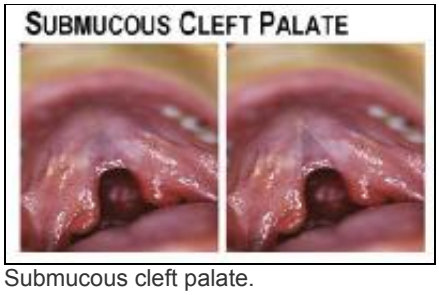


Examples of cleft lip and palate.

A wide range of severity may be observed. The cleft line may be interrupted by soft (skin or mucosa) bridges, hard (bone) bridges, or both, corresponding to a diagnosis of an incomplete cleft. This occurs in unilateral and bilateral cleft lip and palate.

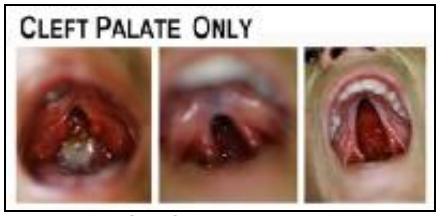
Cleft palate (see the images below) is etiologically and embryologically different from cleft lip with or without cleft palate.

Examples of cleft palate.



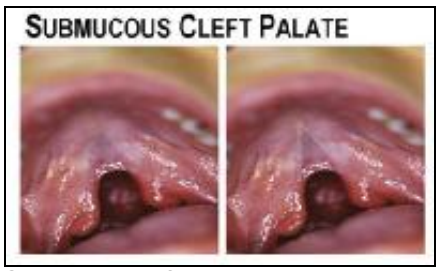
Submucous cleft palate.

Several subtypes of cleft palate can be diagnosed based on severity. The uvula is the place where the minimal form of clefting of the palate is observed. (However, a relatively high prevalence of this anomaly in the general population suggests that a certain proportion may represent the very far end of a normal variability.) A more severe form is a cleft of the soft palate. A complete cleft palate constitutes a cleft of the hard palate, soft palate, and cleft uvula. The clefting posterior to the incisive foramen is defined as a cleft of secondary palate (see the image below).



Examples of cleft palate.

In a significant proportion of patients, the cleft of the hard palate is covered by mucosa and continues through the soft palate, forming a so-called submucous cleft palate. A submucous CP may occur in the hard palate only and continue to the open cleft of the soft palate, or it may occur as a submucous cleft of the soft palate with or without a notch into the hard palate. Careful clinical examination may reveal a blue triangle in continuation of the cleft of the soft palate, which represents a cleft of the bone palate underneath mucosa (see the image below).



Submucous cleft palate.

The palate cleft may take 2 distinguishable forms—a V shape, which is most common in isolated clefts, or a U shape, which is most common in Robin sequence (see Pierre Robin Malformation) and in syndromic clefts.

As is described below, the cleft palate posterior to the incisive foramen is defined as the cleft of the secondary palate. Cleft lip and cleft of the palate anterior to the incisive foramen (unilateral or bilateral) is defined as the cleft of primary palate (thus, in bilateral cleft lip, premaxilla is separated from lateral palatal segments). The bifid uvula is a sign that adenoidectomy may result in hypernasal speech if a complete adenoidectomy is done.

Embryology

In facial morphogenesis, neural crest cells migrate into the facial region, where they form the skeletal and connective tissue and all dental tissues except the enamel. Vascular endothelium and muscle are of mesodermal origin.[4]

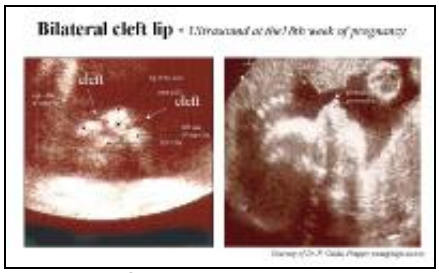
The upper lip is derived from medial nasal and maxillary processes. Failure of merging between the medial nasal and maxillary processes at 5 weeks' gestation, on one or both sides, results in cleft lip. Cleft lip usually occurs at the junction between the central and lateral parts of the upper lip on either side. The cleft may affect only the upper lip, or it may extend more deeply into the maxilla and the primary palate. (Cleft of the primary palate includes cleft lip and cleft of the alveolus.) If the fusion of palatal shelves is impaired also, the cleft lip is accompanied by cleft palate, forming the cleft lip and palate abnormality.

Cleft palate is a partial or total lack of fusion of palatal shelves. It can occur in numerous ways:

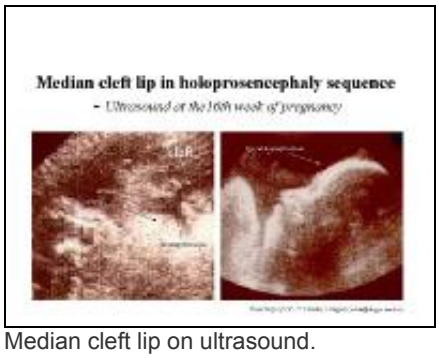
- Defective growth of palatal shelves
- Failure of the shelves to attain a horizontal position
- Lack of contact between shelves
- Rupture after fusion of shelves

The secondary palate develops from the right and left palatal processes. Fusion of palatal shelves begins at 8 weeks' gestation and continues usually until 12 weeks' gestation. One hypothesis is that a threshold is noted beyond which delayed movement of palatal shelves does not allow closure to take place, and this results in a cleft palate.

Cleft lip can be easily diagnosed by performing ultrasonography in the second trimester of pregnancy when the position of the fetal face is located correctly (see the images below).



Bilateral cleft lip on ultrasound.



Median cleft lip on ultrasound.

Usually, diagnosing a cleft palate with ultrasonography is not possible; however, an experienced physician or technician may catch an atypical movement of the fetal tongue in a lateral view. In the case of a large cleft palate, the tongue moves up into an open space (cleft) in the roof of the oral cavity. Three-dimensional imaging has been introduced to prenatal ultrasonography diagnostics of cleft anomalies and appears to be promising for recognizing a cleft palate in a fetus.

Epidemiology

Frequency

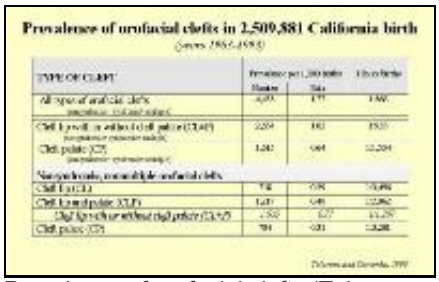
Reported data on the frequency of orofacial clefts vary according to the investigator and the country. In general, all typical orofacial cleft types combined occur in white populations with a frequency of 1 per 500-550 live births. Although the total combined frequency of cleft lip, cleft lip and palate, and cleft palate is often used in statistics, combining the 2 etiologically different groups (cleft lip with or without cleft palate and cleft palate) represents a misclassification bias similar to that of combining clefts with other congenital malformations.

The sex ratio in patients with clefts varies. In whites, cleft lip and cleft lip and palate occur significantly more often in males, and cleft palate occurs significantly more often in females. In cleft lip with or without cleft palate, the sex ratio correlates with the severity and laterality of the cleft. A large study of 8,952 orofacial clefts in whites found the male-to-female sex ratio to be 1.5-1.59:1 for cleft lip, 1.98-2.07:1 for cleft lip and palate, and 0.72-0.74:1 for cleft palate.[5]

The prevalence rate of clefts in different racial groups is considerable. The lowest rate is for blacks. A high prevalence of cleft lip with or without cleft palate was found for the Japanese population, and the highest prevalence was found for the North American Indian populations. In contrast, no remarkable variation among races

was found in isolated cleft palate. In particular, its prevalence did not significantly vary between black and white infants or between infants of Japanese and European origin in Hawaii. Leck (1984) considered that such findings may reflect a higher etiological heterogeneity of cleft palate than of cleft lip with or without cleft palate. Methods of ascertainment and classification criteria undoubtedly have major influence on the prevalence values.[2]

In a large population-based study of 4,433 children born with orofacial cleft (ascertained from 2,509,881 California births), the birth prevalence of nonsyndromic cleft lip with or without cleft palate was 0.77 per 1,000 births (cleft lip, 0.29/1,000; cleft palate, 0.48/1,000) and prevalence of nonsyndromic cleft palate was 0.31 per 1,000 births (see the image below).[6]



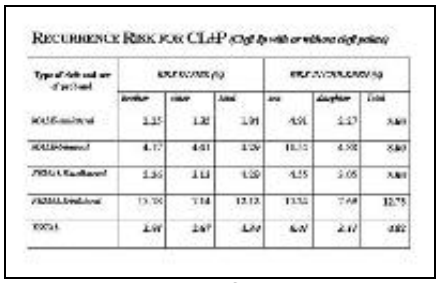
Prevalence of orofacial clefts (Tolarova and Cervenka, 1998).

In that study, the risk of cleft lip with or without cleft palate was slightly lower among the offspring of non—US-born Chinese women compared to US-born Chinese women and slightly higher among non—US-born Filipinos relative to their US-born counterparts. For cleft palate, lower prevalences were observed among blacks and Hispanics than among whites. The risk of cleft palate was higher among non—US-born Filipinos compared to US-born Filipinos. These prevalence variations may reflect differences in both environmental and genetic factors affecting risk for development of orofacial cleft.

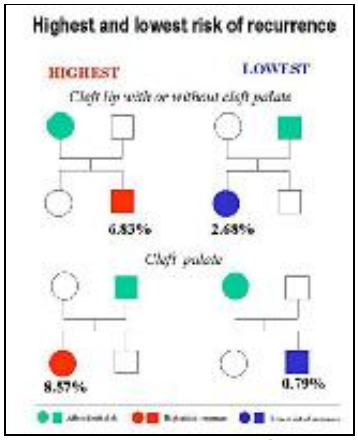
Risk of recurrence

Genetic factors (ie, genes participating in the etiology of nonsyndromic orofacial clefts) are passed to the next generation, thus creating an increased risk for such anomaly in offspring. The risk of recurrence also differs with respect to proportion of genetic and nongenetic factors. In cleft lip with or without cleft palate, the hypothetical 4-threshold model (see Etiology) closely corresponds with differences in the risk of recurrence.

From a clinical point of view, 2 factors are most important when evaluating the risk of recurrence for cleft lip with or without cleft palate: the sex of the individuals (ie, patient and individual at risk) and the severity of the affect in the patient (eg, unilateral vs bilateral). The lowest recurrence risk for cleft lip with or without cleft palate is for the subcategory of male patients with unilateral cleft (see the first image below) and, within this category, for sisters of males with a unilateral cleft and for daughters of fathers with a unilateral cleft lip with or without cleft palate (see the second image below). The highest risk of recurrence of CL/P is for the subcategory of female patients affected with a bilateral CL/P.

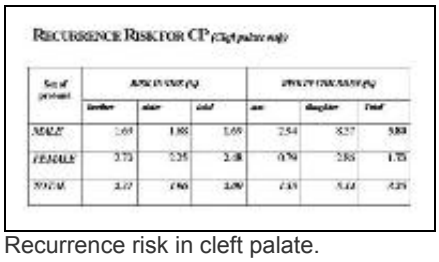


Recurrence risk in cleft lip with or without cleft palate.



Highest and lowest risk of recurrence of cleft lip with or without cleft palate.

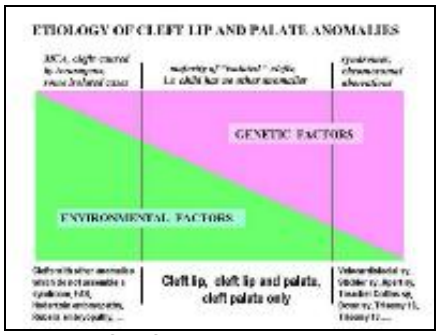
The risk of recurrence for cleft palate seems to be influenced only by sex. The risk is highest for daughters of fathers affected with a cleft palate and lowest for sons of mothers affected with a cleft palate (see the image below).



Recurrence risk in cleft palate.

Etiology

Most orofacial clefts, like most common congenital anomalies, are caused by the interaction between genetic and environmental factors (see the image below).

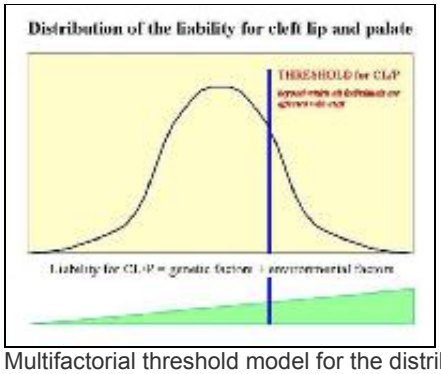


Etiology of cleft lip and palate anomalies.

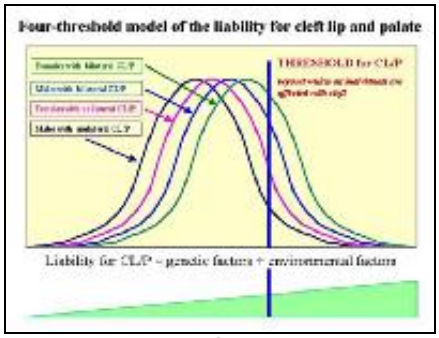
In those instances, genetic factors create a susceptibility for clefts. When environmental factors (ie, triggers) interact with a genetically susceptible genotype, a cleft develops during an early stage of development.

The proportion of environmental and genetic factors varies with the sex of the individual affected with cleft. In cleft lip and cleft palate, it also varies with the severity and the unilaterality or bilaterality of the cleft anomaly; the highest proportion of genetic factors are in the subgroup of females with a bilateral cleft, and the smallest proportion is in the subgroup of males with a unilateral cleft.

Thus, the classic multifactorial threshold (MFT) model of liability (see the first image below) can be applied to cleft lip with or without cleft palate as the multifactorial model of liability with 4 different thresholds (see the second image below).



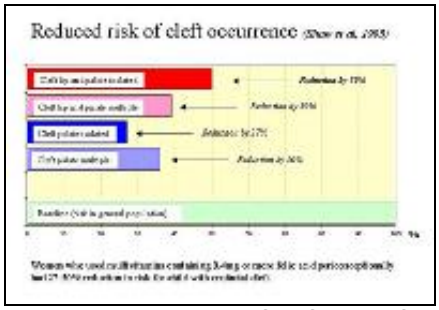
Multifactorial threshold model for the distribution of liability for cleft lip and palate.



Four-threshold multifactorial threshold model of the liability for cleft lip and palate.

This model can help to better understand differences in values of risk of recurrence as well as differences in prevention approaches between different subgroups of clefts.[5]

Theoretically, the subgroup of clefts closest to the population average should have the highest population prevalence, the lowest value of heritability, and, thus, the lowest risk of recurrence. This has been confirmed on a large, population-based study of whites with clefts (see the image below).[5]



Decreased occurrence of orofacial clefts.

The value of heritability expresses a ratio of genetic and nongenetic factors. Heritability is equal to 1 for conditions completely controlled by genetic factors and equal to 0 for conditions completely controlled by environmental factors.

A higher proportion of environmental factors indicates a lower risk of recurrence and also gives a better chance to act in prevention, because the only etiological factors that can be changed are environmental factors. Thus, the subgroup whose average prevalence is closest to the population average represents males affected with a unilateral cleft lip with or without cleft palate. This subgroup is most common among orofacial clefts; the risk of recurrence for siblings and for offspring of an individual with cleft is the lowest, the value of heritability is the lowest, and efficacy of primary prevention is the highest (see details for other subgroups in Future and Controversies).

As mentioned in the previous section, a cleft develops when embryonic parts called processes (which are programmed to grow, move, and join with each other to form an individual part of the embryo) do not reach each other in time and an open space (cleft) between them persists. In the normal situation, the processes grow into an open space by means of cellular migration and multiplication, touch each other, and fuse together.

In general, any factor that could prevent the processes from reaching each other by slowing down migration, multiplication, or both of neural crest cells by stopping tissue growth and development for a time or by killing some cells that are already in that location would cause a persistence of a cleft. Also, the epithelium that covers the

mesenchyme may not undergo programmed cell death, so that fusion of processes cannot take place.[4]

DNA studies

Over the past decade, a considerable interest has developed in the identification of genes that contribute to the etiology of orofacial clefting. Advances in modern molecular biology, new methods of genome manipulation, and availability of complete genome sequences led to an understanding of the roles of particular genes that are associated with embryonic development of the orofacial complex.

The first candidate gene was transforming growth factor-a (*TGFA*), which showed an association with nonsyndromic cleft lip and palate (NCLP) in a white population.[7] Lidral et al investigated 5 different genes (*TGFA, BCL3, DLX2, MSX1, TGFB3*) in a largely white population from Iowa.[8, 9] They found a significant linkage disequilibrium between cleft lip with or without cleft palate and both *MSX1* and *TGFB3* and between CP and *MSX1*. The *TGFB3* gene was identified as a strong candidate for clefting in humans based on both the mouse model[10] and the linkage disequilibrium studies.[11, 9, 12] Other candidate genes that show an association with nonsyndromic cleft lip and palate include *D4S192, RARA, MTHFR, RFC1, GABRB3, PVRL1,* and *IRF6.*

MSX1 was found to be a strong candidate gene involved in orofacial clefts and dental anomalies. Recent analysis of the *MSX1* sequence in a multiplex Dutch family showed that a nonsense mutation (Ser104stop) in exon 1 segregated with the phenotype of nonsyndromic cleft lip and palate.[13] Some have proposed that cleft palate in *MSX1* knock-out mice is due to insufficiency of the palatal mesenchyme.[14]

Zucchero et al reported that variants of *IRF6* may be responsible for 12% of nonsyndromic cleft lip and palate, suggesting that this gene would play a substantial role in the causation of orofacial clefts.[15] A meta-analysis of all-genome scans of subjects with nonsyndromic cleft lip and palate, including Filipino, Chinese, Indian, and Colombian families, found a significant evidence of linkage to the region that contains interferon regulatory factor 6 (IRF6).[16]

Also, gene-gene interactions have been examined. A complex interplay of several genes, each making a small contribution to the overall risk, may lead to formation of clefts. Jugessur et al reported a strong effect of the *TGFA* variant among children homozygous for the *MSX1 A4* allele (9 CA repeats).[17]

Evaluation of gene-environment interactions is still in a preliminary stage. Studies of the role of smoking in *TGFA* and *MSX1* as covariates suggested that these loci might be susceptible to detrimental effects of maternal smoking.[12, 18] Folate-metabolizing enzymes such as methylenetetrahydrofolate reductase (*MTHFR*), which is a key player in etiology of neural tube defects, and *RFC1* are considered candidate genes based on data that suggest that folic acid supplementation can reduce incidence of nonsyndromic cleft lip and palate.[19]

Recently, more than 30 potential candidate loci and candidate genes throughout the human genome were identified as strong susceptibility genes for orofacial clefts. The *MSX1* (4p16.1), *TGFA* (2p13), *TGFB1* (19q13.1), *TGFB2* (1q41), *TGFB3* (14q24), *RARA* (17q12), and *MTHFR* (1p36.3) genes are among the strongest candidates.[16, 20, 21]

The *TGFB3* gene was identified as a strong candidate for clefting in humans based on a mouse model. Generally, palatogenesis in mice parallels that of humans and shows that comparable genes are involved.[22] Kaartinen demonstrated that mice lacking the TGFB3 peptide exhibit cleft palate.[10] In addition, the exogenous TGFB3 peptide can induce palatal fusion in chicken embryos, although the cleft palate is a normal feature in chickens.[23]

In humans, association studies between the *TGFB3* gene and nonsyndromic cleft lip with or without cleft palate have shown conflicting results. Lidral reported failure to observe an association of a new allelic variant of *TGFB3* with nonsyndromic cleft lip with or without cleft palate in a case-control study of the Philippines' population.[8] Another study by Tanabe analyzed DNA samples from 43 Japanese patients and compared results with those from 73 control subjects with respect to 4 candidate genes, including *TGFB3*.[24] No significant differences in variants of *TGFB3* between case and control populations were observed.

On the other hand, more recent case-control association studies, family based studies, and genome scans have supported a role of *TGFB3* in cleft development. Beaty examined markers in 5 candidate genes in 269 case-parent trios ascertained through a child with nonsyndromic orofacial clefts;[12] 85% of the probands in the study were white. Markers at 2 of the 5 candidate genes (*TGFB3* and *MSX1*) showed consistent evidence of linkage and disequilibrium due to linkage. Similarly, Vieira attempted to detect transmission distortion of *MSX1* and *TGFB3* in

217 South American children from their respective mothers.[25] A joint analysis of *MSX1* and *TGFB3* suggested a possible interaction between these 2 genes, increasing cleft susceptibility. These results suggest that *MSX1* and *TGFB3* mutations make a contribution to clefts in South American populations.

In a study of the Korean population, Kim reported that the G allele at the SfaN1 polymorphism of *TGFB3* is associated with an increased risk of nonsyndromic cleft lip with or without cleft palate. The population study consisted of 28 patients with nonsyndromic cleft lip with or without cleft palate and 41 healthy controls.[26]

In 2004, Marazita performed a meta-analysis of 13 genome scans of 388 extended multiplex families with nonsyndromic cleft lip with or without cleft palate.[16] The families came from 7 diverse populations including 2,551 genotyped individuals. The meta-analysis revealed multiple genes in 6 chromosomal regions including the region containing *TGFB3* (14q24).

In the Japanese population, blood samples from 20 families with nonsyndromic cleft lip with or without cleft palate have been analyzed using *TGFB3* CA repeat polymorphic marker. Based on the results of the study, the investigators concluded that either the *TGFB3* gene itself or an adjacent DNA sequence may contribute to the development of cleft lip and palate.[27]

Another study by Ichikawa and colleagues, investigated the relationship between nonsyndromic cleft lip with or without cleft palate and 7 candidate genes (*TGFB3, DLX3, PAX9, CLPTM1, TBX10, PVRL1, TBX22*) in a Japanese population.[28] The sample consisted of 112 patients with their parents and 192 controls. Both population based case-control analysis and family based transmission disequilibrium test (TDT) were used. The results showed significant associations of single nucleotide polymorphisms (SNPs) in *TGFB3* and nonsyndromic cleft lip with or without cleft palate, especially IVS+5321(rs2300607), with a P value of 0.0016. Although IVS-1572 (rs2268625) alone did not show a significant difference between cases and controls, the haplotype "A/A" for rs2300607- rs2268625 showed significant association. The author concluded that the results demonstrated positive association of *TGFB3* with nonsyndromic cleft lip with or without cleft palate in Japanese patients.

Several micromanifestations of orofacial clefts have been studied,[29, 30] and additional candidate genes associated with these minimal, clinically less significant anomalies have been suggested.[29, 31]

Associations of specific candidate genes with nonsyndromic cleft lip and palate have not been found consistent across different populations. This may suggest that multiplicative effects of several candidate genes or gene-environmental interactions are noted in different populations.

The identification of factors that contribute to the etiology of nonsyndromic cleft lip and palate is important for prevention, treatment planning, and education. With an increasing number of couples who seek genetic counseling as a part of their family planning, the knowledge of how specific genes contribute to formation of nonsyndromic cleft lip and palate has gained an increased importance.

Indications

Children who have an orofacial cleft require several surgical procedures and complex medical treatments.

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