Bilateral Asymmetry in Chinese Families With Cleft Lip With or Without Cleft Palate

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Objective: **To determine if Chinese individuals with nonsyndromic cleft lip with or without cleft palate (CL/P) display more bilateral asymmetry than do their unaffected relatives.**

Design/Subjects: **A case-control study of 313 individuals with CL/P from Shanghai, China, with 201 unaffected relatives as controls.**

Methods: **Size-adjusted asymmetry scores were defined by data on middle-finger length, palm length, palpebral fissure width, and ear length. Case-control comparisons used a multivariate repeated measures analysis of variance, paired *t* tests, and the Wilcoxon signed rank test.**

Results: **The ear-length measure showed a significant increase in fluctuating asymmetry (FA) in individuals with CL/P compared with their unaffected relatives, which was most pronounced in the female cleft lip and palate subgroup ($p = .04$). No other measures showed any increase in FA.**

Conclusion: **Evidence was found for increased FA, as measured by overall ear length, in Chinese individuals with nonsyndromic CL/P, compared with their unaffected family members. The use of bilateral measurements other than dermatoglyphics may prove to be a valuable means of assessing overall developmental stability in individuals with developmental malformations and in their families.**

KEY WORDS: *China, cleft lip, cleft palate, fluctuating asymmetry*

Nonsyndromic cleft lip with or without cleft palate (CL/P) is a relatively common condition among the world's populations, occurring in 1 in 700 to 2000 live births, with the highest prevalence in Asian ethnic groups (Croen et al., 1998; Cooper et al., 2000). Although we have a good descriptive understanding of the embryogenesis of the primary and secondary palate, the precise mechanisms at work in the development of this particular craniofacial anomaly have eluded us, and the relative contributions of genetic and environmental influences remain unknown.

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Regardless of pathogenesis or genetics, anomalous developmental conditions such as CL/P are often associated with deviations in lateralization (e.g., non–right handedness in CL/P: Rintala, 1985; Wentzlaff et al., 1997) or an increased level of bilateral or fluctuating asymmetry (FA) (e.g., dermatoglyphic asymmetry in CL/P: Woolf and Gianas, 1976; Kobyliansky et al., 1999). Deviations in lateralization can often lead to severe malformations across multiple developmental fields, although mosaic problems may result in subtle bilateral asymmetries (Opitz and Utkus, 2001). On the other hand, FA is the residual asymmetry inherent in any normal bilateral developmental process. For FA, there is no mean difference between right- and left-side measurements; the variance of the difference between right- and left-side measurements determines the amount of FA. FA is distinguished from directional asymmetry (DA), in which the mean difference between the two sides is different from 0, implying that one side of a bilateral trait is systematically larger than the other (Auffray et al., 1999).

FA has been extensively measured in experimental, natural, and agricultural animal populations and has been shown to increase with increased genetic, environmental, or industry-induced stressors (Whitlock, 1996; Møller and Manning, 2003).

In normal human populations, FA—measured with a wide range of dental, dermatoglyphic, and other bilateral traits—has been correlated with variables that may indicate developmental stability or fitness, including gestational length (Livshits et al., 1988); morbidity and number of offspring (Waynforth, 1998); semen quality (Firman et al., 2003); timing of ovulation (Scutt and Manning, 1996); performance in track runners (Manning and Pickup, 1998); psychometric intelligence (Furlow et al., 1997); and offspring of obese mothers, particularly if they smoked during pregnancy (Kieser et al., 1997).

Increased FA in individuals with specific disorders may reflect a generalized pattern of developmental instability caused by genetic or environmental stressors affecting both the specific condition and the overall development (Livshits and Kobyliansky, 1991; Naugler and Ludman, 1996; Opitz and Utkus, 2001). Along these lines, increased FA has been reported in Down syndrome (Townsend, 1983), fragile X syndrome (Peretz et al., 1988), other nonspecific forms of mental retardation (Malina and Buschang, 1984), fetal alcohol syndrome (Wilber et al., 1993), and schizophrenia (Mellor, 1992; Reilly et al., 2001).

Regarding nonsyndromic CL/P, both Caucasian and Chinese patients with CL/P exhibit increased FA in various dermatoglyphic traits (Adams and Niswander, 1967; Woolf and Gianas, 1976; Deshmukh et al., 1979; Vormittag et al., 1979; Crawford and Sofaer, 1987; Balgir, 1993; Kobyliansky et al., 1999; Neiswanger et al., 2002), although conflicting reports exist (DeBie et al., 1977). If a generalized pattern of developmental instability is contributing to nonsyndromic CL/P, then other bilateral traits may also exhibit increased FA in affected individuals. However, other than dermatoglyphics, little has been reported about the nature of FA in cleft populations.

To search for increased FA in individuals with CL/P, this study evaluated ear-, eye-, palm-, and finger-length differences between right and left sides of the body in a sample of Chinese individuals with CL/P and their unaffected relatives.

Materials and Methods

Subjects

As part of a larger study of the genetics of nonsyndromic CL/P (Marazita et al., 2002), about 2000 patients with CL/P and their families were ascertained through the surgical records of hospitals in Shanghai, China, between the years 1956 and 1983 (Marazita et al., 1992). After approval by the Institutional Review Boards of the University of Pittsburgh and the Zhabei Eye Hospital, descriptive information was obtained for each family member, including gender, birth date, affection status, CL/P characteristics, presence of other congenital anomalies, and family history of clefting.

For this study, measures of bilateral asymmetry were collected from a subset of 313 nonsyndromic individuals with CL/P and 201 unaffected relatives. Table 1 provides gender and cleft information for the sample.

TABLE 1 Clefting Status and Gender in Chinese Individuals*

	Male	*Female*	*Total*
Unaffected relatives	46	155	201
Individuals with CL/P	196	117	313
Cleft type			
CL only	47	55	
CL + CP	149	62	
Cleft laterality			
Unilateral	149	90	
Bilateral	47	27	

* CL = cleft lip; CP = cleft palate.

Symmetry Measures

Four bilateral features—ear length, middle-finger length, palm length, and palpebral fissure width—were chosen from standard anthropometric measures. Palm length is the distance from the distal flexion crease at the wrist to the proximal flexion crease of the third (middle) finger. Middle-finger length is measured from the proximal flexion crease to the tip of the middle finger. Total ear length is the distance between the most inferior and the most superior points of the ear. The distance across the greatest horizontal axis of the eye from medial to lateral canthus defines palpebral fissure width.

Ear- and finger-length measurements have been widely used to estimate FA in humans (Livshits and Kobyliansky, 1991; Gray and Marlowe, 2002), whereas palm length is one of several standard hand measurements. In addition to these standard measures of FA, palpebral fissure width was measured because it is a para-midline facial feature that is not directly affected by the presence of a cleft. All anthropometric measurements were obtained with a millimeter-ruled vernier caliper and were determined to the nearest tenth of a millimeter. One researcher (Y.L.) took all measurements. Because of limitations in the field protocol, measurements were taken only once, which precluded any estimation of measurement error. However, measurement reliability is generally reported to be very good for both ear and middle-finger length and acceptable for palpebral fissure width (Ward and Jamison, 1991; Trivers et al., 1999; Gray and Marlowe, 2002).

Data Analysis

This study used a case-control design, with unaffected relatives serving as controls. Symmetry for each anthropometric measure was assessed by subtracting the left-side from the right-side measurement to arrive at a difference score. The mean difference scores were then compared with 0 by using two-way *t* tests. None of the mean scores differed significantly from 0, so there was no evidence for DA in any of the measures.

After checking for evidence of DA, the difference scores were adjusted for absolute size by the formula $|R - L|/[(R + L)/2]$ (Palmer and Strobeck, 1986). This was necessary to compensate for age differences between the cases and controls. In particular, several children were among the cases with their unaffected mothers in the control group.

Because there are likely to be both genetic and within-family environmental influences on clefting, each affected individual was matched to one of his or her unaffected relatives to create a sample of 187 family-matched pairs. FA was analyzed for each measure by calculating the difference in the size-adjusted difference scores between the members of each pair. We then conducted a multivariate repeated measures analysis of variance (ANOVA) of these calculated variables to evaluate variability among the 187 family-matched pairs. This enabled us to search efficiently for the possible effects of cleft status (cleft lip only versus cleft lip and palate), laterality (unilateral versus bilateral clefts), and gender, as well as interactions among these factors, on FA.

Substantial gender differences existed between cases (63% male) and controls (23% male). In particular, the most common controls were mothers of affected individuals. Thus, the effect of gender was further examined in the paired analysis by placing the pairs into 74 gender-matched pairs (28 male CL/P–male unaffected, 46 female CL/P–female unaffected) and 113 non–gender-matched pairs (103 male CL/P–female unaffected, 10 female CL/P–male unaffected).

After the ANOVA found a significant effect for ear length, paired *t* tests were used to verify this result for the family-matched pairs. Finally, the degree of FA for ear length was compared in the entire, unmatched data set of 313 cases and 201 controls. Because the size-adjusted difference scores are not normally distributed, the nonparametric Wilcoxon signed rank test was used to make statistical inferences in the unmatched sample. All statistical analyses were performed by SAS (SAS Institute Inc., 1994).

Results

Table 2 provides the mean measurements (±SD) and ranges for the four bilateral measurements, along with the adjusted mean difference scores, grouped according to affection status and gender.

When the gender-matched pairs (n = 74 male-male and female-female pairs) were analyzed with the multivariate repeated measures analysis (ANOVA), there was a significant interaction effect on ear-length asymmetry ($p = .03$) between pair gender (male-male versus female-female) and the type of cleft (cleft lip only versus cleft lip and palate). This interaction was also seen in the gender-matched unilateral cleft group ($p = .03$; N = 56 pairs) but was not seen in the non–gender-matched sample (n = 113 male-female and female-male pairs). Similarly, the paired *t* tests showed significantly more ear-length asymmetry ($p = .04$) in the 24 females with cleft lip and palate than in their paired female unaffected relatives, which was not seen in any other pairs with different genders or with cleft lip only. No symmetry differences were seen in the family-matched pairs for any of the other measures.

Finally, the nonparametric Wilcoxon signed rank tests of the overall sample revealed a trend toward increased FA in the ear-length measurement in individuals with CL/P compared with their unaffected relatives ($p = .07$), which was present

TABLE 2 Mean (± SD), Ranges, and Adjusted Difference Scores for Four Measures of Bilateral Symmetry in Males and Females With CL/P and in Their Unaffected Relatives*

	Palpebral Fissure, mm			*Ear, mm*			*Middle Finger, mm*			*Palm, mm*		
Subjects (N)	*Right*	*Left*	*Adjusted Difference*	*Right*	*Left*	*Adjusted Difference*	*Right*	*Left*	*Adjusted Difference*	*Right*	*Left*	*Adjusted Difference*
Males with CL/P (196)												
Mean (± SD)	23.8 (± 3.8)	23.9 (± 3.8)	0.010 (± 0.02)	52.9 (± 12.0)	52.8 (± 11.7)	0.012 (± 0.02)	52.6 (± 19.2)	52.5 (± 19.2)	0.013 (± 0.02)	71.0 (± 25.0)	71.1 (± 25.0)	0.013 (± 0.02)
Minimum	15	13	0	25	27	0	21	21	0	30	32	0
Maximum	35	34	0.14	78	75	0.15	89	90	0.12	117	118	0.09
Females with CL/P (117)												
Mean (± SD)	24.3 (± 3.5)	24.3 (± 3.5)	0.004 (± 0.01)	53.2 (± 11.5)	53.4 (± 11.5)	0.010 (± 0.02)	58.7 (± 18.3)	58.9 (± 18.3)	0.011 (± 0.01)	77.2 (± 24.6)	77.2 (± 24.5)	0.015 (± 0.02)
Minimum	15	15	0	25	25	0	23	23	0	32	32	0
Maximum	33	33	0.07	70	70	0.07	88	88	0.07	115	120	0.11
Unaffected male relatives (46)												
Mean (± SD)	26.9 (± 2.8)	26.9 (± 2.8)	0.007 (± 0.02)	64.9 (± 6.2)	65.1 (± 6.1)	0.005 (± 0.01)	78.6 (± 7.6)	78.9 (± 7.6)	0.013 (± 0.02)	105.0 (± 9.4)	105.0 (± 9.3)	0.011 (± 0.02)
Minimum	22	22	0	45	45	0	55	55	0	72	72	0
Maximum	36	35	0.07	75	75	0.08	94	93	0.08	118	124	0.06
Unaffected female relatives (155)												
Mean (± SD)	27.2 (± 3.4)	27.2 (± 3.4)	0.008 (± 0.02)	62.6 (± 4.5)	62.6 (± 4.5)	0.009 (± 0.02)	75.3 (± 4.3)	75.5 (± 4.6)	0.014 (± 0.03)	99.1 (± 5.5)	99.2 (± 5.0)	0.014 (± 0.02)
Minimum	21	21	0	50	50	0	65	50	0	79	80	0
Maximum	41	40	0.11	75	76	0.10	92	92	0.35	111	113	0.11

* CL/P = cleft lip with or without cleft palate.

more strongly in the males ($p = .02$) but not in the females ($p = .31$).

Discussion

A significant increase in ear-length FA in Chinese individuals with nonsyndromic CL/P was observed, compared with their unaffected relatives. Previous studies have reported DA for ear length (Trivers et al., 1999; Gray and Marlowe, 2002). In the present sample, however, there was no evidence for DA. The multivariate repeated measures ANOVA found a significant interaction between gender (female-female versus male-male pairs) and cleft type (cleft lip alone versus cleft lip and palate) but no single effect of either gender or cleft type alone. The paired *t* tests supported this result. When the overall sample was analyzed, increased FA was seen in males with CL/P compared with unaffected male relatives but not in females. There were no significant asymmetry differences between individuals with CL/P and unaffected relatives with respect to palm length, middle-finger length, or palpebral fissure width.

Thus, increased FA in ear length was detected in both genders of individuals with CL/P, most apparently in the subset of females with cleft lip and palate. A general increase in FA was also observed in unaffected male relatives compared with unaffected females (Wilcoxon signed rank test, $p = .05$). This suggests that males with CL/P might have been expected to show more ear length asymmetry than their family-matched female controls, which did not occur. Taken together, these results suggest that a mild degree of increased FA in ear length may be present in both genders of Chinese individuals with CL/P, which may be occurring most strongly in the cleft lip and palate phenotype.

Ear-length asymmetry might be a secondary effect of the cleft itself. If so, one would expect to see some degree of directional ear-length asymmetry in the unilateral cleft group that would be opposite in direction, depending on whether the cleft is right or left sided. To check this hypothesis, we compared the unadjusted mean difference scores with 0 separately for the individuals with right- and left-sided unilateral clefts. For the left unilateral cleft group (n = 145), the mean difference score was +0.06; for the right group (n = 94), it was −0.15. Although these numbers are in the opposite direction, neither was significantly different from 0 ($p = .50$ for the left group and .17 for the right group; two-tailed *t* tests). Thus, there does not appear to be any direct relationship between ear-length asymmetry and laterality of the cleft.

In addition to the gender differences discussed above, age differences existed between our cases and controls, necessitating the use of size-adjusted variables. To assess the potential effect of age on the analysis, the adjusted difference scores were correlated with the year of each subject's birth. There was no correlation between year of birth and the adjusted difference scores for ear, middle finger, or palm length, which implies that age differences did not confound the analysis of these measures. However, the adjusted difference scores for palpebral fissure width correlated with year of birth in the female controls ($r = -.20$, $p = .01$) and the males with CL/P ($r = -.21$, $p = .004$). This suggests that the age differences between cases and controls were not completely eliminated by the adjusted difference scores for palpebral fissure width. However, no differences in FA were seen for this variable; therefore, potential age differences in palpebral fissure width did not create false-positive results.

Because measurements were taken only once in this study, the effect of measurement error on the analysis could not be evaluated. However, the measurements used are among the standard bilateral variables reported extensively in studies of FA in normal human populations (Furlow et al., 1997; Waynforth, 1998; Trivers et al., 1999; Gray and Marlowe, 2002). As such, their reliability is generally considered to be good to excellent. Interrater measurement error in this study was controlled for by having all measurements performed by one individual. Intrarater reliability can be compromised for bilateral measurements if the result of a measurement on one side influences how the measurement is taken for the second side. When this occurs, the rater's expectation that the two sides should be the same can cause the two measurements to be more similar than they should be. If this happened in the present study, we would expect to lose evidence for FA. Thus, the increase in ear-length asymmetry reported in this study might, in fact, be even greater than what we observed.

The controls in this study were conservative (i.e., they were unaffected relatives of individuals with CL/P who may themselves have more FA than individuals with no family history of clefting). Increased FA has been reported in the parents of preterm infants (Livshits et al., 1988) and in unaffected relatives of individuals with CL/P with a positive family history (Woolf and Gianas, 1977). Therefore, the observation of increased ear-length FA in individuals with CL/P could be confirmed or strengthened by comparison with controls with no family history of clefting.

If confirmed, the results of this analysis support the long-standing hypothesis that individuals with a developmental anomaly, in this case nonsyndromic CL/P, also show increased generalized developmental instability that can be measured by assessing FA. This hypothesis is further supported by reports of increased dermatoglyphic asymmetry in nonsyndromic CL/P in this sample of Chinese individuals (Neiswanger et al., 2002), as well as in other ethnic populations (Adams and Niswander, 1967; Woolf and Gianas, 1976; Deshmukh et al., 1979; Vormittag et al., 1979; Crawford and Sofaer, 1987; Balgir, 1993; Kobyliansky et al., 1999). Dermatoglyphics are formed in a short time period during embryogenesis, at approximately the same time during which the lips and palate are fusing; however, ear length continues to increase over many years. Increased FA in both measures implies a truly global increase in developmental instability, both in separate developmental fields and temporally. This underscores the importance of using multiple independent variables when assessing bilateral symmetry. With the accumulation of extensive symmetry data on patients with a range of developmental

anomalies, the potential of FA to measure underlying developmental stability may become realized.

Conclusion

We report an increased asymmetry in ear length for Chinese individuals with CL/P when they were compared with their unaffected relatives. No increased asymmetry was seen for palm length, middle-finger length, or palpebral fissure width. The results of this study are conservative because the controls are unaffected relatives of individuals with CL/P, who may themselves show more asymmetry than do individuals with no family history of clefting. The use of bilateral measurements other than dermatoglyphics may prove to be a valuable means of assessing overall developmental stability in individuals with developmental malformations and in their families.

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