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REVIEW ARTICLE

Twin Studies in Craniofacial Genetics: A Review

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Abstract. A review of the literature on twin studies in craniofacial genetics is presented. The following areas are particularly dealt with: tooth form and size, tooth formation and eruption, dental arch and occlusion, facial form and size, and cleft lip and palate.

Key words: Teeth, Facial skeleton, Clefting, Craniofacial genetics, Twins

It is known that most orofacial traits, are multifactorially determined. Therefore, when one analyzes causes of variations in this region, it is essential to refer to both heredity and environment, so that research done by the twin method has a great significance. This article reviews twin studies in craniofacial genetics, with particular emphasis on morphology and size of the craniofacial complex.

TOOTH

Tooth Form

Since a tooth is a hard tissue and never changes its final form and size, it is a convenient object for studying the relative roles of hereditary and environmental factors contributing to its growth.

Carabelli's tubercle. A small tubercle, which appears on the lingual side of the upper first molar and is named after its discoverer "Carabelli's tubercle", is mostly seen among Caucasians, while shovel-shaped incisors (teeth in recessed condition on lingual side by prominent lateral margins) are common among Mongoloids. In fact, dental traits can be indicative of strong heredity and even represent racial characteristics [23,62].

Siemens [98] reported an example of concordance in a pair of twins in 1928. Later, Zeiger [116] ascertained concordance in all 16 pairs of MZ twins vs 6 out of 21 pairs of DZ twins.

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Furthermore, Von Verschuer [110] compiled literatures published between 1924 and 1931 showing concordance in 69 out of 70 pairs of MZ (99%) vs 46 out of 98 pairs of DZ twins (47%).

According to a recent report by Saheki [95], concordance rates in Japanese twins were found to be 68% for MZ and 33% for DZ twins, Biggerstaff [11] also observed concordance in 64 out of 97 MZ vs 42 out of 94 DZ twin pairs (66% vs 45%), the difference being statistically significant. He also surveyed the concordance between the teeth on the opposite side in each pair of twins, but found no difference between MZ and DZ twins, indicating absence of mirror imaging for this trait.

Shovel-shaped incisors. Studies on twins with shovel-shaped incisors were so far only for Japanese twins. Saheki [95] reported concordance rates for upper central incisors of 96% for MZ vs 50% for DZ twins. The high frequency of the trait among the Japanese (73%) may be the main reason for such a high concordance in DZ twins.

Mizoguchi [70] estimated tetrachoric correlations for each group of twins by evaluating morphologic variation of shovel-shaped incisors in four grades, from "absence" to "highly developed". He obtained tetrachoric correlation coefficients of 0.90 for MZ vs 0.59 for DZ twins.

Mandibular second premolars. High individual variations were observed in lingual cusps in regard to this trait. Wood and Green [113] studied 18 pairs of serologically concordant MZ twins obtaining a concordance rate between 87.5% and 88.2%. Homolateral comparisons of mandibular second premolars in twins were accurate enough to be used for determining monozygosity. Ludwig [58] made comparisons of the various morphologic traits of this particular tooth in 17 pairs of MZ and 12 pairs of DZ twins. He concluded the MZ twins showed significantly higher similarity than DZ twins. Again, according to the tetrachoric correlations of Mizoguchi [70], the values of 0.69 for MZ twins and 0.34 for DZ twins were presented, as well as an heritability estimate of 0.71. On the other hand, Staley and Green [107] who employed an "all or none" method, simply presence or absence of the cusps, failed to find a meaningful difference in concordance between MZ and DZ twins in a sample of 90 pairs.

Therefore, introducing a quantitative method in the study of heritability of tooth configuration has an important significance.

Mandibular first molar. Saheki [75] reported presence or absence of the sixth cusp of this tooth to be concordant in 69% of MZ vs 33% of DZ twins. Moreover, in a study of 100 MZ and 99 DZ pairs, Biggerstaff [10] reported complete concordance in such morphologic variations of this tooth as number of cusps, occlusal groove pattern, etc, in 69.5% of MZ vs 58.5% of DZ twins.

Tooth Size

Tooth size is expressed mainly by measurement of either mesiodistal or labiolingual diameter of the tooth crown.

As for primary teeth, Asano [4] and Ochiai et al [82] measured mesiodistal diameters of tooth-crowns of Japanese twins of 36 MZ and 26 DZ pairs obtaining small intrapair differences in MZ twins, particularly for primary cuspids and primary molars. The heritability estimate based on variance values was as high as 0.63 in maxillary primary cuspids, and genetic components appeared to be larger in the lower than upper primary teeth.

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Di Salvo et al [18] also measured the primary teeth in twins. Although detailed results of measurements have not yet been presented, they indicated that there was at least a remarkable difference between zygosities in maxillary and mandibular primary cuspids, and that genetic control was high.

In the case of the size of permanent teeth of twins, relatively more studies have been made due to the case of obtaining data on permanent teeth in comparison with primary teeth. Generally speaking, there are many reports stating that tooth size is much more similar in MZ twins [2,38]. Also, observations have been made on detailed points, eg, not only size of total dentition, but also comparison of size of cusps between twins [12].

Shimizu [101,102] reported intrapair differences in mesiodistal diameters of permanent teeth crowns in 24 MZ and 25 DZ Japanese twin pairs. The difference in MZ twins fell within 0.0~0.9 mm. The percentage of pairs whose difference fell within 0.5 mm was 97.6% in MZ twins, 79.6% in DZ twins and 67.1% in unlike-sexed DZ twins. Based on these results, Shimizu suggested that any twin pair with a difference within 0.2 mm might well be diagnosed as a MZ twin pair.

Hunter [40] calculated F-ratios of mean intrapair variance in 37 pairs of MZ and 33 pairs of DZ twins. He reported that significantly high F values were observed from all kinds of teeth with the exception of maxillary and mandibular second molars. His study indicates a high contribution of genetic factors to size in particular teeth which complete formation of their crowns at a relatively early stage.

Similarly, it was found that tooth size of mesiodistal diameters in all permanent teeth, with the exception of second and third molars, show memorable genetic variability. Mizoguchi [71] confirmed the finding from intraclass correlations for tooth size in 191 pairs of MZ and 75 pairs of DZ twins.

Whether the differences in tooth size between left and right teeth are controlled by hereditary factors has also been studied with twin data, but could not be confirmed [85].

Osborne et al [83] claimed that the similarity of action in the growth of adjacent teeth could be shown comparing MZ cotwins. For example, they compared the central incisor of one twin with the adjacent lateral incisor of the cotwin. In the case of DZ twins, the effect of mutual common environment could be found. Thus, this method was called "cross-twin analysis". This method was used for analyzing 12 maxillary and mandibular anterior teeth of 32 pairs of MZ and 21 pairs of DZ twins. It revealed that such cross-twin correlations were high, especially between adjacent teeth in MZ twins. This suggests the possibility of hereditary factors that control tooth size and act commonly upon several teeth.

Potter et al [86] expanded this concept and performed a multivariate analysis on the covariance matrices of both MZ and DZ within-pair differences for mesiodistal and buccolingual diameters of 28 permanent teeth. Their results provided evidence that dimensional correlations of teeth are primarily genetic in origin. Maxillary and mandibular dentitions were further shown to be controlled by relatively independent genetic factors.

Tooth Formation and Eruption

There are two main steps in the human "diphyodont" dentition, from the formation of the 20 primary teeth to that of the succeeding and 8 additional permanent teeth. In order

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to develop the normal occlusion between the maxillary and the mandibular dentition it is extremely important to maintain a fixed and orderly sequence of the dental formation period and dental eruption. Because of this regularity, the evaluation of individual growth, based on both the dental formation and the eruption, becomes possible and supports the concept of dental age and bone age.

Twin studies in this area were first conducted for an evaluation of the growth of primary teeth in the embryonic period. Stack [105] reported that ash weight measurements of calcified primary incisors taken from 10 pairs of aborted twin fetuses of 24~32 embryonic weeks revealed a very small intrapair difference in primary central incisors. On the contrary, considerable variance was found in primary lateral incisors. As to the comparison of dental growth stages, Stack reported that the maximum value of the intrapair difference was approximately 2 weeks [106]. In the same manner, Goodman and Kraus [31] also examined 15-week-old fetuses of 8 pairs of twins and 3 pairs of triplets with respect to similarity in the form of primary tooth germs, finding extremely high similarity in MZ pairs. Goodman and Kraus further commented that the similarity could be evaluated more positively in the form of tooth germs than in the degree of bone growth.

X-ray for observing calcified images is mostly used to study the formation of permanent teeth. Garn et al [26] ascertained a correlation value of 0.91 in MZ twins, vs one of 0.33 in DZ twins, for X-ray observations of growth stages of mandibular first and second molars. Gedda and Brenci [29] studied degrees of calcification of permanent teeth in 40 pairs of twins and reported correlations of 0.95 for MZ and 0.84 for DZ twins. Green and Aszkler [33] completed observations in 38 pairs of MZ twins and 31 pairs of DZ twins by means of "Panorex" X-ray, finding that intrapair variances for growth of tooth germs of mandibular permanent incisors, premolars, and molars were remarkably small in MZ twins.

Visible appearance of primary teeth in an oral cavity for the first time after birth is called "first dentition". In connection with this first dentition period, Von Verschuer [110] observed an intrapair variability restricted to 0~2 days in 27 out of 35 pairs (77%) in MZ twins and in 9 out of 24 pairs (38%) in DZ twins. In the remaining DZ pairs, variability ranged from 1 week to 2 months or more. Hatton [34] obtained intraclass correlations in timing of primary teeth eruption of 0.91 in MZ twins and 0.56 in DZ twins, with a resulting heritability coefficient of 0.78. Gedda and Brenci [28] also estimated heritability based on the observation of 408 pairs of twins. They obtained values of 0.82 for the timing of the first dentition, 0.80 for the shedding of primary teeth, and 0.75 for the eruption of permanent teeth. Environmental factors are suggested to influence the eruption of permanent teeth more than the eruption of primary teeth.

Up to date, quite a few reports have been published with observations of twins showing abnormalities in number of teeth due to initiation of tooth germ, in eruption and in structures of teeth.

Praeger [88], Zeiger and Winkler [117], and Burman [14] reported an identical number of congenital tooth missing in both members of MZ twins.

On the contrary, Tanner [108] reported an example of inconformity in which one of MZ twins had missing mandibular second premolar, but the cotwin was normal. Gravely and Johnson [32] found cases in which almost all numbers and locations of missing teeth were coincidental, but a part of the missing teeth did not conform between MZ cotwins.

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They assumed that hypodontia was genetically determined but its expression was affected by nongenetic factors. Keene [45] held a similar view and found that the frequency of congenital missing teeth was generally high in twins. In cases where missing teeth were discordant in MZ twins, the frequency was even higher in a twin whose birth weight was lighter [46]. In short, Keene's report suggests that some nongenetic factor associated with birth weight difference may also play a role in missing teeth, in addition to the existing genetic factors mentioned.

An unusual case was reported of ectodermal displasia associated with partial anodontia in both unlike-sexed DZ twins [93].

During the eruption of the first permanent molar in the distal position of the primary dentition, an abnormal resorption may occur at the distal root of the secondary primary molar. Therefore, the eruption would take place at an adjacent location rather than at its specific one. This is called "ectopic eruption of the first molar". This phenomenon, coincidentally seen in MZ twins, was reported by Ashley-Montague [5] and Jarvinen and Väätäjä [44]. This can be considered the result of interaction between the locations of tooth germs and the sizes of jaw bones, both genetically determined, where growth of tooth germs takes place.

It is well known that most abnormalities in tooth structures are of genetic nature. However, it appears that not so many examples of such occurrences in twins have been seen. In his book "Twins in History and Science", Gedda [27] cited Hider's report in 1846 [37] that rose-colored teeth were found in a pair of female twins. Later, an assumption was made in connection to this by Korkhaus [47]. He speculated that the subject with rose-colored teeth had been suffering from dentinogenesis imperfecta in which reddish dental pulp might have been seen through the teeth. Color of the tooth crown has a close relation with the tooth material. According to Korkhaus [47], the ratios of highly resembled color of tooth crowns were 94% (48/51) in MZ twins, 33% (11/33) in DZ twins and 22% (2/9) in unlike-sexed DZ twins.

As to abnormality of the enamel, a few reports can be found because of the relative ease of observation with the naked eye. Bachrach and Young [6] reported that, in the case of enamel hypoplasia in primary teeth, the rates of concordance were 5.2% in MZ twins and 3.6% in DZ twins. However, in the case of permanent teeth, the concordances were 16.7% in MZ twins and 6.2% in DZ twins. Von Verschuer [110] reviewed previous reports in the literature, finding that the concordances of enamel hypoplasia were 76% (27/33) in MZ twins and 60% (28/47) in DZ twins. He also indicated a strong genetic influence on these abnormalities.

Nakano et al [74] observed that morphology of surface layers of enamel obtained by scanning electron microscopy demonstrated exceedingly high similarity in a pair of MZ female twins in both of which amelogenesis imperfecta was seen.

CRANIO-FACIAL COMPLEX

Dental Arch and Occlusion

The book by Gedda [27] indicates that the first report on dentitions in twins was made by Bergfors [9]. He reported on tooth forms and conditions of configurations in 4 pairs of MZ and 3 pairs of DZ twins, finding that configurations were more similar in MZ than

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in DZ twins. Zygosity diagnosis and observation method in most early reports, however, were not always fully described in detail.

In 1929, Zeiger [116] took measurements of widths of dental arches in more than 80 pairs of twins and found that a genetic factor was a strong contributor in the distal portion of dentition. Goldberg [30] measured, using sheets of section paper, the size and shape of dental arches in 15 pairs of MZ twins and concluded that the small variances were attributable to environmental factors. Similar reports were made by Euler and Ritter [21], Braun [13], Fujita and Saheki [25], Menzes et al [68] and Yoda [115].

Variance between MZ twins is due to environmental factors and oral habit, which affects the forms of dental arches: Korkhaus [49,50] showed that the form of dental arch, though genetically determined, could be modified by environmental factors. This is also shown by a number of observations: a case in which similar upper anterior protrusion was observed in a pair of MZ twins with an oral habit [65]; a 10-year-old MZ twin whose distorted form of dentition was restored to resemble his cotwin as the oral habit disappeared [96]; a pair of 13-year-old MZ twins who had different occlusions due to both an oral habit and activity of muscuralis oris which were electromyographically different [54]; a pair of 13-year-old MZ twins whose mandibular first molars on both sides were extracted at an early stage causing difference in dental arches because of different periods of time after extractions [1]; a pair of 11-year-old MZ twins whose occlusions were different from each other due to different forces of their lips [8]; and a pair of MZ twins who both had oral habits of thumb-sucking with consequent protruded upper primary anterior teeth, but who both restored normal forms of dentition after spontaneously discontinuing the habit [77].

After examining forms of dentition, rotation, inclination, spacing, etc, among twins, Fujita and Kasai [24] concluded that tooth rotation would take place environmentally, but dental spacing would depend strongly upon genetic factors. This genetic dependency of spacing was reviewed later by Eto [20] for primary dentition, and by Potter et al [84] for permanent dentition in 87 pairs of MZ and 70 pairs of DZ twins. Results similar to those obtained by Fujita and Kasai were obtained. Lundström [63] observed 36 pairs of MZ and 38 pairs of DZ twins and found that the difference in crowding between right or left sides of MZ cotwins was no greater than the right-left difference within individuals. On the other hand, it was pointed out that caution is needed in measurements of this kind because the extent of total variance tends not to be the same between MZ and DZ twins [15,16,87].

As human teeth are diphyodont, the fulfillment of the masticatory function requires that the teeth properly occlude between upper and lower dentitions. Since accomplishment of proper occlusion comprises such elements as bone structure, nerve-muscle systems, teeth, etc, the genetic factors contributing to normal or abnormal occlusion should necessarily be regarded as the collective result of hereditary and enviromental factors.

There are several methods to diagnose the condition of occlusion between upper and lower dentitions. Angle's system, which determines the condition of occlusion on the basis of mesio-distal relationships between upper and lower first molars, is the most popular method. In cases where the mesio-distal relationship between upper and lower first molars is normal, it is classified as class I. In cases where maxillary teeth are more proximal than mandibular teeth, it is class II. Where mandibular teeth are more proximal

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than maxillary teeth, it is classified as class III. Lundström [59] investigated concordance in twins, based on the three classifications for occlusal relationships. He could not observe any difference of concordance rates in class I, these being 87.3% for MZ and 84.6% for DZ. Concordance rates in class II were found to be 76.7% for MZ and 23.8% for DZ. Distinct differences of concordance rates, 83.3% for MZ vs 10.0% for DZ, were observed in Class III. Furthermore, higher concordance of abnormal occlusions in MZ twins was exemplified by Ritter [92] who suggested strong genetic factors influencing variations of occlusion. In 1924, Baker [7] reported concordance of mandibular prognathism in two pairs of MZ twins. Later, Markovic [67] reviewed the twin case reports during the period from 1924 to 1965 and found concordance rates as different as 86.1% for MZ twins against 13.6% for DZ twins.

As a contributing factor to the formation and variation of occlusion, musculature cannot be disregarded. A report that an analysis by electromyogram indicated higher degree of similarity in MZ than DZ twins are published by Jacobs [43]. Similarities of electromyographic observations were also studied in unrelated pairs whose dentitions, occlusions and facial skeleton were very similar. The results failed to show positive relationship between electromyographic function and craniofacial morphology. In other words, a functioning role is not always of primary significance among the factors contributing to the morphological formation.

In addition, the concordance in number of minute facets on the occlusive surface of each individual tooth were investigated by Lindquist [57] and found to be 96% for MZ and 57% for DZ twins. Sognaes et al [104] processed these facets by morphologic images, and then tried to overlap them in MZ twins. Although similar forms of dentition appeared, they reported that individual bitemarks of each dentition differed to some extent from one another. As described so far, circumstances have developed from the observation of morphological similarities to a method of investigation incorporating functional studies.

Twin studies concerning the form of the palate were reported by Less [55] in 1934, and recently by Shapiro [97] and Riquelme and Green [91]. All reports clearly indicated, after taking measurements of height, width and antero-posterior length, that both height and width were highly influenced by genetic factors but length was not.

Facial Form and Size

There is keen interest in the form and size of the facial skeleton in various branches of science other than dentistry. The facial skeleton not only comprises the plural bones, but also involves the organs for vocalization, respiration, mastication, etc, in addition to a number of sensoriums. The methods for the evaluation of its form and size are complex and uneasy to adopt.

In dentistry, ever since cephalometric roentgenography was developed during the 1930s, analytical methods for measuring facial skeleton have been developed particularly for sagittal images. Wylie [114] first applied this roentgenocephalometry to pedigree analysis and observed 13 pairs of twins whose zygosities had not yet been determined. But he did not find any significant similarities. On the other hand, Snordgrasse [103] asserted that similarities in twins were higher than in siblings.

The method described above is a qualitative technique to determine similarities, by laying entire X-ray images over each other. Such observations are not only crude in terms of scientific methodology, but also lack a sufficient number of subjects.

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Lundström [60,61] initiated to conduct scientific, objective, and quantitative researches over a sufficient number of twins. Based on evaluations of mid-sagittal images obtained by measuring 16 variable angles with 50 pairs of MZ and DZ twins between 12 and 15 years old, Lundström ascertained that the ratio of genetic to nongenetic factors was 1.5:1 for 12 variables and nearly 2:1 for 4 variables. The genetic factors always exceeded the nongenetic factors, particularly in mandibular bones. He measured also 5 variables of linearity in the same samples [61] and observed a very high degree of genetic control in face length.

However, a problem arises from the fact that such methods for measuring the size of the facial skeleton involve a number of bone components altogether, the anatomic morphology of which is not reflected specifically in the measurements. In this regard, Kraus et al [51] proposed 17 items of the minimum bone components observable on lateral and postanterior cephalograms. They used 6 pairs of triplets and clearly demonstrated the similarities in MZ twins by overlapping each bone unit within each twin pair. Based on these observations, Kraus et al concluded that the structure of the individual bone unit of the craniofacial complex was under the rigid control of hereditary factors, but that environmental factors would also contribute when the individual bones combine to compose the face.

Form and size vary with age throughout human growth and development and the facial skeleton also undergoes complex changes during growth.

In order to clarify the role of genetic factors in facial formation during childhood, Nakata [75] made roentgenocephalometric analyses in 19 pairs of MZ and 11 pairs of DZ twins aged 3 years and 6 months, and reported that the area closer to the cranial base was more strongly controlled by genetic factors than the lower portion of the face.

In order to verify the degree of genetic contribution to the growth of the facial skeleton, Nakata et al [78] made a two-year observation on a group of twins aged 3½ years and Hayes [36] conducted a study on a group of twins aged 6 and 7 years for five years. Lundström [64] continued his observations for 13 years on twins from puberty to the adult age. According to their results, MZ twins were more similar than DZ twins not only in the extent of growth of the facial skeleton but also in its developmental processes.

It would be interesting to know how intrapair differences in MZ twins vary with age during the course of growth and development. However, this particular point was not made clear by the above studies. Müller [73] observed 61 pairs of MZ twins of several age groups but could not find such differences. In this regard, Nakata [76] compiled the results of his craniofacial observations over 7 years, beginning when the twin subjects were 3 years old. He found that intrapair differences in size of facial skeleton increased with age four times more in DZ than MZ twins. With respect to the intrapair differences of forms observed in the said studies, it was apparent that the morphological similarity was significantly higher in MZ than DZ twins and that this condition was uniform throughout the observed period.

As to the area of facial cranium, intrapair variances differed significantly between DZ and MZ twins, particularly for height, more than for anteroposterior diameters, in preadolescence [41]. In adult twins, facial height also showed strong genetic control, higher for mandibular heights than for maxillary heights [39]. Arya et al [3] also observed strong genetic effects in the mandibular part. In addition, Watnick [111] suggested that the rate of genetic control varied with the areas within mandibular bone.

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Prorok [89] proposed that combinations of the various measurements of the facial skeleton could be applied to diagnose twin zygosity within an error of 10.3%.

A number of factors affect mandibular formation. In order to study the relationship between the respiratory function and these factors, investigations were made. For example, Dunn et al [19] indicated that the form of mandibular bones differed between MZ twins who had different airway size as observed on X-ray photographs.

As it is widely known, the form of the human body is not symmetrical, Mulick [72] investigated whether the asymmetry of craniofacial forms could be genetically determined using a longitudinal material, but he could not obtain definite evidence.

Recently, multivariate analysis became applicable to twin studies and some interesting approaches have been reported.

Kurisu et al [53] attempted to derive environmental covariance matrices from covariance matrices of within-MZ-pair differences of seven anatomical measurements of the head. They concluded that four common factors exist independently, ie, cranial size factor, cranial breadth factor, facial height factor, and mandibular breadth factor.

Using the method proposed by Vandenberg [109], Nakata et al [79] and Nance et al [82] obtained covariance matrices in MZ and DZ twins consisting of within-pair differences in craniofacial multiple measurements. They also applied factor analysis and showed the existence of independent genetic determinants which influence these traits along with particular variables. They pointed out that the values of maxillary and mandibular measurements were not always affected by the same genetic factors, thus offering a useful tool for considering the causes of malocclusions.

Another interesting method was proposed recently, based on the concept that children whose father or mother is a MZ twin can be regarded as half siblings. As the similarity of the craniofacial shape among relatives was quantified in terms of one single parameter [80,81], this could be examined statistically. Similarity was thus found to increase as one proceeds from duplicate measurements on the same individual to measurements in MZ twins, DZ twins, full siblings, half siblings, and finally husband-wife pairs.

Cleft Lip and Palate

Twin studies have also been conducted with regard to cleft lip with or without palate (CL/P) and cleft palate (CP). Special caution is needed, however, ascertainment bias being likely in genetic studies using twins, given the tendency to pay more attentions to cases of concordance of abnormal formations, or of discordance particularly in MZ twin pairs.

Already in 1928 Levy [56] reported a case of MZ twins who both had unilateral cleft lip (CL) on the right side. On the other hand, Shea and Nelson [99] observed a case in which one of male DZ twins had a bilateral CL and the cotwin had unilateral CP on the left side. Furthermore, Watnick [111] reported a case in which a pair of 8-year-old male MZ twins had CL/P. However, one of them had unilateral and the other bilateral CL/P.

Fogh-Andersen [22] made an early review of twin cases reporting CL/P concordance in 1 out of 2 pairs of MZ twins and 1 out 23 pairs of DZ twins, and CP discordance in 2 pairs of DZ twins.

Metrakos et al [69] later reported 10 cases of twin pairs and combined them with the other 98 pairs reported by earlier authors, obtaining a CL/P concordance rate of 42% for MZ and 50% for DZ twins. Concordance for CP was 10% and 8% for MZ and DZ twins, respectively. Pruzansky et al [90] reported 4 concordant MZ pairs and 6 discordant DZ

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pairs with CL/P, and 3 concordant out of 5 MZ pairs and 4 discordant out of 4 DZ pairs with CP. However, they pointed out that too many cases of concordant MZ twins might have been referred intentionally.

Shields et al [100] published a report including additional twin cases during the period from 1949 to 1969 after the survey made by Fogh-Andersen [22]. Concordance for CL/P was found to be 36% in MZ and 1.5% in DZ twins, and concordance for CP 33% in MZ and 0% in DZ twins.

A more recent investigation in the United States [35] covering the period from 1961 to 1966, reported concordance for CL/P in 9 out of 51 MZ pairs (17.6%) and 2 out of 84 DZ pairs (2.4%), and concordance for CP in 6 out of 15 MZ pairs (40%) and 2 out of 42 DZ pairs (4.8%).

It is extremely difficult to determine whether the characteristics of craniofacial growth of an individual with a cleft are genetic in origin or determined by the clefting itself or by its surgical correction. Discordant MZ twin pairs may allow to verify the effect of the clefting on craniofacial growth by comparing the course of growth of the affected twin with that of his normal cotwin.

Ross and Coupe [94] conducted roentgenocephalometric analysis based on these viewpoints on a total of 6 discordant MZ twin pairs, 3 for CP, 2 for CL/P, and 1 for CL. No clear change was found for CL, except in the upper anterior facial area, but changes in the relationships between cranial base and facial skeleton were observed in the CL/P pairs.

In addition to these changes in the relationship between cranial base and facial skeleton of the CP twins, retarded growth of the lower face was also noted. It was stated that in both cases the posterior position of the maxilla appeared to be influenced by operative surgery.

Cronin and Hunter [17] and Hunter [42] reported similar variations, such as a slight degree of posterior rotation of the mandible in CL twins. They also noted a remarkable degree of posterior rotation of the mandible in CL/P twins. Furthermore, they observed a reduction of the anteroposterior diameter of the maxilla or a shortening of the mandible in CP twins. They concluded that the variations were influenced by the extent of the impediment.

A case of unilateral CL/P was observed in a pair of MZ twins, concordant but on opposite sides in the two twins, by Kraus and Oka [52]. A similar case of conjoined twin fetuses of 20 weeks of age was reported by Markovic [66]. These cases can be taken as examples of the mirror image phenomenon in clefting.

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