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Hypertelorism and Orofacial Clefting Revisited

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Abstract

Objective—Since the 1960s, multiple studies have reported a tendency toward hypertelorism in individuals with nonsyndromic orofacial clefts (OFCs). However, the association between specific cleft types and increased interorbital distance has been inconsistent. Using 3D surface imaging, we tested whether different forms of clefting showed evidence of increased interorbital distance.

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Methods—Intercanthal and outercanthal distances and intercanthal indices were calculated from 3D facial surface images of 287 individuals with repaired OFCs. Raw measurements were converted to sex and age-normalized Z-scores. Mean Z-scores for individuals with cleft lip (CL), cleft lip and palate (CLP) and cleft palate (CP) were compared to reference normative values (controls) and one another directly using t-tests and ANOVA.

Results—The CLP group showed a significant increase in intercanthal width ($p = 0.001$) and intercanthal index ($p < 0.001$) compared to reference norms. The CP group showed a significant decrease ($p < 0.001$) in outercanthal width. The CL group showed no difference from reference norms. The proportion of clinically hyperteloric individuals was generally low, but highest in the CLP group (7.4%). Cleft severity had little effect on interorbital spacing.

Conclusions—Individuals with CLP exhibited on average a tendency toward mild hypertelorism, driven primarily by an increase in intercanthal distance. This tendency was not seen in CL or CP.

Keywords

Cleft lip; Cleft palate; Hypertelorism; Intercanthal width

INTRODUCTION

Altered spacing between the orbits (absolute and relative) has been reported in numerous studies of the facial characteristics associated with isolated orofacial clefting (OFC). Since the original publication on the topic by Moss (1965), most studies report that individuals with isolated orofacial clefts (OFCs) tend to be mildly hyperteloric compared to healthy controls (Dixon et al., 1966; Aduss et al., 1971; Farkas and Lindsay, 1972; Hirschfeld and Aduss, 1974; Figalová et al., 1974; Šmahel and Brejcha, 1983; Šmahel, 1984a; 1984b; Šmahel et al., 1985; Athanasios et al., 1991; 1996; Motohashi et al., 1994; Hood et al., 2004; Krimmel et al., 2006). This tendency, however, appears more pronounced in forms of clefting that involve the primary palate (Aduss et al., 1971; Dahl et al., 1982; Jain and Krogman, 1983). In contrast to isolated cleft lip (CL) or cleft lip and palate (CLP), several studies of isolated cleft palate (CP) report either no change in orbital spacing or a tendency toward hypotelorism (Farkas and Lindsay, 1972; Šmahel, 1984c; Šmahel et al., 1985; Šmahel et al., 1987; Hermann et al., 2002; 2003). There is also some evidence that the degree of abnormality is related to the severity of the cleft (Aduss et al., 1971; Hirschfeld and Aduss, 1974; Ishiguro et al., 1976; Jain and Krogman, 1983).

Importantly, several lines of evidence suggest that the changes in interorbital spacing observed in affected individuals are not merely the result of cleft surgical repairs. A number of studies report the same morphological pattern in unrepaired children (Figalová et al., 1974; Šmahel et al., 1985; Hood et al., 2004; Krimmel et al., 2006). Motohashi et al. (1994) found that both repaired and unrepaired children with CLP displayed wider interorbital distances from control children, but did not differ from one another. Further, even mildly affected individuals including adults with incomplete OFCs (Šmahel and Brejcha, 1983) and individuals with CL (Figalová et al., 1974; Šmahel et al., 1985) have been show to exhibit the same general hyperteloric pattern. Finally, the unaffected biological relatives of

individuals with OFCs have also been shown to demonstrate a tendency toward hypertelorism. In a meta-analysis of the cephalometric literature, Weinberg et al. (2006a) reported that the unaffected parents of children with OFCs had significantly increased interorbital distances compared with controls. Collectively, these findings point to increased distance between the orbits as an intrinsically dysmorphic feature associated with clefting (at least when it involves the primary palate).

All published studies, however, are not in agreement regarding the relationship between OFC and hypertelorism. A handful of studies, for example, report either no evidence of increased distance between the orbits in OFCs involving the primary palate (Šmahel and Müllerová, 1986; Han et al., 1995) or evidence showing a contrasting tendency toward *hypotelorism* (Duffy et al., 2000; Singh et al., 2003) in affected individuals. Even in the majority of studies where increased interorbital distances are reported, the exact nature of the morphological change is not always consistent. While virtually all studies report increased width between points on the medial orbital walls (or inner canthi), there is greater disagreement regarding the lateral (or outer) portions of the orbit with some studies reporting increased width (Farkas and Lindsay, 1972; Šmahel, 1984b; 1984c; Athanasios et al., 1996; Hood et al., 2004) and others reporting no change (Figalová et al., 1974; Šmahel and Brejcha, 1983; Šmahel et al., 1985; Motohashi et al., 1994; Krimmel et al., 2006). This is important because hypertelorism involving both medial and lateral orbital components may reflect an underlying etiology different from hypertelorism driven solely by the medial orbital dimension (Tan and Mulliken, 1997). Finally, while several studies support the relationship of more pronounced hypertelorism with increased cleft severity (Aduss et al., 1971; Hirschfeld and Aduss, 1974; Ishiguro et al., 1976; Jain and Krogman, 1983) others have failed to find a severity effect (Hermann et al., 2002; 2004; Hood et al., 2004). Some of these disagreements are likely due in part to methodological differences among studies and/or sampling biases.

In the present study, we investigate several questions related to interorbital spacing and OFC, focusing on a sample of surgically repaired individuals with available 3D facial surface scans. We test (1) whether individuals with OFCs involving the primary palate (CL and CLP) exhibit greater interorbital widths compared to controls; (2) whether individuals with CL and CLP show a greater tendency toward hypertelorism than individuals with CP; and (3) whether the degree of orbital spacing is related to cleft severity. To facilitate the morphological comparisons, we draw upon a large publically available sample of ethnicity-, age- and sex-matched 3D craniofacial anthropometric norms.

METHODS

Study Sample

The case sample consisted of 287 individuals with isolated OFC. These participants were recruited as part of a large US and international genetic study of clefting (Weinberg et al., 2006c). Cases were identified from the patient databases of craniofacial centers in Pittsburgh, Iowa City, Saint Louis, Houston, Denver, and Odense (Denmark). Cases ranged in age from 3 to 49 years. Cleft type was recorded through detailed health history interviews with affected cases (or their family members). All cases were surgically repaired prior to the

time of enrollment; however, due to limitations in the design of the study (self-report), it was not possible to obtain detailed information regarding surgical history. The sample breakdown by cleft type is provided in Table 1. Inclusion was limited to individuals of self-identified European ancestry. Individuals with syndromic forms of OFC were excluded. All research activities were approved by each recruitment site's institutional ethics committee. Written informed consent was obtained prior to enrollment.

3D Imaging and Measurements

3D facial surface images were captured on each participant with a 3dMDface digital stereophotogrammetry system. Multiple independent investigators have established the accuracy and reliability of this imaging system (Aldridge et al., 2005; Weinberg et al., 2006b; Heike et al., 2009). Participants were instructed to keep their eyes open and direct their pupils upward during 3D image capture; this was done to maximize the visibility of the outer corner of the eye on the resulting 3D surface model. The left and right endocanthion (*en*) and exocanthion (*ex*) points (Kolar and Salter, 1997) were collected from each 3D facial surface by trained staff. Prior to collecting data on participant's 3D scans, all landmarking staff were evaluated for inter- and intra-rater landmark localization error using an independent 3D training sample; achieving an intraclass correlation coefficient of at least 0.90 for each landmark was required before proceeding with data collection. The resulting landmark coordinates were error-checked for left-right reversals.

For each participant, three different measures of orbital spacing were calculated. Two of these measures were linear distances: the intercanthal width, measured as the linear distance between the left and right *en* landmarks, and the outercanthal (or biocular) width, measured as the linear distance between the left and right *ex* landmarks. The intercanthal index was also calculated as the intercanthal width divided by the outercanthal width, multiplied by 100. The intercanthal index provides a measure of the relative spacing between the orbits; a higher index value indicates increased relative intercanthal width.

Z-score Calculation

The values for all three measurements were converted to Z-scores by comparing against existing age-, sex- and ethnicity-matched anthropometric norms. The anthropometric norms were available through the 3D Facial Norms (3DFN) Database (Weinberg et al., in press), which can be accessed through the FaceBase Consortium (Hochheiser et al., 2011; www.facebase.org). The 3DFN Database contains a variety of standard craniofacial anthropometric measures collected from 3D facial surface scans on over 2400 healthy males and females ranging in age from 3–40 years. Z-scores were calculated by subtracting the average sex- and age-specific value for a measurement in the 3DFN Database from the individual observed values in our case sample, then dividing the result by the reported 3DFN standard deviation. In this way, every subject in the sample is given a Z-score for each of the three measurements. When calculated in this manner, Z-scores represent sex-and age-normalized values represented in standard deviation units. A Z-score of +1.0 represents a one standard deviation increase over the baseline population value for a given trait. A Z-score of −2.0 represents a two standard deviation decrease over the baseline population

value. A Z-score of 0.0 would represent no change from the normal population baseline state.

Statistical Analysis

To statistically assess the degree of morphological deviation in our case sample, mean Z-scores were calculated for all three measurements for each of the three main groups (CL, CLP and CP). The mean Z-scores for each group were then tested against a baseline value of 0.0 (representing no deviation from the 3DFN control average) using one-sample t-tests. To test for differences directly among the three main case groups, the mean Z-scores for each measurement were compared using ANOVA followed by pairwise Bonferroni post-hoc tests. To test for possible severity effects, each of the main case groups were further broken down into less and more severely affected subgroups: the CL group was broken down into unilateral cleft lip (UCL) and bilateral cleft lip (BCL), the CLP group into unilateral cleft lip and palate (UCLP) and bilateral cleft lip and palate (BCLP), and the CP group into soft palate only (included submucous cases) and soft + hard palate subgroups. The mean Z-scores on the three measurements were subsequently compared between the two subgroups for a given cleft type via t-test. Based on the distribution of Z-scores, the proportion of mildly hyperteloric (defined as having a score between +1.0 and +2.0 standard deviations) and clinically hyperteloric (defined as having a score exceeding +2.0 standard deviations) was described for each cleft type (Farkas and Lindsay, 1972; Tan and Mulliken, 1997) and compared using chi-square tests. Finally, Pearson correlations between the Z-scores for each measure and age were calculated to determine whether hypertelorism tended to increase or decrease from childhood to adulthood. All statistical tests were conducted in SPSS v.21. The threshold for statistical significance was set at 0.05.

RESULTS

The results of the one-sample t-tests comparing the main cleft groups to the 3DFN reference sample are shown in Figure 1. For intercanthal width, the CLP group showed a significant increase ($p = 0.001$) compared to the population baseline. The magnitude of the difference was small, however, with a mean Z-score of only +0.356 standard deviations. Both the CL and CP groups showed no significant differences from the reference sample. For outercanthal width, a significant decrease was observed in the CP group (mean $Z = -0.509$; $p < 0.001$); no differences were found in either the CL or CLP groups. Intercanthal index showed the same pattern as intercanthal width; a significant increase (mean $Z = +0.348$; $p < 0.001$) was observed in the CLP group, while the remaining two groups did not differ from controls.

Comparing the three main cleft groups to one another directly, the CLP group showed a significant increase in intercanthal width ($p = 0.004$) over the CP group. For outercanthal width, the CP group showed a significant decrease ($p < 0.001$) over the CLP group (Table 2). There were no differences between CL and CLP or between CL and CP on any of the measurements. Further, there were no differences among any of the three cleft groups in intercanthal index. For the severity analysis, no statistically significant differences were

noted between the less and more severely affected cleft types; this negative result was also confirmed using non-parametric Mann-Whitney tests.

Finally, the observed proportion of mildly hyperteloric (Z-score +1.0–1.99 sd) and clinically hyperteloric (Z-score +2.0 sd) individuals in our case sample is provided in Table 3. The proportion of mildly hyperteloric individuals was highest in the CLP group, followed by the CL and CP groups. This held true for all three measures of interorbital distance. The identical pattern was observed for clinical hypertelorism. For intercanthal width, for example, 7.4% of individuals in the CLP group demonstrated clinical hypertelorism, followed by 2.6% of CL cases and 1.3% of CP cases. Within each of the main cleft types, the proportion of clinically hyperteloric individuals was not consistently associated with increased severity. Among individuals in the CLP groups, for example, those with UCLP tended to have an increased rate of clinical hypertelorism compared with BCLP. The opposite tended to be true for CL and CP, with a slightly higher proportion of clinically hyperteloric cases in the more severely affected subtypes. None of the observed group differences in proportions were statistically significant as determined by chi-square tests. The correlation between the extent of hypertelorism and age was not statistically significant in males (intercanthal width, $r = -0.01$; outercanthal width, $r = -0.01$; intercanthal index, $r = -0.01$) or females (intercanthal width, $r = -0.08$; outercanthal width, $r = -0.15$; intercanthal index, $r = -0.10$).

DISCUSSION

The study investigated the association between OFC and differences in interorbital distance. The first hypothesis was that individuals with CL and CLP (but not CP) would exhibit increased interorbital distances compared with controls. To test this hypothesis we compared averaged measures from each cleft type against normative population baseline values. The second hypothesis we tested was that interorbital distances would be increased in OFCs involving the primary palate compared to CP. To test this hypothesis, mean Z-scores from the three main cleft groups (CL, CLP and CP) were compared directly. Our results provided partial support for each claim. On average, individuals with CLP had slightly increased intercanthal width compared to the general population. The CL group, however, did not show a similar tendency. The CP group, as expected, did not exhibit any evidence in increased interorbital distance; on the contrary, the CP group showed evidence of significantly reduced outercanthal width. When the main cleft groups were compared directly, distinct differences between the CLP and CP groups were noted, with the CLP group demonstrating significantly increased intercanthal width and the CP group characterized by significantly reduced outercanthal width. The CL group did not differ from the CP group on any of the three measures.

Taken together, the above results suggest that OFCs involving the primary palate are not universally associated with increased interorbital distance. The finding of increased intercanthal width in CLP is in broad agreement with the majority of previous anthropometric and cephalometric studies (Dixon et al., 1966; Aduss et al., 1971; Farkas and Lindsay, 1972; Hirschfeld and Aduss, 1974; Figalová et al., 1974; Šmahel and Brejcha, 1983; Šmahel, 1984a; 1984b; Šmahel et al., 1985; Athanasios et al., 1991; 1996; Motohashi

et al., 1994; Hood et al., 2004; Krimmel et al., 2006). Our finding that CL did not differ from controls is in agreement with Hood et al. (2004), who also used 3D surface-based anthropometry. However, at least one cephalometric study has reported increased interorbital width in CL cases (Aduss et al., 1971). Šmahel (1984a) also reported increased interorbital distances in CL compared with controls based on cephalometric measures, but when anthropometric soft-tissue measures were examined, no differences were noted. In contrast, both Figalová et al. (1974) and Šmahel et al. (1985) used direct anthropometry to show that CL cases had increased intercanthal width (but not outercanthal width) over controls. The differences in CL may be subtler than in CLP, and small changes in the composition of cases (e.g., the relative proportion of complete versus incomplete CL) could explain some of the variation among studies.

Previous case-control studies on CP have been inconsistent, with some showing increased interorbital distances (Athanasios et al., 1991) and others showing no change (Farkas and Lindsay, 1972; Šmahel, 1984c; Šmahel et al., 1985; Šmahel et al., 1987; Duffy et al., 2000) or even reductions (Figalová et al., 1974). Our results revealed no change in intercanthal width in CP, but a significant reduction in outercanthal width, compared to controls. This finding suggests a possible reduction in the size of the soft-tissue orbits in CP. The inconsistent findings in CP could be explained in part by differences in study methodology or sample composition, particularly since the potential for unrecognized syndromes is much higher than in other forms of clefting. Our findings, however, were largely consistent with prior cephalometric and anthropometric studies comparing different cleft types directly (Aduss et al, 1971; Dahl et al., 1982; Jain and Krogman, 1983; Šmahel et al., 1987; Hermann et al., 2002; 2003). Compared directly to CLP, our CP sample had significant reductions in both intercanthal and outercanthal width.

The proportion of clinically hyperteloric individuals (intercanthal width > +2 sd) in our cleft groups ranged from 1.3% in CP to 2.6% in CL to 7.4% in CLP (overall 4.5% among all cleft types). In prior studies, the proportion of truly hyperteloric individuals varies greatly, in part due to the use of different measures and thresholds. Dixon et al. (1966) reported about 20% of their OFC sample exhibited clinical hypertelorism (defined as having an intercanthal index > 42). Using a relatively relaxed threshold (> +1 sd), Aduss et al. (1971) reported that 2.5% of their sample of mixed clefts displayed hypertelorism, based on cephalometry. Figalová et al. (1974), using a much more stringent threshold, reported that 7.6% of individuals with primary palate clefts had an intercanthal index in excess of +3 standard deviations from the norm. Using the same definition for clinical hypertelorism as the present study (intercanthal width > +2 sd), Farkas and Lindsay (1972) reported that overall 6.9% of their cleft sample exhibited clinical hypertelorism; CLP cases were at 8.7%, while CP cases were at 2.4%. These numbers are very similar to ours. Taken together, these results suggest that the proportion of severely hyperteloric individuals with OFCs is relatively small, with the majority of cases falling within 1 standard deviation of the general population mean.

The third hypothesis tested in this study was that more severely affected individuals would demonstrate increased interorbital distances. We tested this by comparing the mean Z-scores of unilateral versus bilateral OFCs involving the primary palate; for CP we compared clefts only involving the soft palate to clefts involving the soft and hard palate. However, we did

not find strong evidence of relationship between interorbital distance and cleft severity. Within each of the three main cleft groups, when less and more severely affected case subsets were compared directly, no significant differences were observed. When looking at the proportion of cases that met the clinical/statistical definition of hypertelorism, although there were also no statistical differences, some trends were apparent. Both the CL and CP groups showed an increase in the more severely affected subset (although in CL the total number of bilaterally affected cases was very small). In contrast, for the CLP group the opposite pattern was observed; unilateral cases had higher rates of clinically defined hypertelorism than bilateral cases.

Only a handful of prior studies have assessed severity effects in the manner above, but each of these studies reported an increase in interorbital width (cephalometrically-defined) in BCLP cases compared to UCLP cases (Aduss et al., 1971; Hirschfeld and Aduss, 1974; Ishiguro et al., 1976; Jain and Krogman, 1983). Although our measurements were limited to soft-tissue, it is not entirely clear why we did not replicate these previous findings for our CLP sample. An alternative approach to testing for severity is to treat CL and CLP as a continuum, although there is now emerging evidence from genetic studies that these two types of cleft might be etiologically distinct rather than simply variants of the same trait (Rahimov et al., 2008; Ludwig et al., 2012). Aduss et al. (1971) and later Hirschfeld and Aduss (1974) did report an increased in interorbital distance in CLP compared with CL, but several other studies have failed to find such an effect (Hermann et al., 2002; 2004; Hood et al., 2004). Notably, in the present study we also failed to find significant differences between CL and CLP on any of the three interorbital distance measures. The proportion of clinically hyperteloric individuals was higher in our CLP group than in our CL group, but again this difference was not statistically significant.

The observed trend toward hypertelorism in our CLP group was driven entirely by increased intercanthal width. Building on the work of Tessier (1972) and others, Tan and Mulliken (1997) refer to this condition as interorbital hypertelorism, when the lateral displacement is limited to the medial orbital walls. This pattern can be distinguished from true orbital hypertelorism, which involves lateral displacement of the entire orbital complex. There has been very little investigation into the causal factors underlying the association between hypertelorism and OFC. The cleft surgical repair is an unlikely factor, since the same hyperteloric tendency has been reported in both unrepaired cases (Motohashi et al., 1994) and the unaffected first-degree relatives of affected cases (Weinberg et al., 2006a). Greig (1924) proposed a general relationship between dysmorphology of the anterior cranial base and hypertelorism. Moss (1965) offered two different explanations in his study of hypertelorism in OFC, one involving the anterior cranial base and the other involving intrinsic dysplasia of the nasal capsule. Tessier (1972), based on an analysis of skull images in clinical cases of hypertelorism, believed that the problem was intimately related to abnormal transverse enlargement of the ethmoid. Several PA cephalometric studies showing increased interorbital distance in OFC report concomitant increases in nasal cavity and/or cranial base width (Ishiguro et al., 1976; Šmahel and Brejcha, 1983; Šmahel, 1984b; Motohashi et al., 1994). These findings suggest that the observed increased interorbital spacing is part of a broader pattern of increased transverse craniofacial dimensions.

In cases of rare syndromes characterized by prominent hypertelorism, the condition can sometimes be attributed to a specific genetic mutation that disrupts early craniofacial development. Several of these syndromes (e.g., Greig cephalopolysyndactyly syndrome, OMIM: #175700) have been shown to involve mutations in sonic hedgehog (*SHH*) pathway genes (Balk and Biesecker, 2008). Experimental activation and inhibition of the SHH signaling pathway has been shown to directly influence the breadth of the upper face in a dose-dependent manner in chick embryos (Marcucio et al., 2005; Hu and Marcucio, 2009; Young et al., 2010). In humans, genetic syndromes that include clefting and hypertelorism as features can result from mutations in *SHH* pathway genes (e.g., basal cell nevus syndrome, OMIM: #109400). However, the genetic factors involved in nonsyndromic forms of clefting are still largely unknown (Leslie and Marazita, 2013). In a study examining *SHH* variants in a South American OFC cohort, Orioli et al. (2002) found little evidence of functional mutations. Further, *SHH* pathway genes have not been identified in any of the genome-wide association studies of OFC to date (Leslie and Marazita, 2013). A detailed examination of *SHH* pathway genes in a subset of cases with both clefting and more pronounced hypertelorism may uncover associations between these genes and OFC.

Several important limitations must be considered when interpreting the results of the present study. Foremost among these was the lack of access to measurements of skeletal morphology. Thus, it was not possible for us to determine to what extent our soft-tissue findings extended to the underlying bony orbits. It must be noted, however, that our findings were largely in agreement with the results of prior hard-tissue studies, suggesting that we are reporting on the same general phenomenon. Data on corresponding skull measures could have important implications for the surgical correction of hypertelorism and the fusion of 3D facial surface images with CBCT scans would provide one avenue to explore both types of measurements simultaneously. The general lack of detailed information about cleft surgical repairs in our affected cases was another limitation. The number, type, and timing of surgery could all be important factors to consider. The impact of epicanthal folds on our measurements was also not explicitly considered in the analysis, as this is difficult to assess on some 3D facial surface scans.

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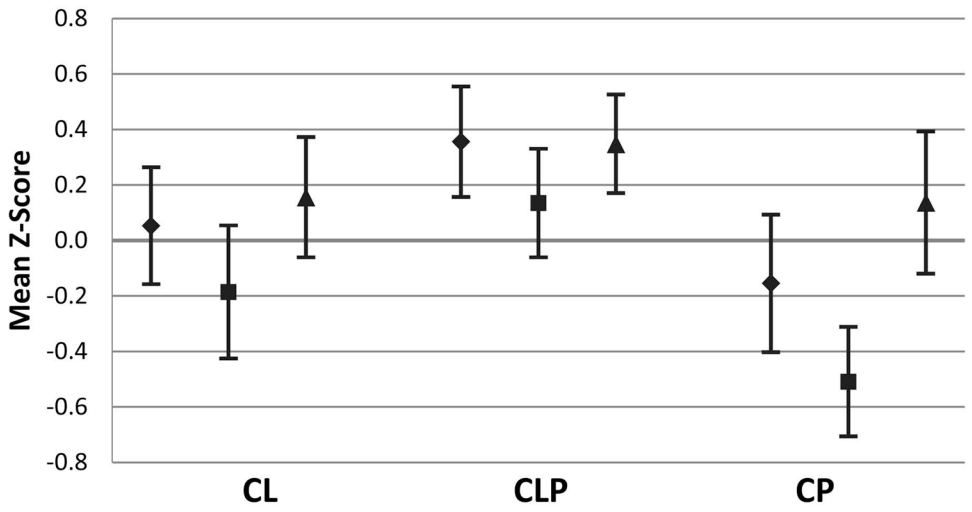

Figure 1.

Mean Z-scores for each of the three measures organized by cleft group. The upper and lower bounds indicate the 95% confidence interval around the mean. Statistical significance was assessed using one-sample t-tests (see text) and is indicated here when the confidence interval does not include zero. The different variables are indicated by different shapes: intercanthal width is indicated by the black diamond (◆); outercanthal width is indicated by the black square (■); intercanthal index is indicated by the black triangle (▲).

Table 1

Sample breakdown by cleft type (subtype) and sex

	Male	Female	Total
All CL	44 (25.9%)	32 (27.3%)	76 (26.5%)
UCL	40 (23.5%)	28 (23.9%)	68 (23.7%)
BCL	4 (2.4%)	4 (3.4%)	8 (2.8%)
All CLP	96 (56.5%)	40 (34.2%)	136 (47.4%)
UCLP	63 (37.1%)	30 (25.6%)	93 (32.4%)
BCLP	33 (19.4%)	10 (8.5%)	43 (15.0%)
All CP	30 (17.6%)	45 (38.5%)	75 (26.1%)
Soft Only	13 (7.6%)	22 (18.8%)	35 (12.2%)
Hard+Soft	17 (10.0%)	23 (19.7%)	40 (13.9%)
All Clefts	170	117	287

See text for cleft type definitions

Table 2

ANOVA comparing mean Z-scores among cleft groups

	Mean Z-Score			ANOVA Statistics		
	CL	CLP	CP	F test	p	Post-hoc
Intercanthal width	0.053	0.356	−0.154	5.688	0.004	CLP > CP
Outercanthal width	−0.186	0.135	−0.509	9.184	< 0.001	CLP > CP
Intercanthal Index	0.156	0.348	0.137	1.344	ns	-

Table 3

Frequency of mild and clinical hypertelorism by cleft type

	Intercanthal width		Outercanthal width		Intercanthal index	
	+1 – 1.99 SD [a]	**+2 SD**	**+1 – 1.99 SD**	**+2 SD**	**+1 – 1.99 SD**	**+2 SD**
All CL (n=76)	12 (15.8%)	2 (2.6%)	5 (6.6%)	3 (3.9%)	12 (15.8%)	3 (3.9%)
UCL (n=68)	11 (16.2%)	1 (1.5%)	4 (5.9%)	2 (2.9%)	11 (16.2%)	2 (2.9%)
BCL (n=8)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
All CLP (n=136)	30 (22.1%)	10 (7.4%)	18 (13.2%)	8 (5.9%)	28 (20.6%)	7 (5.1%)
UCLP (n=93)	20 (21.5%)	9 (9.7%)	10 (10.8%)	6 (6.5%)	20 (21.5%)	6 (6.5%)
BCLP (n=43)	10 (23.3%)	1 (2.3%)	8 (18.6%)	2 (4.7%)	8 (18.6%)	1 (2.3%)
All CP (n=75)	9 (12.0%)	1 (1.3%)	3 (4.0%)	0 (0%)	11 (14.7%)	2 (2.7%)
Soft CP (n=35)	4 (11.4%)	1 (2.9%)	2 (5.7%)	0 (0%)	3 (8.6%)	1 (2.9%)
Full CP (n=40)[b]	5 (12.5%)	0 (0%)	1 (2.5%)	0 (0%)	8 (20.0%)	1 (2.5%)
All Clefts (n-287)	51 (17.8%)	13 (4.5%)	26 (9.1%)	11 (3.8%)	51 (17.8%)	12 (4.2%)

[a] SD = Standard deviations;

[b] Full CP = soft + hard palate