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Cleft lip with or without cleft palate and dermatoglyphic asymmetry: evaluation of a Chinese population

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Structured Abstract

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Objective – To determine if Chinese individuals with non syndromic cleft lip with or without cleft palate (CL/P) display more dermatoglyphic asymmetry than unaffected relatives or controls.

Design – Case – control study with two control groups (genetically related and unrelated).

Setting and Sample Population – A total of 500 CL/P probands from Shanghai, China, 421 unaffected relatives, and 66 controls of Chinese heritage.

Methods – Finger and palm prints were collected, and pattern frequencies, total ridge counts (TRC), and *atd* angles were calculated. Asymmetry scores between right and left hands were defined for each of the three dermatoglyphic measures. Probands' asymmetry scores were compared statistically with the scores of unaffected relatives and controls.

Results – In general, the probands' asymmetry scores for TRC and *atd* angle did not differ significantly from the scores of either unaffected relatives or controls. However, probands with a positive family history of clefting showed significantly more asymmetry in their pattern types than either probands without a family history, unaffected relatives or controls.

Conclusion – These results suggest that a unique genetic mechanism of developmental instability may obtain in CL/P individuals with a positive family history of clefting.

Key words: cleft lip; cleft palate; China; dermatoglyphics; developmental asymmetry

Introduction

Since the original observation by Cummins in 1939 (1) that individuals affected with Down's syndrome possess abnormal finger and palm prints, many studies have associated altered dermatoglyphic patterns or delayed epidermal ridge development with both diverse congenital defects (for reviews, see 2–4) and spontaneous abortions (5, 6). This relationship stems from the fact that dermatoglyphic traits may reflect prenatal developmental stability (7–9), because epidermal ridge patterns are formed embryologically between the 10th and 17th weeks of life (10).

A major phenotypic indicator of developmental instability in general is the presence of asymmetry between normally symmetric, bilateral traits (8, 11–18). It follows, then, that excessive asymmetry between the dermatoglyphic patterns of the left and right hands may signify relatively unstable genetic control during embryogenesis (7, 9, 19), which, in turn, may contribute to the development of congenital malformations.

Cleft lip with or without cleft palate (CL/P) is a congenital anomaly affecting between 0.4 and 1.7 per 1000 live births every year, with the lowest prevalences in African populations and the highest in Asians (20–22). However, despite the high prevalence of CL/P and the known relationship between congenital malformations and abnormal dermatoglyphics, reports investigating the relationship between CL/P and dermatoglyphic deviations are relatively sparse. The majority of these studies have reported mean frequency differences between affected subjects and controls for several dermatoglyphic traits on both fingers and palms (23–27). Very few studies, however, have examined dermatoglyphic asymmetry specifically.

Among the early studies of dermatoglyphic asymmetry and CL/P, Adams and Niswander (7) demonstrated that children with familial CL/P showed greater asymmetry in their palmar *atd* angles (defined below) than either sporadically affected individuals (i.e. with no family history of clefting) or unaffected controls. They speculated that the simultaneous presence of dermatoglyphic asymmetry and clefts might be related to a common developmental disturbance decreasing the fitness of pleiotropic polygenic systems active during early development. Woolf and Gianas (28) studied the sibs and parents of probands who were either sporadically affected or had a family history of CL/P. They concluded that only probands with positive family histories had increased *atd* angle asymmetry, while all other groups did not differ significantly from controls. They then looked at asymmetry in fingerprint patterns and palmar *a–b* ridge counts, finding that probands with positive family histories and their unaffected relatives were significantly more asymmetric than controls, while sporadically affected probands and their relatives were not (19).

A handful of later studies have supported the association between dermatoglyphic asymmetry and clefting (27, 29–32). However, other authors have concluded that no dermatoglyphic differences whatsoever exist between clefted individuals and controls (2, 33–35). De Bie et al. (35), in fact, reported a higher degree of palmar symmetry in his cleft sample, compared with controls. In summary, the relatively few studies that have investigated the relationship between CL/P and dermatoglyphic asymmetry have provided conflicting results.

This study examined several dermatoglyphic traits and their degree of asymmetry in a large sample of CL/P probands and unaffected relatives from Shanghai, China – a relatively homogeneous, understudied population with a high incidence of CL/P. The purpose of this study was to test the hypothesis that affected CL/P probands with positive family histories possess greater levels of dermatoglyphic asymmetry than sporadically affected probands, unaffected relatives, or unaffected controls.

Materials and methods

Subjects

Information on approximately 2000 probands and their families was obtained for family studies of non syndromic CL/P in Shanghai, China (36), including data on each proband's gender, affection status, cleft type, family relationships, and details concerning the mother's pregnancy. Finger and palm prints were also obtained from a subset of 500 probands and 421 first-degree relatives, using a standard inkless method (2). In addition, dermatoglyphic prints were collected from 66 unrelated controls with no family history of clefting. Thirty-nine were volunteers living in Los Angeles who

indicated verbally that their heritage was 100% Chinese; the remaining 27 were ethnic Chinese from Hawaii collected for a separate study of dermatoglyphics (37).

Dermatoglyphics

We looked for asymmetry in three different dermatoglyphic features. First, we classified fingerprint patterns as arches, loops, or whorls, with loops broken down further into ulnar or radial loops, depending on which side of the finger the loop originated (38). Next, we calculated total ridge counts (TRC) – a quantitative measure of fingerprint size summed over all fingers. Epidermal ridges were counted as described in (39), by drawing straight lines between the center of the fingerprint pattern and the center of the corresponding triradius. Ridges that cut through or touched the lines were counted, and both centers were excluded from the count. The TRC was then calculated by summing the larger of the two ridge counts for each finger over all 10 fingers, and for each hand separately. Finally, we measured *atd* angles – a feature of the palm that captures the relative position of three triradii – *a* and *d*, usually located on the distal palm just inferior to the second and fifth fingers, respectively, and *t*, whose location can vary on the proximal palm from just distal to the wrist up to the center of the palm. *Atd* angles were measured for each palm print by drawing two straight lines through the *a* and *t* triradii and the *d* and *t* triradii, and measuring the resulting angle. Two trained investigators independently evaluated the prints, while a third performed random checks on approximately 10% of the data. A fourth investigator spot-checked the TRC counts.

Asymmetry between right and left hands was determined for each measure. First, to examine asymmetry in pattern types, we calculated dissimilarity scores by assigning a '0' when the fingerprint pattern type was identical for the same digit on right and left hands, a '1' when the patterns were different, and then summing the score over all five pairs of digits (19). Thus, for each individual the dissimilarity score could range from 0 (when all five pairs of digits had identical patterns) to 5 (when all five pairs had different patterns). Following the study of Woolf and Gianas (19) the radial and ulnar loops were scored as identical patterns. Secondly, a TRC difference score was calculated by subtracting the TRC of the right hand from the TRC of the left hand. Similarly, a difference score for the *atd* angle was calculated by subtracting the right hand *atd* angle from the left hand *atd* angle.

Statistical analysis

SAS (40) was used for the descriptive and general statistical analyses. Parent–child correlations for TRC were estimated using FCOR, part of the SAGE (1992) genetic analysis package (41). Differences in means for all measures were compared using standard *t*-tests. Mean values and variances of the pattern dissimilarity scores and TRC and *atd* angle difference scores were compared using ANOVA and standard χ^2 and *t*-tests, employing Tukey's studentized range test for multiple comparisons.

Results

Table 1 provides detail on the clefting types and laterality for the probands. There were 500 probands available – 320 males and 180 females, for an overall male to female sex ratio of 1.8. Cleft lip with cleft palate (CL + P) was more common than cleft lip alone (62% of all probands had CL + P). Although males are more common in the overall sample, they are relatively more frequent in the CL + P cases (M:F – 2.04:1) than the

Table 1. **Gender and cleft type with laterality for CL/P probands**

Cleft status	Male	Female	Total
Cleft lip alone	112 (22%)	78 (16%)	190 (38%)
Right unilateral	33	29	62
Left unilateral	66	42	108
Bilateral	13	7	20
Cleft lip and palate	208 (42%)	102 (20%)	310 (62%)
Right unilateral	67	23	90
Left unilateral	88	47	135
Bilateral	52	31	83
Unknown type	1	1	2
Total	320 (64%)	180 (36%)	500

cases with cleft lip only (M:F – 1.4:1). Among all probands, 79% of the clefts were unilateral, with a preponderance (62%) of left-sided clefts. The palate was more likely to be involved with bilateral clefts than with unilateral clefts in both sexes. In males with bilateral cleft lip, 80% had a cleft palate, while only 61% of the males with a unilateral cleft lip also had a cleft palate. Eighty-two percent of females with bilateral cleft lip had cleft palate, compared with 57% of the unilateral cases. Fifty-eight probands had a positive family history of CL/P.

Table 2 provides the distribution of fingerprint patterns in probands, unaffected relatives, and controls. The frequencies of the pattern types of the three groups did not differ when the genders were pooled ($\chi^2_{(6)} = 9.42$; $p = 0.15$). However, when the females of all three groups were combined and compared with the males, there was a significantly increased frequency of ulnar loops in females, along with a decreased frequency of whorls ($\chi^2_{(3)} = 7.67$; $p = 0.05$). This gender difference stemmed from a significant gender effect in the unaffected relatives ($\chi^2_{(3)} = 8.71$; $p = 0.03$), and was not evident in either the probands or unaffected controls.

Table 3 presents the mean TRC (±SD) and *atd* angles (±SD) for probands and both control groups by gender. The mean TRC was 130.5 (±45.6) for probands, 136.1 (±46.6) for unaffected relatives, and 131.4 (±41.4) for controls. There were no significant differences in the mean TRC among the three groups ($p = 0.43$). After controlling for group, the mean TRC values for all males and females differed at a p-value of 0.06; therefore, gender was analyzed separately for each group. The mean TRC values differed between males and females only in the unaffected relatives ($p = 0.04$), with unaffected male relatives having the highest

Table 3. **Mean total ridge counts and *atd* angles**

Subject	Total ridge counts		*atd* angle degrees	
	N*	Mean (SD)	N**	Mean (SD)
Probands	359	130.5 (45.6)	948	44.1 (6.1)
Male	238	132.7 (46.1)	612	43.8 (6.4)
Female	121	126.3 (44.5)	336	44.5 (5.8)
Unaffected relatives	163	136.1 (46.6)	390	41.2 (5.0)
Male	43	148.4 (49.4)	111	40.4 (5.7)
Female	120	131.7 (44.9)	279	41.5 (4.7)
Controls	53	131.4 (41.4)	58	41.9 (3.9)
Male	28	127.8 (40.8)	28	40.7 (2.3)
Female	25	135.3 (42.4)	30	42.9 (4.8)

*Number of people with 10 countable fingerprint patterns.
** Number of hands with definable *atd* angles.

Table 2. **Frequencies (%) of dermatoglyphic patterns**

Subject	N	Pattern types				Total known patterns*	Unknown or missing patterns	Total prints
		Whorl	Ulnar loop	Radial loop	Arch			
Probands	500	2393 (50%)	2161 (45%)	110 (2%)	142 (3%)	4806	194	5000
Male	320	1577	1374	71	100	3122	78	3200
Female	180	816	787	39	42	1684	116	1800
Unaffected relatives	421	1020 (51%)	897 (45%)	46 (2%)	46 (2%)	2009	2201	4210
Male	210	306	227	9	17	559	1541	2100
Female	211	714	670	37	29	1450	660	2110
Controls	66	305 (47%)	314 (48%)	21 (3%)	12 (2%)	652	8	660
Male	37	174	179	12	3	368	2	370
Female	29	131	135	9	9	284	6	290

*Percentages are based on the total known fingerprint patterns.

mean TRC of any group (mean = 148.4). The parent–child correlation for TRC was estimated to be 0.44 (41), in good agreement with the expected correlation of 0.5 (39).

The mean sizes of the *atd* angles were 44.1° (±6.1) for probands, 41.2° (±5.0) for unaffected relatives, and 41.9° (±3.9) for controls. We did not formally analyze mean *atd* angle differences. The *atd* angle tends to be smaller in adults than children, because hands grow more in length than breadth (39). The probands in our sample are primarily children, while the unaffected relatives are primarily adults, and the controls are entirely adults. Therefore, it is not meaningful to compare mean *atd* angles in this sample.

The results of the three analyses of dermatoglyphic asymmetry are presented in Table 4. For these analyses we split the probands into two groups – sporadic cases vs. cases with a positive family history of clefting – in order to compare our data with similar reports in the literature (7, 28). First, the mean pattern dissimilarity scores were 1.64 (±1.1) for probands with a positive family history of clefting, 1.19 (±1.0) for probands with no family history of clefting, 1.15 (±1.0) for unaffected relatives, and 1.08 (±1.0) for controls. When all four groups were compared simultaneously, these mean values differed significantly ($p = 0.01$). Pair-wise comparisons showed that probands with a positive family history had a higher degree of pattern dissimilarity than those with no family history ($p = 0.01$), unaffected relatives ($p = 0.01$), or controls ($p = 0.02$). The other three groups did not differ from one another. Thus, probands with a positive family history of CL/P have significantly more dermatoglyphic pattern asymmetry than all other groups, including probands without a family history, unaffected relatives, and unrelated controls. There were no gender differences in the pattern dissimilarity scores.

Secondly, there were no significant differences in the mean TRC difference scores among the four groups, either when the genders were pooled or when males and females were considered separately (see Table 4). Finally, a*td* angle difference scores did not vary among the two proband groups, unaffected relatives and controls. The *atd* angle difference scores did show a difference between genders (male mean = 0.14, female mean = –0.56; $p = 0.02$), with males averaging slightly wider *atd* angles on their left hands and females on their right. This difference was most pronounced among the sporadic probands, and not significantly different in the other groups.

Table 4. **Asymmetry analysis: mean (SD) pattern dissimilarity, TRC difference, and *atd* angle difference scores**

Subjects	Pattern dissimilarity score		TRC difference score		*atd* angle difference score	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Probands*						
+Family history	50	1.64 (1.1)	39	0.46 (11.0)	48	–0.22 (2.9)
Males	34	1.71 (1.1)	27	–0.37 (11.9)	34	0.13 (2.3)
Females	16	1.50 (1.1)	12	2.33 (8.8)	14	–1.07 (4.0)
–Family history	399	1.19 (1.0)	320	0.42 (9.7)	411	0.02 (4.3)
Males	262	1.21 (1.0)	211	0.01 (9.8)	264	0.31 (4.1)
Females	137	1.13 (0.9)	109	1.22 (9.6)	147	–0.50 (4.5)
Unaffected relatives	189	1.15 (1.0)	163	–0.36 (10.0)	189	–0.49 (3.3)
Males	53	1.13 (1.0)	43	–1.98 (8.4)	55	–0.49 (3.1)
Females	136	1.15 (1.0)	120	0.22 (10.5)	134	–0.48 (3.4)
Controls	61	1.08 (1.0)	53	1.58 (9.2)	25	–1.12 (4.6)
Males	36	1.17 (0.9)	28	2.18 (7.4)	11	–0.59 (3.9)
Females	25	0.96 (1.1)	25	0.92 (11.0)	14	–1.54 (5.2)

*Probands split by the presence or absence of a positive family history of clefting.

Discussion

In general, we found no differences among probands, unaffected relatives, and controls in the frequencies of pattern types. This agrees with Silver (33), who reported that pattern frequencies did not differ between his cleft and non-cleft groups. Our sample was also consistent with Holt (39), who also reported that the Chinese have the highest frequency of whorls of all major racial groups. Balgir (25) found an increased frequency of loops and a decreased frequency of whorls in his sample of Indian CL/P patients. DeBie et al. (35), studying Belgian CL/P populations, reported that male CL/P patients had a lower frequency of ulnar loops and a higher frequency of whorls. Kanematsu et al. (26) found the same trend for both male and female CL/P subjects in a Japanese sample. We found a decrease in ulnar loops and an increase in whorls in the males in our sample, but it occurred mainly in the unaffected relatives, and did not appear related to clefting. As there were no overall pattern frequency differences between the probands and controls in our sample, the meaning of this gender effect is unclear.

We also found that male unaffected relatives had a higher mean TRC than females. This may reflect the higher frequency of whorls in the male unaffected relatives or it may occur independently. Unlike the absolute ridge count, which sums two values for whorls and only one for loops, the TRC is thought to measure pattern size independently of pattern type (39). This is obviously not completely true, because arches contribute no counts to the TRC, and thus the smallest TRC values are almost always derived from hands with multiple arches. As arches comprise only 2–3% of all pattern types (39), the influence of arches on the TRC should, in practice, be small. However, if the larger of the two ridge counts for a whorl is greater than the ridge count for a loop, then the TRC might also correlate with the number of whorls. Comparison of the average ridge count for loops with the average maximum ridge count for whorls would easily test this hypothesis.

The asymmetry analysis found that probands in families with a positive family history of clefting had significantly more asymmetry in their pattern types than all other groups. There were no differences in asymmetry for either the TRCs or the *atd* angles. Woolf and Gianas (19) also saw an increase in mean dissimilarity scores among probands with a positive family history, compared either with probands without a family history or with controls. Thus, in families with multiple occurrences of clefting, unaffected relatives show the same degree of pattern asymmetry as controls, while affected probands show a higher degree of pattern asymmetry.

To speculate, this observation may reflect the segregation of genetic risk factors affecting general developmental stability. Thus, individuals in multiplex CL/P families who inherit a sufficient number of at-risk alleles to develop CL/P would also show more asymmetry in their dermatoglyphic patterns. Unaffected individuals in these families may not carry a sufficient number of risk factors to disturb their dermatoglyphic pattern symmetry more than the general population.

Conclusion

Dermatoglyphic pattern types, total ridge counts, and *atd* angles did not differ significantly between a Chinese sample of 500 CL/P cases and both genetically related and unrelated controls. Thus, the hypothesis that significant dermatoglyphic asymmetry is present in all non syndromic CL/P probands is rejected. However, probands with a positive family history of clefting showed significantly more dissimilarity in their pattern types on corresponding fingers than controls, unaffected relatives, and probands without family history. This suggests that a positive family history of clefting, or a genetic load, is one element that may impact developmental fitness. With further study it may be possible to identify those individuals in whom developmental instability seems to be a contributing factor to the development of non syndromic CL/P.

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