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Handedness and bilateral asymmetry of second to fourth finger digit ratio (2D:4D) in adults from Merida, Mexico

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ABSTRACT

Background: High relative androgen level (testosterone/estrogens) *in utero* plays an important role in the etiology of differential second digit (2D) and fourth digit (4D) lengths of hands, bilateral asymmetry, digit ratio (2D:4D), and handedness in males and females. ***Methods:*** Present study was done in a sample of 20 to 50 year-old men (n= 56) and women (n= 53) from Merida, Mexico. Lengths of 2D and 4D were measured; 2D:4D and absolute fluctuating asymmetry were estimated; handedness was recorded.

Results: Mean value of age in men (35.46 years) and women (38.30 years) was not significantly different (p>0.05). Left-handedness was more frequent in men (16%) than women (9%). Mean of 2D length in men was lower than 4D that was reverse in women; men had mean of 2D:4D <1.0 (left 0.96, right 0.98) whereas the value was >1.0 in women (1.03 in both hands) with significant sex difference (p<0.05). Discriminant function analysis showed 2D:4D as the significant predictor for handedness in both sex.

Conclusion: Lower 2D length, 2D:4D in men, particularly in left-handed individuals, support the hypothesis of earlier studies suggesting these characteristics interact with relatively higher pre-natal testosterone exposure. Low bilateral asymmetry indicate canalization, similarities in environmental and developmental-genetic programs for digit lengths and ratio.

***Key words*: Second-to-fourth digit ratio, handedness, asymmetry.**

INTRODUCTION

Androgen exposure *in utero* influences handedness and also the development of fingers, which leads to bilateral asymmetry and sexual dimorphism of such characteristics that vary across ethnicity (Manning et al., 1998). The earlier studies evidenced probable impacts of prenatal testosterone on lengthening fourth or ring finger (particularly in males) and prenatal estrogen lengthening second or index finger (particularly in females) (Manning, 2011; Manning et al., 1998). Therefore, ratio between index finger (2D) and ring finger (4D), commonly known as digit ratio (2D:4D) as well as handedness are considered to be the reliable biomarkers or proxy indicators of negative correlates of high prenatal levels of androgens (high ratio of testosterone/estrogens), determining lower values (<1.0) of 2D:4D and left-handedness in male ('masculinity'). The hypothesis for females is inverse, stating an exposure to lower relative testosterone-estrogen ratio *in utero* leads to higher values of 2D:4D (more feminine) and higher frequency of right-handedness (Cohen-Bendahan et al., 2005; Hönekopp et al., 2007; Lutchmaya et al., 2004; Manning et al.,1998; McIntyre, 2006; Putz et al., 2004; Stoyanov et al., 2009, 2011; Zheng & Cohn, 2011). Differential lengths of 2D and 4D and thereby digit ratio is reported to be developed by the 13th week of gestation (Malas et al., 2006; Manning et al., 1998).

It is also reported that prenatal testosterone exposure has an interaction with the homeobox genes (*Hoxa* and *Hoxd*) that controls differentiation of digits (Hönekopp et al., 2007; Lutchmaya et al., 2004; Manning et al., 1998, 2010). It is further reported that pre-natal exposure to higher relative testosterone (early development of masculinity) probably impacts on the delay in the development of somatic characteristics (Geschwind & Behan, 1982; Geschwind & Galaburda, 1985a, 1985b) that may lead to stronger sexual dimorphism in bilateral morphological traits and handedness in humans. The hypothesis suggested by the authors (Geschwind & Behan, 1982; Geschwind & Galaburda, 1985a, 1985b; Kelly, 1993) stated that exposure to relatively high level of testosterone *in utero* causes dominance of right cerebral hemisphere, which eventually influences left-handedness. However, maternal testosterone (produced in the ovaries and adrenals) cross placental barriers and might influence also the development of differential 2D and 4D lengths and left-handedness ("male-type") in female fetus (van de Beek et al., 2009). Another little different hypothesis stated that a probable association between level of testosterone in males and development of temporo-parietal regions of brain results in the increased left-handedness (Grimshaw et al., 1995; Witelson, 1991).

Asymmetry studies on bilateral measurements of 2D, 4D and digit ratio (2D:4D) are also useful to explain the traits as biomarkers of prenatal exposure to androgens (Fink et al., 2004; Gillam et al., 2008; Manning et al., 2004). It is reported that right hand fingers were longer than the left for dextrals but not for sinistrals (Nicholls et al., 2008). Studies among Australian children also reported higher bilateral asymmetry in boys with low 2D:4D and reverse with high 2D:4D in girls related to sex differential androgen exposure *in utero* (Fink et al., 2004). Bilateral asymmetry of 2D:4D in relation to handedness are also reported earlier (Beaton et al., 2011; Stoyanov et al., 2009, 2011; Voracek et al., 2006). Organic evolution is shaped by natural selection where genotype is under constant interaction with environmental change. Phenotypic plasticity in organisms has adaptive effects linked with mutation, migration, genetic admixture and other environmental factors. The ability in the organisms of producing consistent phenotype in spite of these factors are referred to as canalization that predicts a stabilization of selection in favor of genetic variants to reduce environmental variability and effects of mutation (Gibson & Wagner, 2000). Bilateral asymmetry study of morphological traits might be important in estimation of developmental stability and canalization, particularly in human populations (Livshits & Kobyliansky, 1989; Livshits & Smouse, 1993). Fluctuating asymmetry (FA) is defined as random and minor deviations from perfect symmetry in paired or bilateral morphological characteristics where mean population difference between right and left sides is zero (Palmer & Strobeck, 1986, 1992, 1997, 2003; Van Valen, 1962). Therefore, FA is a measure of developmental instability of the phenotypes, affected by genetic and environmental stress.

In this background, the general aim of the present study was to test further the hypothesis of digit ratio and handedness, separately or jointly are the proxy indicators of differential relative androgen exposure *in utero* in male and female individuals. The particular objectives of the preset study were:

1) To study sex difference of lengths of second digit (2D) and fourth digit (4D) of hands and their ratios (2D:4D) in right and left sides in a sample of 20 to 50 year-old adults from Mexico.
2) To observe frequencies of handedness (hand preference of writing, left or right) among the participants and how far this trait was related to the bilateral digit lengths and ratios (2D:4D) in men and women.
3) To understand bilateral difference of digit lengths and 2D:4D through estimated absolute fluctuating asymmetry (FA) and simple difference value (right minus left) in both sex.

PARTICIPANTS AND METHODS

The study was done among 109 adult individuals (56 men, 53 women) aged 20 to 50 years from Merida city in Yucatan, Mexico in 2016 (ongoing research). The men and women were selected from a sample of 150 individuals of this age range in connection with a recently completed research project (see acknowledgement). A sub-sample of 109 adults for the present study was obtained from that sample with 5% margin of error and 95% confidence level. The sample was non-probability type and not representative of any particular population from this part of Mexico (Cochran, 1977). Ethical approval was obtained from the appropriate institutional committee as a part of ongoing project for Master's thesis, and following Helsinki declaration (WHO, 2001; World Medical Association, 2008). The second (index) and fourth (ring) finger lengths were measured on the palmar or ventral surface of both left and right hands using vernier calipers with a precision to the nearest 0.01 mm. The finger lengths were recorded from the mid-point of the basal crease, most proximal to palm to the tip of the particular digit (Manning, 2002). Information on writing hand preference (handedness) was collected (Manning & Peters, 2009). Based on that criterion, the participants were grouped into either dextrals (right-handed) or sinistrals (left-handed). There was no participant reported to be ambidextrous and there was no physical handicap in the hands. Informed consent was obtained from the participants before recording of the measurements.

Measurements were taken by two trained personnel. Technical errors of measurements (TEMs) were found to be within reference values (Ulijaszek & Kerr, 1988). Inter and Intra-observer technical error of measurements (TEM) validated the measurement quality and consistency for repeating measurements. Test-retest reliability was computed using intra-class correlation coefficients (ICC, repeated measures) with 95% confidence intervals (Bland & Altman, 1986); in all measurements, ICC values were >0.85 (Altman, 1999).

Descriptive statistics including mean and standard deviations of the measurements (second and fourth digits on right and left hands) and derived variables (relative lengths of index and ring fingers or digit ratio, 2D:4D) were calculated in the samples of men and women. The distributions of bilateral measurements of digit lengths and ratios were normal, following assumptions of standard statistical test (Shapiro-Wilk test, $p > 0.05$), run separately in the samples of men and women. Sex difference of characters was estimated using Student's t-test. Frequencies of left and right-handed individuals by sex was calculated. Digit ratio (2D:4D) in the right hand, left hand and the difference between right and left digit ratio (DR_{r-l} = 2D:4D of right hand minus 2D:4D of left hand) were calculated and compared between dextrals and sinistrals in men and women (Beaton et al., 2011; Stoyanov et al., 2011). The individual absolute fluctuating asymmetry (FA) of bilateral measurements of second digit (2D) and fourth digit (4D) and their ratio (2D:4D) was estimated using standard formula (Karmakar et al., 2013):

$$FA_{ij} = (X_iR - X_iL) - 1/n \ \Sigma(X_iR - X_iL)$$

Where, X_i = trait (X) of individual (i); R, L = right and left, n = size of the sample and FA_{ij} is the value of FA of trait (j) in the i-th individual. A discriminant function analysis was done to understand how far sex (male= 1, female= 0) and digit ratio (continuous variable, left and right hand separately) as predictors could explain handedness (right= 1, left= 0). Moreover, to understand either sex or handedness as predictor had more of a contribution towards the discrimination of those groups (right-handed and left-handed). All statistical analyses were done using the SPSS program (Version 13.00, Chicago IL, USA)**.** All analyses were run using a 5% significance level (α= 0.05).

RESULTS

In the studied sample (n= 109), results show mean age of women participants (38.30 years) was higher than men (35.46 years) however, without significant sex difference ($p>0.05$) (Table 1). In general, bilateral 2D and 4D lengths in women were longer than in men. Mean values of 2D length in men was lower than 4D length that was reverse in women. Mean values of second digit (2D) lengths and digit ratio (2D:4D) of left and right sides showed significant sex difference ($p<0.05$) (Table 1). Mean values of digit ratio (2D:4D) in men (n= 56) was significantly lower ($p<0.05$) than women (n= 53) in both right and left hands and sex difference with respect to this trait was observed to be higher in right hands. Bilateral difference, estimated by absolute fluctuating asymmetry (FA) of 2D, 4D and digit ratio was marginal in men and women. Significant sex difference (<0.05) of FA was observed for 4D and digit ratio.

Distribution of the mean values of bilateral digit lengths, ratios, and asymmetry in left and right-handed men and women are presented in Table 2. High correlation between bilateral measures of 2D, 4D, and 2D:4D was found in men and women. In all cases, Pearson correlation coefficients were very high ($r\geq 8.9$, $p< 0.0001$) (not presented in a separate table). In the present study, considerable number of men (16%) and women (9%) were observed to be left-handed (left hand preference of writing). Mean of second digit length (2D) was lower in left-handed individuals (sinistrals) of both sex than right-handed (dextrals) peers. Significant sex difference ($p< 0.05$) was observed with respect to the difference of mean of 2D among dextrals in their both right and left hands. Mean values of digit ratio in both left and right hands were lower among sinistral men and women than the dextral individuals of either sex with significant difference between the groups ($p<0.05$) (Table 2). Absolute fluctuating asymmetry (FA) was very low in 2D and 4D in both dextral and sinistral men and women. However, bilateral digit ratio difference (DR_{r-}

$_{l}$) had negative signs between dextral and sinistral men and women indicating relatively higher mean value of difference (though marginal) in left-handed individuals (Table 2).

In a discriminant function analysis (Table 3), run separately for digit ratio in left and right hands (model 1 and model 2 respectively), there was no missing value (n= 109). One function for the discriminating ability of the predictors (sex and digit ratio) was obtained for two sides separately (left and right hands). In test of homogeneity of covariance matrices, log determinants were relatively equal for the predictors with respect to handedness. The discriminant function models did not violate assumptions of multivariate normality ($p > 0.05$) as tested by Box's M test (value= 10.20 for digit ratio in left hand, value= 9.92 for digit ratio in right hand). In the test of equality of group means, Wilk’s Lambda for digit ratio was 0.91 in both model 1 and model 2 showing them statistically significant ($p < 0.001$). However, in the same test, sex as one of the predictors, was not found to be significant in either model. In test of homogeneity of covariance matrices, eigen values were 1.12 for left side and 1.02 for right side in the two separate discriminant function models.

Association between discriminant function and the dependent variable as tested by canonical correlation that was moderate (0.56) in the discriminant function models and correct classification rate was 85.3% in both models. Chi-square statistic (value= 9.71 for left side and 10.63 for right side) also demonstrated significant discriminant function of the models of digit ratio in both sides predicting handedness ($p < 0.05$). Digit ratio was found to be powerful predictive factor (indicating high correlation with discriminant function) in the structure matrix for both sides (left 0.85 and right 0.82). Another predictor sex in either model had relatively low value in the structure matrix. Based on canonical discriminant function coefficients (unstandardized), the models for handedness are presented in Table 3. In the model 1 (left side), the standardized coefficients of sex and digit ratio were 0.02 and 1.01 respectively. In model 2 (right side), the standardized coefficients of sex and digit ratio were 0.34 and 1.15 respectively (Table 3).

DISCUSSION

In the present study, men had lower digit ratio (<1.0) than women in both left and right hands (Table 1). However, mean values of digit ratio were marginally same (up to second decimal) in both hands of women. Similar results were also obtained in previous studies from India and Poland (Chakraborty et al., 2014), Poland (Kociuba et al., 2016), UK (Gillam et al., 2008; Lutchmaya et al., 2004; Manning et al., 1998), China (Zhao et al., 2013) and other studies (Cohen-Bendahan et al., 2005; Manning, 2002).

In the present sample from Merida, Mexico, significant sex difference (<0.05) was observed with respect to digit ratio (2D:4D) in both sides (left and right hands) showing lower values in men compared to women (Table 1). The results conform to the earlier reports representing different populations as mentioned before (Chakraborty et al., 2014; Cohen-Bendahan et al., 2005; Gillam et al., 2008; Lutchmaya et al., 2004; Kociuba et al., 2016; Manning, 2002; Manning et al., 1998). Higher magnitude of sex difference was found in digit ratio of right hand ($t = 7.12$, $p<0.0001$) than the left hand ($t = 3.94$, $p<0.001$). This result also corresponds to those of earlier studies (Hönekopp & Watson, 2010; Manning et al., 1998; McFadden & Shubel, 2002; Williams et al., 2000).

In the present context, left hand preference was more common among men (16%) than women (9%); similar trend was also found in earlier studies (Manning & Peters, 2009; Nicholls et al., 2008). Lengths of second and fourth digits (2D and 4D) also varied between left-handed (sinistrals) and right-handed (dextrals) men and women. The sinistrals of both sex consistently had lower mean length of 2D and 4D compared to the dextrals. Among dextral men and women, there was a tendency of having longer 4D in the right hand. However, length of 2D in right and left hands of either dextrals or sinistrals did not show any consistent pattern. Similar results of longer right fingers than left in dextrals were also reported earlier (Gillam et al., 2008; Nicholls et al., 2008).

Digit ratio was associated with laterality and handedness in the present study; mean value of digit ratio in general was lower in the left hand. Along with, dextral individuals of either sex had higher mean of digit ratio that was observed through the patterns of differences in mean values and also in the magnitude ($p < 0.05$) of sexual dimorphism (Table 2). Mean value of digit ratio in both left and right hands was lower among sinistrals than in the dextral individuals. The results in the present study therefore, indicate an association between low 2D:4D and increased likelihood of left-handedness, the particular pattern that was more prevalent in men compared to women in the studied sample. The previous studies also reported similar trends (Reio et al., 2004).

Significant sex difference ($p < 0.05$) of 2D in both right and left hands (higher magnitude in the right hand, estimated by t-value= 4.48) among dextral individuals was another result in this study. Greater sexual dimorphism in right hand than left with respect to both digit length and ratio support the hypothesis of sensitiveness of right hand to fetal androgens as reported earlier (Gillam et al., 2008; Manning et al., 1998; McFadden & Shubel, 2002; Hönekopp & Watson, 2010).

Bilateral asymmetry of 2D, 4D lengths and their ratio (2D:4D) was very little as evident from the results of either absolute estimate of fluctuating asymmetry (FA) or simple bilateral difference (right minus left) of the values. Absolute FA of 4D was observed to be lower (mean value) among sinistral men and significantly different from the dextral peers ($p = 0.04$). Significant sex difference of absolute FA of 4D and 2D:4D was also noted. The finding of lower bilateral digit ratio difference (DR_{r-l}) among dextrals in the present study also supports similar results reported earlier (Stoyanov et al., 2009, 2011).

CONCLUSION

Therefore, results in the present study clearly show sexual dimorphism in digit ratio (2D:4D) characteristic and its association with lower value and higher prevalence of left-handedness, particularly in males. The results in the present study showed left-handed women had mean of digit ratio (<1.0) that is common among men. Therefore, male bias for left-handedness and simultaneous lower value of digit ratio (<1.0) might be summarized. The results in the present context altogether therefore, further support the hypothesis of earlier studies suggesting low 2D:4D and left-handedness interacts with pre-natal testosterone exposure (Fink et al., 2004; Geschwind & Behan, 1982; Geschwind & Galaburda, 1985a, 1985b; Gillam et al., 2008; Manning et al., 2004; Stoyanov et al., 2009, 2011; Voracek et al., 2006). Low bilateral asymmetry and high correlation between sides indicate canalization, similarities in environmental as well as developmental-genetic programs for digit lengths and ratio (Debat & David, 2001; Wagner et al., 1997; Gibson & Wagner, 2000). However, the present study was done in a relatively small sample and also in a particular age range of the adults; the results need further verification through studies in other populations with higher sample size by age and sex. In this context, future research, representing different populations across the world, if find similar results as reported earlier including the present one, will help us to support the hypothesis of maleness of left-handedness and lower digit ratio (2D:4D). Cross-cultural studies on sexual dimorphism bilateral asymmetry, and handedness in relation to 2D:4D are still interesting (Sorokowski et al., 2012, Voracek et al., 2006).

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Table 1. Descriptive statistics of bilateral digit ratio (2D:4D) in men (n = 56) and women (n = 53) from Merida, Mexico

Variables	Men Mean (SD)	Women Mean (SD)	t*	p-value
Age (years)	35.46 (7.59)	38.30 (8.93)	-1.79	0.08
Second digit (2D) Left	6.52 (0.64)	6.88 (0.43)	-3.48	<0.001
Second digit (2D) Right	6.41 (0.56)	6.89 (0.42)	-4.99	<0.0001
Fourth digit (4D) Left	6.64 (0.54)	6.71 (0.43)	-0.76	0.45
Fourth digit (4D) Right	6.65 (0.53)	6.72 (0.44)	-0.76	0.45
Digit ratio (2D:4D) Left	0.96 (0.07)	1.03 (0.03)	-3.94	<0.001
Digit ratio (2D:4D) Right	0.98 (0.06)	1.03 (0.03)	-7.12	<0.0001
FA** (2D)	0.02 (0.07)	0.01 (0.01)	1.56	0.12
FA (4D)	0.02 (0.02)	0.01 (0.01)	3.06	<0.01
FA (digit ratio)	0.04 (0.07)	0.01 (0.00)	2.99	<0.01

*Negative sign indicates higher mean value in women. **FA: Absolute fluctuating asymmetry.

Table 2. Distribution of mean values of bilateral digit lengths, ratio and asymmetry in men (n= 56) and women (n= 53).

Variables	Handedness*	Men				Women				Sex difference in left handed individuals		Sex difference in right handed individuals	
		Mean	SD	t	p-value	Mean	SD	t	p-value	t	p-value	t	p-value
Second digit (2D) Right	Right handed	6.44	0.58			6.91	0.42						
	Left handed	6.26	0.40	1.16	0.26	6.68	0.42	1.16	0.30	-1.84	0.10	-4.48	**<0.001**
Second digit (2D) Left	Right handed	6.55	0.67			6.91	0.42						
	Left handed	6.34	0.41	1.22	0.24	6.62	0.46	1.33	0.24	-1.11	0.30	-3.08	**<0.001**
Fourth digit (4D) Right	Right handed	6.64	0.54			6.71	0.45						
	Left handed	6.71	0.52	-0.39	0.70	6.76	0.44	-0.22	0.84	-0.19	0.86	-0.77	0.44
Fourth digit (4D) Left	Right handed	6.63	0.55			6.70	0.43						
	Left handed	6.70	0.45	-0.43	0.68	6.80	0.43	-0.49	0.64	-0.41	0.69	-0.71	0.48
Digit ratio (2D:4D) Left	Right handed	0.99	0.08			1.03	0.02						
	Left handed	0.95	0.02	3.04	**<0.001**	0.97	0.03	3.69	**0.02**	-1.55	0.17	-3.41	**<0.001**
Digit ratio (2D:4D) Right	Right handed	0.97	0.06			1.03	0.03						
	Left handed	0.93	0.04	2.56	**0.02**	0.99	0.02	3.52	**0.02**	-3.32	0.01	-6.33	**<0.001**
Fluctuating asymmetry (absolute) 2D	Right handed	0.03	0.07			0.01	0.01						
	Left handed	0.02	0.01	0.73	0.47	0.01	0.01	-0.50	0.64	1.26	0.23	1.45	0.15
Fluctuating asymmetry (absolute) 4D	Right handed	0.02	0.03			0.01	0.01						
	Left handed	0.01	0.01	2.10	**0.04**	0.01	0.00	0.52	0.62	0.66	0.52	3.04	**<0.001**
Fluctuating asymmetry (absolute) 2D:4D	Right handed	0.04	0.07			0.01	0.01						
	Left handed	0.02	0.04	1.16	0.26	0.01	0.01	-3.46	<0.001	0.46	0.67	2.92	**<0.01**
Bilateral difference 2D (right minus left side)	Right handed	-0.11	0.57			0.00	0.11						
	Left handed	-0.09	0.16	-0.22	0.83	0.06	0.09	-1.34	0.23	-2.22	0.05	-1.33	0.19
Bilateral difference 4D (right minus left side)	Right handed	0.01	0.26			0.01	0.09						
	Left handed	0.01	0.15	-0.04	0.97	-0.04	0.05	1.99	0.09	0.90	0.39	-0.15	0.88
Bilateral difference of digit ratio (right minus left side)	Right handed	-0.02	0.09			0.00	0.02						
	Left handed	-0.02	0.03	-0.21	0.84	0.01	0.02	-2.04	0.09	-2.24	0.05	-1.30	0.20

*Men: Left handed = 16%; Women: left handed = 9%. SD: Standard deviation.

Table 3. Canonical discriminant function coefficients in the models for handedness (right or left-handed), predicted by sex (male and female) and digit ratio (2D:4D).

Predictors	Left side (Model 1)	Right side (Model 2)
Constant	17.30	22.15
Sex	0.04	0.67
Digit ratio	17.21	21.93