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Epidemiologic Study of the Sexually Dimorphic Second to Fourth Digit Ratio (2D:4D) and Other Finger Ratios in Greek Population

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A B S T R A C T

The 2nd to 4th digit ratio (2D:4D) is a sexually dimorphic biometric marker, related to prenatal estrogen and testosterone levels in utero, and determined genetically by the HOX genes. 2D:4D presents a population variation, which seems to be dependent on geographical position or ethnicity, and may reflect differences in prenatal steroid hormone levels among different ethnic groups. In view of its clinical importance, this study investigates the 2D:4D ratio, as well as other digit ratios, in Greek population. A sample of 60 Greek men and 60 Greek women (age range 19–25 years) was selected by random procedures. Fingers' length was measured twice, using an electronic vernier calliper (precision 0.01 mm). Men had lower 2D:4D ratio (0.974 ± 0.035 for the right hand and 0.973 ± 0.044 for the left hand) than women (1.002 ± 0.04 for the right hand and 1.001 ± 0.045 for the left hand). This difference in 2D:4D ratio between sexes was statistically significant ($p<0.0001$ for the right hand and $p<0.001$ for the left hand). The other digit ratios were also lower in men than women for both hands; this difference was statistically significant for all digit ratios of the right hand and for the 2nd to 3rd (2D:3D) and 2nd to 5th (2D:5D) digit ratios of the left hand. The digit ratios are lateralized and sexually dimorphic in Greek population. The sexual dimorphism of all digit ratios (except 2D:3D) is stronger in right than left hand.

Key words: *digit ratio, 2D:4D, 2D:3D, 2D:5D, 3D:4D, 3D:5D, 4D:5D, sexual dimorphism, prenatal estrogens, prenatal androgens, HOX genes, disease predisposition*

Introduction

The ratio between the lengths of index finger (2nd digit) and ring finger (4th digit), that is the second to fourth digit ratio (2D:4D), is a sexually dimorphic biometric marker which had been neglected for years. The last years it has attracted attention, as it was realized that 2D:4D is influenced by prenatal estrogen and testosterone levels in utero[1], and it may predict disease predisposition[2].

The values of 2D:4D are generally lower in males than in females, i.e., males have average longer 4th digits relative to their 2nd digits than females. The values of 2D:4D are generally higher in females, i.e., females have relatively longer 2nd digits, although their 2nd digits are not necessarily longer than their 4th digits[3,4]. Relative finger lengths are determined before birth[5], the sex difference in 2D:4D is present in children as young as 2 years old[4], and sex differences in 2D:4D are reliably consistent across a number of ethnic groups and races[6].

The genetic basis linking patterns of digit formation and prenatal testosterone and estrogen levels may lie in the action of *HOX* genes (homeodomain-containing homeotic genes). In vertebrates, including humans, *Hox* genes play an important role in the differentiation of both the urogenital system (including the testes and ovaries) and the digits length[7,8]. In mice, deregulation of *Hoxd* alters the relative lengths of digits and affects growth of the genital bud and differentiation of the penis[9]. In humans the hand-foot-genital syndrome is characterised by defects in the digits, toes and genitalia and is the result of mutation of *HOXA13*[10].

The bone-to-bone ratios of the digits are established by the end of week 13 of pregnancy[5] and there appears to

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be little change in the 2D:4D ratio at puberty[4]. There is evidence that the 2D:4D ratio is a marker for testosterone and estrogen levels towards the end of the first trimester of pregnancy[1,4,6] and reflects the action of *HOX* genes on differentiation during early pregnancy. Therefore, 2D:4D ratio may be a predictor of fertility, the pattern of differentiation of the central nervous system (CNS) and the expression of a number of adult-onset diseases, like immune dysfunction, myocardial infarction and breast cancer[2]. Further evidence comes from the finding that children with congenital adrenal hyperplasia (CAH), a condition associated with high prenatal androgens, have lower 2D:4D ratios than controls[11]. Also, mothers with low 2D:4D tend to have children with low 2D:4D ratio and their children have high concentrations of testosterone relative to estrogen in their amniotic fluid[1,6,12].

Several studies have investigated the 2D:4D ratio in many ethnic groups[1,6,13] but studies on the other digits ratios are rather limited. To our knowledge, there is no epidemiologic study of 2D:4D and other digit ratios in Greek people. In view of the clinical interest that 2D:4D and other finger ratios may have as markers of disease predisposition, and as markers of genetic or environmental influence, we decided to study the 2D:4D and other digit ratios in a sample of Greek population.

Materials and Methods

Subjects

A stratified sample of 120 Greek young adults (60 males and 60 females, age range 19–25 years, mean age 21.9 for men and 22.1 for women) was selected by random procedures. The age of the sample was determined according to previous studies in other ethnic groups. All participating persons gave their consent to the study, which was approved by the Faculty Ethics Committee. The participating persons and the persons taking measurements were ignorant of the physiological meaning of 2D:4D ratio. Individuals with former hand lesions, endocrinopathies, chromosomal abnormalities and those who identified themselves as homosexual or bisexual or left-handed were excluded from the study[14–17].

Measurement of digits' length

The lengths of the second (2D), third (3D), fourth (4D) and fifth (5D) fingers of both hands were measured with an electronic vernier calliper (precision 0.01 mm), as described by Fink et al.[18]. The length of each finger was defined as the distance from the ventral proximal crease of the digit to the tip. If there was a band of creases at the base of the digit, measurements were made from the most proximal of these. Measurements were performed twice, with the second measurement made blinded to the first. Finger lengths were calculated as the mean values of the first and second measurement of the length of each digit.

Biostatistical analysis was performed with the statistical package SPSS 15.0 (SPSS Inc, Chicago, IL) using the criteria t, z and r.

Digit ratios were calculated and their mean values were compared by means of Student's t-test, and one-way ANOVA, because the 2D:4D boxplot for both sexes presented no outliers and the distribution of the values was normal (Kolmogorov-Smirnov normality test, $p<0.05$).

Results

Digits length

The mean digit lengths of all digits of the right and left hand in both sexes are presented in Table 1. No significant difference was found either between each individual's first and second measurement of digits' length, or between their right and left hands' measurements. Women had all their fingers significantly shorter than men ($p<0.001$), a fact reflecting the respective difference in median heights.

2D:4D ratio

The 2D:4D ratios of the right and left hand in both sexes are presented in Table 2. Men had lower 2D:4D ratio (0.974 ± 0.035 for the right hand and 0.973 ± 0.044 for the left hand) than women (1.002 ± 0.04 for the right hand and 1.001 ± 0.045 for the left hand). This difference in 2D:4D ratio between sexes was statistically significant ($p<0.0001$ for the right and $p<0.001$ for the left hand).

TABLE 1
MEAN DIGIT LENGTHS OF ALL DIGITS OF THE RIGHT AND LEFT HAND IN GREEK PEOPLE

Digit	Females (N=60)		Males (N=60)	
	Right hand (mean ± SD)	Left hand (mean ± SD)	Right hand (mean ± SD)	Left hand (mean ± SD)
2D	67.68 (± 4.18)	67.71 (± 4.05)	72.62 (± 3.79)	72.49 (± 3.71)
3D	72.93 (± 4.43)	72.90 (± 4.52)	79.75 (± 4.30)	80.03 (± 4.03)
4D	67.63 (± 4.34)	67.76 (± 4.59)	74.66 (± 4.45)	74.61 (± 4.35)
5D	55.03 (± 4.21)	55.54 (± 4.25)	61.58 (± 4.14)	61.40 (± 4.23)

N – sample size, SD – standard deviation, 2D – 2nd digit (index finger), 3D – 3rd digit (middle finger), 4D – 4th digit (ring finger), 5D – 5th digit (little finger). Length is expressed in mm.

TABLE 2
SECOND TO FOURTH DIGIT RATIO (2D:4D) OF THE RIGHT AND LEFT HAND IN GREEK PEOPLE AND THE DIFFERENCE OF 2D:4D RATIO BETWEEN SEXES

2D:4D	Females (mean ± SD) (N=60)	Males (mean ± SD) (N=60)	Difference
Right hand	1.002 (± 0.04)	0.974 (± 0.035)	$p < 0.0001$
Left hand	1.001 (± 0.045)	0.973 (± 0.044)	$p < 0.001$
Mean	1.002 (± 0.044)	0.974 (± 0.042)	$p < 0.001$

N – sample size, SD – standard deviation, 2D:4D – 2nd to 4th digit ratio

No significant correlation was estimated between 2D:4D and age.

Inter-individual differences were significantly greater ($p<0.01$) than measurement errors in 2D:4D ratio (i.e. the differences between two successive measurements of 2D:4D ratio). Pearson's correlation coefficient for the right hand measurements of 2D:4D was $r=0.639$ ($p=0.01$, 2-tailed), while Spearman's rank correlation coefficient for the left hand was $r_s=0.691$ ($p=0.01$, 2-tailed). So, the calculated values of 2D:4D do reflect real differences among individuals.

Other digit ratios

The ratios of other digits (except 2D:4D) of the right and left hand in both sexes are presented in Tables 3 and 4. Men had lower digit ratios than women in both hands. This difference in digits ratio between sexes was statistically significant for all digit ratios of the right hand and for the 2D:3D and 2D:5D ratio of the left hand. The highest difference in digits ratio between sexes was observed in 2D:3D and 2D:5D ratios of both hands, with p values lower than 0.001 and z ranging from 4.887 to 3.370.

Sexual dimorphism of digit ratios

The sexual dimorphism of digits ratio appears to descend as follows:

1) Right hand: 2D:4D > 2D:5D > 2D:3D > 3D:5D > 3D:4D > 4D:5D
2) Left hand: 2D:3D > 2D:4D > 2D:5D > 3D:5D > 3D:4D > 4D:5D

The difference in digit ratios between sexes was statistically significant for all digit ratios of the right hand and for 2D:3D, 2D:4D and 2D:5D ratio of the left hand. The sexual dimorphism of digit ratios was stronger for the right than for the left hand, with the exception of

TABLE 3
DIGIT RATIO OF ALL DIGITS* OF THE RIGHT HAND IN GREEK PEOPLE AND THEIR DIFFERENCE BETWEEN SEXES

Digit ratio	Females (mean ± SD) (N=60)	Males (mean ± SD) (N=60)	Difference
2D:3D	0.929 (± 0.033)	0.911 (± 0.025)	$p < 0.001$
2D:5D	1.233 (± 0.065)	1.181 (± 0.051)	$p < 0.001$
3D:4D	1.079 (± 0.026)	1.069 (± 0.030)	$p = 0.026$
3D:5D	1.328 (± 0.053)	1.297 (± 0.055)	$p = 0.001$
4D:5D	1.231 (± 0.052)	1.214 (± 0.046)	$p = 0.029$

* – except 2D:4D, N – sample size, SD – standard deviation, 2D – 2nd digit (index finger), 3D – 3rd digit (middle finger), 4D – 4th digit (ring finger), 5D – 5th digit (little finger), NS – non significant

TABLE 4
DIGIT RATIO OF ALL DIGITS* OF THE LEFT HAND IN GREEK PEOPLE AND THEIR DIFFERENCE BETWEEN SEXES

Digit ratio	Females (mean ± SD) (N=60)	Males (mean ± SD) (N=60)	Difference
2D:3D	0.930 (± 0.035)	0.906 (± 0.037)	$p < 0.001$
2D:5D	1.222 (± 0.060)	1.184 (± 0.063)	$p < 0.001$
3D:4D	1.077 (± 0.027)	1.073 (± 0.024)	$p = 0.195$ (NS)
3D:5D	1.315 (± 0.051)	1.306 (± 0.063)	$p = 0.195$ (NS)
4D:5D	1.221 (± 0.041)	1.217 (± 0.052)	$p = 0.319$ (NS)

* – except 2D:4D, N – sample size, SD – standard deviation, 2D – 2nd digit (index finger), 3D – 3rd digit (middle finger), 4D – 4th digit (ring finger), 5D – 5th digit (little finger), NS – non significant

2D:3D ratio, which presented a higher difference in left hand (z=3.651 for the left hand and z=3.370 for the right hand). In the left hand, the 2D:3D ratio presented the highest sexual dimorphism of all digit ratios, even higher than that of 2D:4D (z=3.651 for 2D:3D versus z=3.446 for 2D:4D).

Discussion

2D:4D (digit 2 to digit 4) ratio is a sexually dimorphic biometric marker[3] that is determined genetically by the *HOX* genes[7–9]. 2D:4D is under the influence of prenatal estrogen and testosterone levels in utero[1,12]. Alterations of 2D:4D ratio seem to be present in gender related pathophysiology and 2D:4D appears to be a useful marker of disease predisposition[2].

While it is clear why men and women have sexually dimorphic reproductive organs, it remains unclear why they evolved a sexually dimorphic digit ratio. Male digit ratio pattern may be functional, because a longer ring finger helps the stabilization of the third digit when throwing objects, thus increasing throwing accuracy. Since throwing accuracy was required for successful hunting in the past, it was of sufficient importance to drive the evolution to this trait. Sexual dimorphism was developed, as ancestral women did not need this extra stability. Today, this sex difference may be seen in male superiority in throwing darts. Another hypothesis for the origin of this sexually dimorphic trait is that of the direct sexual selection (the female choice). This implies that women may be particularly attracted to men with low 2D:4D and masculine-looking characteristics although they may not be conscious of the low digit ratio[6,19].

In our study women had all their fingers significantly shorter than men ($p<0.001$), a fact reflecting the respective difference in median heights. This sexual dimorphism in fingers' length is consistent with similar findings in studies of other populations[5,6,20,21].

The 2D:4D ratio in the sample of Greek population that was studied was found significantly higher in women than in men, a finding that is in agreement with other studies of 2D:4D in other ethnic groups. In our study we found that the mean 2D:4D ratio was 0.974 ± 0.042 in males and 1.002 ± 0.044 in females. In previous studies the mean 2D:4D ratio in males and females was found to be respectively 0.98 and 1.00 in U.K., 0.95 and 0.98 in Austria, 0.93 and 0.94 in Jamaica, 0.93 and 0.95 in Finland, 0.96 and 0.97 in USA, 0.95 and 0.97 in Canada[4,13,20,21].

An interesting point is that 2D:4D in Greek men is lower than 2D:4D of women in Greece, UK and Austria, but it is higher than 2D:4D of women in Jamaica and Finland, and equal to 2D:4D of women in USA and Canada – although 2D:4D of women in Jamaica, Finland, USA and Canada is higher than the corresponding 2D:4D of men in these countries. It seems that females in some ethnic groups may have a lower 2D:4D ratio than males of other ethnic groups, although men have a lower 2D:4D than women within the same population.

The 2D:4D ratio in Zulu (0.95) and Sardinian (0.98) was found to be equal in men and women[13], that is it did not present sexual dimorphism, which is contrary to all other findings from studies on other ethnic groups, in which the 2D:4D ratio was found to be sexually dimorphic. This difference in Zulu and Sardinian, may be explained by ethnic or geographical or environmental differences, which may be related to different prenatal estrogen and testosterone influence on finger development.

Another interesting point is the exceptionally high mean 2D:4D ratio in Danish men (1.02), implying a high degree of feminization[22]. This finding is consistent with the previously reported low sperm quality and quantity and high incidence of testicular cancer in Denmark[23]. In any case, this very high, feminized 2D:4D in Danish men is very interesting, as mean 2D:4D ratio larger than unity for men was never observed in more than 80 reports, with samples from more than 25 different countries or ethnic groups from five continents. In fact, not even female samples with a mean 2D:4D as high as 1.02 are known[24]. As for evidence from countries in proximity to Denmark, male mean 2D:4D levels are 0.93 in Finland, 0.95 in Sweden, 0.95 in Lithuania, 0.955 in Belgium, 0.96 in Germany and 0.99 in Poland[6,24–27].

The cause of between–population variation in sexually dimorphic traits, such as the digit ratio, is certainly puzzling. Rushton's theory supposes that populations closer to the equator are relatively more masculinized in utero and have higher adult testosterone levels[19]. Based on this theory, one might expect to find low digit ratios near the equator and progressively higher digit ratios in populations farther away from it. Indeed, Caucasians tend to have higher 2D:4D ratios than native Africans. On the other hand, Manning's theory suggests that populations in middle latitudes may have higher 2D:4D ratios compared to populations nearer to the equator or nearer to the poles[6]. According to a recent study[28], hypotheses related to latitude were rather excluded as a cause of 2D:4D differences in ethnic groups, making differences in gene pools a plausible explanation.

Beyond any dispute and controversy[29], 2D:4D ratio is a biometric marker that turns to become very useful for the prevention and prognosis of diseases that are dependent on sex hormones. Previous studies have detected correlation of 2D:4D ratio to myocardial infarction and breast cancer[2].

It has been shown that male survivors of myocardial infarction have lower testosterone and higher estradiol levels than age-matched controls[30–34]. Incipience of coronary heart disease may be traced in prenatal life. First-trimester exposure to estrogen and progesterone may lead to cardiovascular anomalies such as ventricular septal defect, atrial septal defect, pulmonic stenosis, patent ductus arteriosis and transposition of the great vessels[35,36]. Thus, high 2D:4D ratios in men are likely to be correlated with premature myocardial infarction and to a better prognosis after myocardial infarction[2].

It has been suggested that exposure to high levels of estrogens in utero is a risk factor for subsequent breast cancer[37,38]. Manning suggested that 2D:4D may be positively associated with breast cancer risk. Women with a high 2D:4D ratio may present breast tumours earlier than women with a low 2D:4D ratio, and prognosis may be worse for women in the former group[2].

2D:4D ratio has attracted attention, since it was realized that it is influenced by prenatal estrogen and testosterone levels in utero[1], and it may predict disease predisposition[2]. Although many studies on 2D:4D have been carried out during the last decade, studies on the other digit ratios are very limited[39–43]. In our study we found that the other digit ratios are also sexually dimorphic: they are lower in men than women. The difference in digits ratio between sexes was statistically significant for all digit ratios of the right hand and for the 2D:3D and 2D:5D ratio of the left hand. Thus, the sexual dimorphism of digit ratios is stronger for the right than for the left hand, with the exception of 2D:3D ratio, which presents a higher sexual dimorphism in left hand. In the left hand, the 2D:3D ratio presents the highest sexual dimorphism of all digit ratios, even higher than that of 2D:4D. It seems possible that the 2D:3D ratio could serve as a better sexually dimorphic biomarker than 2D:4D for the left hand.

Until now, 2D:4D has been studied as a biomarker of masculinization or feminization and as a prognostic factor for disease predisposition and progress. It seems possible that other digit ratios, like 2D:5D for the right hand and 2D:3D for the left hand, could also serve as prognostic markers. The study of 2D:4D and other digit ratios, as well as their variation among population groups and among individuals, may serve as a useful tool for establishing their value as biomarkers. 2D:4D and other digit ratios appear to be attractive anthropometric traits that probably deserve attention by clinicians.

In our study, which is the first study of 2D:4D and other digit ratios in Greece, we found that 2D:4D ratio of both hands was significantly higher in women than in men in the sample of Greek population examined. This finding is in agreement with similar observations in other ethnic groups and supports the consistency of the sexual dimorphism of 2D:4D across ethnic groups. The other digit ratios were also found to be higher in women than in men. Their sexual dimorphism was statistically significant for all digit ratios of the right hand and for the 2D:3D and 2D:5D ratio of the left hand. Our results support the lateralized character and sexual dimorphism of digit ratios. The variation of digit ratios and their patterns of laterality and sexual dimorphism among population groups could be attributed to different digit pattern expression, which may reflect differences in the influence of genetic or environmental parameters.

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EPIDEMIOLOŠKA STUDIJA SPOLNOG DIMORFIZMA OMJERA DRUGOG I ČETVRTOG PRSTA (2D:4D) I OMJERA OSTALIH PRSTIJU U GRČKOJ POPULACIJI

S A Ž E T A K

Omjer drugog i četvrtog prsta (2D:4D) je primjer biometričkog markera spolnog dimorfizma, ovisnog o prenatalnim razinama estrogena i testosterona in utero, a genetički određenog od HOX gena. 2D:4D pokazuje populacijsku varijaciju, koja je, čini se, ovisna o geografskom položaju i etničkom podrijetlu i može odražavati razlike u prenatalnim razinama steroidnih hormona između različitih etničkih grupa. U svjetlu njihove kliničke važnosti, ova studija proučava 2D:4D omjer kao i omjer ostalih prstiju u grčkoj populaciji. Slučajnim odabirom određen je uzorak od 60 grčkih muškaraca i 60 žena (dobni raspon 19–25 godina). Duljina prstiju mjerila se 2 puta pomoću elektroničkog kalipera (preciznost 0,01 mm). Svi ispitanici potpisali su pristanak na sudjelovanje u studiji koja je odobrena od strane etičkog povjerenstava fakulteta. Osobe sa ranijim ozljedama ruku, endokrinopatijama i kromosomskim abnormalnostima isključene su iz studije. Biostatističke analize provedene su korištenjem statističkog paketa SPSS. Muškarci su imali niži 2D:4D omjer (0,974 ± 0,035 za desnu i 0,973 ± 0,044 za lijevu ruku) nego žene (1,002 ± 0,04 za desnu ruku i 1,001 ± 0,045 za lijevu ruku). Ova razlika u 2D:4D omjera među spolovima statistički je bila značajna ($P<0,0001$ za desnu ruku i $P<0,001$ za lijevu ruku). Omjer ostaliih prstiju također je bio niži kod muškaraca nego kod žena za obje ruke: ova razlika je bila statistički značajna za omjer svih prstiju desne ruke i za omjer drugog i trećeg (2D:3D) i omjer drugog i petog (2D:5D) prsta lijeve ruke. Omjeri prstiju razlikuju se s obzirom na spol i lijevu i desnu stranu kod grčke populacije. Spolni dimorfizam omjera svih prstiju uz iznimku (2D:3D) veći je kod desne ruke.