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SCIENTIFIC SECTION

The craniofacial morphology of the parents of children with orofacial clefting: a systematic review of cephalometric studies

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Abstract

Objective To systematically review the cephalometric studies investigating the craniofacial morphology of the parents of children with orofacial clefting (OFC).

Search strategy The search strategy was based on the keywords 'parent', cephalometry', and 'cleft', identifying 17 studies, of which 15 'case/control' studies met the inclusion criteria

Data abstraction/data synthesis Statistically significant clinically relevant cephalometric variables from univariate statistical tests and multivariate results were collated and presented unweighted.

Results/Conclusions The parental craniofacial complex in OFC is distinctive in comparison to the non-cleft population. However, there is insufficient consistency in study designs and results to accurately characterize the parents of children with OFC. Although the craniofacial morphology of the parents of children with CL(P) differs to the parents of children with CP, there is insufficient information to accurately localize these differences.

Index words: cephalometry, craniofacial morphology, orofacial clefting (OFC), parental, systematic review.

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Introduction

It is widely recognized that craniofacial form of individuals with orofacial clefting (OFC) is distinctive in comparison to that of unaffected people,[1] and that craniofacial form is influenced by hereditary factors.[2] As a result, it could be suggested that the craniofacial morphology of the biological parents of children with OFC could be different to the general population.

The identification of the parental craniofacial form in the aetiopathogenesis of OFC may be important for several reasons:

1 The parental craniofacial form (the phenotype) represents the hereditary influences on the craniofacial form of their offspring (the genotype). The craniofacial form in OFC is considered to be a predisposing factor in the development of OFC; for example, increased head and facial widths would logically mitigate against the palatal shelves from making contact.[3]
2 The identification of microform features in the relatives of subjects with OFC (e.g. craniofacial form) will assist in the elucidation of the interaction of genes, both with other genes and their products, and with environmental factors.
3 The identification of craniofacial features that are similar in several biological relationships (features that may not seem directly related to the aetiopathogenesis of OFC, e.g. dental or auricular anomalies) may assist in the identification of the genes involved in the aetiopathogenesis of OFC.

However, at present, both researchers and clinicians are unsure of which parental cephalometric features are pathognomic for OFC. We, therefore, carried out a systematic literature review to answer the following 'key questions':

1 Does the parental craniofacial morphology in OFC differ to that of the population?
2 Which features of the craniofacial skeleton characterize the parents of children with OFC?

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3 Are the differences in the parental craniofacial morphology in OFC dependent on the OFC subtype possessed by their offspring?

Methods

Search strategy

The search strategy was formulated to identify any previous systematic reviews and meta-analyses in addition to all the published cohort studies (with appropriate comparison groups), case/control studies and case reports. The Cochrane, Medline (via PubMed, Internet Grateful Med, OVID, and Knowledgefinder), HealthSTAR, POPLINE, SDILINE, SPACELINE, Embase, OLDMEDLINE, CINAHL, and ASKSAM Orthodontic Reference Database (1950–1997, European Orthodontic Society, London) databases were searched using a combination of the following keywords: 'parent', 'cephalometry', and 'cleft'. A 'grey literature' search was carried out via the ECHHSR (European Clearing House on Health Systems Reform) web site (www.leeds.ac.uk/nuffield/inforservices/ECHHSR/dbase.html) and the UK National Research Register Database was consulted to identify any ongoing and unpublished relevant studies. The *Cleft Palate Craniofacial Journal* (formerly the *Cleft Palate Journal*) was hand searched, and the reference lists and bibliographies of all previous publications were consulted to identify any publications, not already identified using the electronic search strategy.

Selection criteria

The selection criteria applied to the study abstracts to select reports for inclusion within this systematic review were inclusion of reports in any language, and exclusion of case-reports and case series (a case-series was defined as including less than 25 subjects).

Results of search strategy

Seventeen cephalometric studies investigating the parental craniofacial morphology in OFC were identified. These were published in peer-reviewed journals. Two of the identified studies were excluded at this stage because one examined one family[4] and the other was a case series.[5] Thus, 15 study reports met the inclusion criteria for this systematic review. Table 1 includes details of

Table 1 Details of included parental OFC cephalometric studies

Study number/authors	Experimental group			Comparison group	Population studied	OFC subtypes	Cephalogram types
	Total	Male	Female				
1 Cocarro *et al.* (1972)	40	20	20	40	USA	CLP	Lateral
2 Kurisu *et al.* (1974)	347	141	206	246 (*a*)	USA	CL(P),CP	Lateral, PA
3 Shibasaki *et al.* (1978)	118	58	60	60	Japanese	CL(P)	Lateral
4 Nakasima and Ichinose (1983)	502	251	251	220 (*b*)	Japanese	CL,CLP,CP	Lateral & PA
5 Nakasima and Ichinose (1984)	104	52	52	106 (+200) (*c*)	Japanese	CL(P)	Lateral & PA
6 Prochazkova and Tolarova (1986)	40	20	20	75 (*b*)	Czechoslovakia	CP	Lateral
7 Ward *et al.* (1989)	82	(*e*)	(*e*)	(*d*) (*a*)	USA	CL(P)	Lateral
8 Sato (1989)	100	50	50	30	Japanese	CL(P),CP	Lateral, PA
9 Raghavan *et al.* (1994)	76	38	38	48	India (*i*)	CL(P) no CP	Lateral & PA
10 Prochazkova and Vinsova (1995)	110	52	52	75 (*b*)	Czechoslovakia	CP	Lateral
11 Mossey *et al.* (1997) (*f*)	83	40	43	0 (*g*)	UK	CL(P),CP	Lateral
12 Mossey *et al.* (1998a) (*f*)	83	40	43	100 (*a*)	UK (*i*)	CL(P),CP	Lateral
13 Mossey *et al.* (1998b) (*f*)	83	40	43	99 (*a*)	UK (*i*)	CL(P),CP	Lateral
14 Suzuki *et al.* (1999)	65	25	40	826 (+165) (*h*)	Japan	CL(P),CP	Lateral & PA
15 AlEmran *et al.* (1999)	80	40	40	67 (*b*)	Saudi Arabia (*i*)	CL+/−CP	PA

Notes
(a) Historical control data.
(b) Dental students form a large proportion of comparison group.
(c) 200 added to validate results.
(d) Normative data from Saksena *et al.* (1987)
(e) Numbers of males and females not stated.
(f) Mossey *et al.* (1997),[6] Mossey *et al.* (1998a),[7] and Mossey *et al.* (1998b)[8] reported on same parental data.
(g) No controls needed—study aimed to differentiate between CL(P) and CP only.
(h) 165 controls added to validate discriminant function.
(i) Parents and comparison group ethnically and geographically similar.

these studies and full references are included on the *Journal* website (http://ortho.oupjournals.org/).

Abstraction process

The data derived were abstracted from the individual study reports using a Data Abstraction Pro-forma. This was organized into the following categories: cranial, orbital, maxillo-zygomatic, nasal, mandibular, soft-tissue, vertical dimension, and 'other' parameters. Where results were available from multivariate statistical techniques, these data were recorded on the blank reverse side of the Data Abstraction Pro-forma.

Evaluation of methodological quality

The methodological quality of the selected studies was then evaluated using a checklist (Figure 1). All were retrospective case/control studies. None of the included studies were methodologically ideal, with several differ-

Parental craniofacial morphology in OFC: methodology checklist

Study report

Essential questions

A. How were the cases obtained?

1. Ascertained sample of syndromic/non-syndromic/ 'mixed' consecutive cleft births or haphazard selection of parents attending clinics with their children?
2. Selection of parents of children with CL(P) or CP or combined sample?
3. Proportions of clefts stated, and representative of the population from which they were drawn?
4. Attempts to contact subjects who defaulted for record collection?

B. Appropriate comparison group?

1. Use of historical control data.
2. Selection of subjects for comparison group—systematic or haphazard.
3. Use of self-selected group: either individuals referred for orthodontic treatment or non-orthodontic individuals associated with OFC research institutions.
4. Same geographic and ethnic background and age distribution as those in the experimental group.
5. Numbers in comparison group similar to experimental group.

C. Processes of data collection identical for experimental and comparison groups?

1. Same cephalometers and method of image production?
2. Same observers for experimental and control groups?

Specific questions

1. Study design type?
2. Were there any biases?
3. Was an error study reported?
4. Were the variables used valid?
5. Was sexual dimorphism considered?
6. Could there be confounding?
7. What statistical analyses were used?
8. Was there data dredging?
9. Were important findings overlooked?

Fig. 1 Methodological quality checklist.

ences between these studies. All the included studies stated the cleft types possessed by the offspring of the parents; however, only Mossey *et al*. [6–8] stated the relative proportions of the parents belonging to their respective cleft subtypes from a completely ascertained sample. No study stated an attempt to contact subjects who defaulted for record collection.

Synthesis of the parental cephalometric data in OFC

In this systematic review, meta-analyses could not be carried out using the data produced from the studies, because of widely differing study methods, inclusion and exclusion criteria, measurements, and variables used in the studies. However, we were able to abstract data.

Synthesis of univariate statistical data

The statistically significant variables from univariate statistics were evaluated for clinical significance using the criteria set out in Table 2 and are included in Table 3. As the methodological quality of all the study reports is similar, the data abstracted from them is presented unweighted.

Synthesis of multivariate statistical data

We found that three different multivariate techniques had been used to evaluate the parental craniofacial morphology. Again, because of methodological differences between the various studies, the data from multivariate analyses could not be synthesized.

Cluster analysis. Cluster analysis was used by Ward *et al*. to identify groups of subjects demonstrating similar cephalometric features in their sample of parents of children with clefts.[9] They identified three major clusters, two demonstrating cephalometric similarities to individuals with clefts and one with similar dimensions to published cephalometric values. Another study produced a series of male and female values, above or below which a potential parent could be classified as 'at risk'.[10]

Mahalanobis distance analysis. Mahalanobis distance analysis measures the degree of deviation of an individual from the mean of the group when multiple variables are evaluated simultaneously. Using this technique, Nakasima and Ichinose found that the face shape of the parents of children with cleft lip and palate (CLP), cleft lip (CL), or cleft palate (CP), and the combined experimental group were highly distinguishable from the control group.[11] Similarly, Mossey *et al*. identified a highly significant difference between the craniofacial morphology of their parental sample and controls. One significantly different parameter between the paternal and control groups was mandibular length (Cd–Gn). The Mahalanobis distance was greater for females than males.[7]

Discriminant analysis. Discriminant analysis has been used to identify the parameters that could be used to classify an individual into the correct experimental group. Nakasima and Ichinose identified seven ratios that played an important role in the discrimination between parents and controls, all from PA cephalograms; however, they were unable to classify the three experimental groups according to craniofacial morphology.[11] In their study, the probabilities of misdiscrimination ranged from 13.0 to 17.4 per cent. Mossey *et al*. investigated the morphometric features that predispose to OFC (between parents of CL, CLP and CP).[6] Their whole group analysis and couples analysis yielded no significant differences. Their discriminant analysis indicated that for the maternal group, ramus height, and cranial height are reliable discriminators for CLP (80 per cent) and CP (75 per cent). Mossey *et al*. (parents/ controls) found that for male parents, the useful discriminators were cranial area, parietal chord length, cranial base length, total anterior facial height, ramus length, and the horizontal distance between condyle and sella.[7] A Jack-knifed classification found that 83.3 per cent of parents and 82.6 per cent of controls were correctly classified. For females, the useful discriminators were cranial area, cranial height, parietal chord length, and parietal and

Table 2 Criteria used to select the clinically significant variables (from univariate statistical tests)

Variables	Criteria
Linear distance measurements	>2 mm difference in the means of statistically significant linear distance measurements
Angular measurements	>2 degrees difference in the means of statistically significant angular measurements
Area measurements	>10 per cent difference in the means of statistically significant area measurements
Ratios	>3 per cent difference in the means of statistically significant ratios

Table 3 Parental cephalometric variables of clinical significance in OFC (study numbers as per Table 2)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
S–N length						↑				↑				↑	
N–Ba length													↑	↑	
Occipital subtenuce length															
Cranial base flexion angle	↓								↑						
Head length				↓											
Head width				↓					↓						
Calvarial area (PA cephalogram)					↓										
Bizygomaticofrontal suture width									↓						
Inter-orbital width		↑													
Bizygomatic width									↓						↓
Maxillary width															↓
Maxillary area													↓		
Palatal length						↑			↑	↑					
Nasal width									↑					↑	↑
Bigonial width		↑													↓
Gonial angle		↓							↑						
Mandibular symphyseal area													↓		
Mandibular length	↑	↑				↓				↑			↑		
Mandibular ramus flexion angle										↑					
Total anterior face height		↓								↑			↑		
Lower anterior face height						↑	↑			↑					
Upper anterior face height									↓						
Total craniofacial height				↓											
Face height ratio				↓											
Angle S–N–ANS									↑						
Angle of facial plane										↓					
Total anterior soft tissue height						↑				↑					
Soft tissue lower anterior face height						↑				↑					
Lower lip and chin height						↑				↑					
Posterior face height										↑					
Y-axis length										↑					
Y-axis angle	↓														
Angle A–N–Pg										↑					
Proclination of upper and lower incisors										↑					
Upper and lower incisor protrusion										↑					
Articular angle									↓						
Angle N–A–Pg	↓														
Angle N'–Sn–Pg'	↑														
Angle N'–No–Pg	↑														
Linear distance between pterygo-maxillary fissure and perpendicular to S–N plane through S				↑											

↑: Increased magnitude in parental group.
↓: Decreased magnitude in parental group.

occipital subtenuce measurements. A Jack-knifed classification found that 92.7 per cent of parents and 98 per cent of controls were correctly classified. Other investigators identified the features that classified their parents in comparison to their control group as follows: a larger inter-orbital distance, larger nasal cavity width and larger inter-coronoid distance relative to the maximum head width, and shorter mandibular length relative to the anterior cranial base length.[12] This correctly classified the pooled experimental and control subjects in 67.9 per cent of cases and on the pooled test group in 61.8. Finally, AlEmran *et al.* produced two models using stepwise logistic regression, one for males and one for females.[13] The male model selected increased nasal width and decreased alveolar width for correctly classifying an individual at risk 74.36 per cent, whereas for

females the model selected only a decreased head width for a 76.92 per cent correct classification.

Although ideal, it was not possible to synthesize the results from univariate and multivariate statistics together in addition to synthesizing the results obtained from univariate and multivariate statistics separately.

Analysis of synthesized data

These results confirm that the parental craniofacial morphology in OFC is distinctive compared to the population (Key question 1). However, there is insufficient evidence to accurately localize the anatomical regions (or parameters) that distinguish the parents of children with OFC from the population (Key question 2). Furthermore, there is insufficient evidence to accurately determine whether the parental craniofacial morphology in CL(P) differs to that of CP (Key question 3).

Discussion

The 15 study reports that were included report on retrospective case-'control' observational studies. Although all these reports refer to the use of controls, the term 'comparison group' is more appropriate: 'control' strictly refers to the situation where the subjects within the experimental and control groups are identical, save for the characteristic or intervention under investigation.

Clinical importance of the parental craniofacial morphology in OFC

It would be ideal to be able to collate a set of parental cephalometric variables specific to OFC that would facilitate the distinction between the parents of children with OFC and the non-OFC population. Additionally, this set of variables could be produced in template-form, and could, in the future, potentially become one of a battery of tests to be overlaid on the lateral and PA cephalograms of potential parents who are concerned about the possibility of having children with clefts, thereby allowing health care professionals to advise them appropriately. Both these goals might theoretically be achieved from a meta-analysis of data abstracted from previous parental cephalometric studies in OFC. However, in this systematic review, a meta-analysis of abstracted data was not possible, because of methodological differences between the included studies and, moreover, meta-analyses of non-RCT data are not well established yet.

The reasons for conflicting results from the previous studies investigating the parental craniofacial complex in OFC include:

- methodological differences between the various studies;
- ethnic and geographic variability in (a) the craniofacial morphology, (b) the incidence of OFC, and (c) the ratio of CL(P) to CP of OFC;
- the failure to account for sexual dimorphism in the craniofacial complex;
- the inappropriate use of conventional cephalometric analyses in the assessment of shape.

Further work required

Further cephalometric studies, particularly using PA cephalometry are required to evaluate the non-cleft parental craniofacial complex in the various subtypes of OFC using a combination of different cephalometric analyses. Ideally, the information derived from a conventional cephalometric analysis would be supplemented with that derived using morphometric tools (such as Procrustes superimposition, Euclidean Distance Matrix Analysis, Thin Plate Spline Analysis, and Finite Element Morphometry). This information would allow the identification of the regions that differentiate the parents of children with OFC from the non-cleft population and, when several studies are in agreement, lead to the identification of the morphogenes that code for these specific features. Only one study as yet has sought to examine both affected offspring and their parents.[14] As a result more 'triad' or 'parent and twin' studies to investigate the heritability of craniofacial morphology in both cases and controls are required.

Conclusions

- The parental craniofacial complex in OFC is distinctive in comparison to the parents of children without cleft lip and palate.
- At present, there is insufficient consistency in study design and results to accurately localize the features that characterize the parents of children with OFC.
- Although there is evidence that the craniofacial morphology of the parents of children with CL(P) differs to the craniofacial morphology of the parents of children with CP, there is insufficient information to be able to accurately localize these differences.
- There are major problems with the quality of available data from parental cephalometric studies in OFC due to methodological shortcomings.

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References

1. Da Silva Filho OG, Carvalho Lauris RC, M Cappelozza Filho L, Semb G. Craniofacial morphology in adult patients with unoperated complete bilateral cleft lip and palate. *Cleft Palate Craniofac J* 1998; **35**: 111–119.
2. Suzuki A, Takahama Y. A cephalometric study on the similarity of craniofacial morphology between children and their parents. *Nippon Kyosei Gakkai Zasshi*, 1988; **47**: 7–719.
3. Fraser FC, Pashayan H. Relation of face shape to susceptibility to congenital cleft lip. *J Med Genetics,* 1970; **7**: 112–117.
4. Ward RE, Bixler D, Jamison PL. Cephalometric evidence for a dominantly inherited predisposition to cleft lip and cleft palate in a single large kindred. *Am J of Med Genetics*, 1994; **50**: 57–63.
5. Blanco R, Cifuentes L, Maldonado MJ, Rameau X, Munoz A. Cleft lip and cleft palate: cephalometric characteristics of affected individuals, their relatives and a control population. *Revista Medica Chile* 1992; **120**: 13–19.
6. Mossey PA, McColl JH, Stirrups DR. Differentiation between cleft lip with or without cleft palate and isolated cleft palate using parental cephalometric parameters. *Cleft Palate Craniofac J* 1997; **4**: 27–35.
7. Mossey PA, McColl J. O'Hara M. Cephalometric features in the parents of children with orofacial clefting. *Br J Oral and Maxfac Surg*, 1998; **36**: 202–212.
8. Mossey PA, Arngrimsson R, McColl J, Viatner GM, Connor JM. Prediction of liability to orofacial clefting using genetic and craniofacial data from parents. *J Med Genetics* 1998; **35**: 371–378.
9. Ward RE, Bixler D, Raywood ER. A study of cephalometric features in cleft lip – cleft palate families. I: Phenotypic heterogeneity and genetic predisposition in parents of sporadic cases. *Cleft Palate J* 1989; **26**: 318–325
10. Prochazkova J, Vinsova J. Craniofacial morphology as a marker of predisposition to isolated cleft palate *J Craniofac Genet Dev Biol* 1995; **15**: 162–168.
11. Nakasima A. Ichinose M. Characteristics of craniofacial structures in parents of children with cleft lip and/or palate,. *Am J Orthod* 1983; **84**: 140–146.
12. Suzuki A, Takenoshita Y, Honda Y, Matsuura C. Dentocraniofacial morphology in parents of children with cleft lip and/or palate. *Cleft Palate Craniofac J* 1999; **36**: 131–138.
13. AlEmran SE, Fatani E, Hassanain JE. Craniofacial variability in parents of children with cleft lip and cleft palate. *J Clin Ped Dent* 1999; **23:** 337–341.
14. Nakasima A, Ichinose M. Size of the cranium in parents and their children with cleft lip. *Cleft Palate J* 1984; **21**: 193–203.