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Human Sexual Dimorphism in 2D:4D Digit Ratio & Brain Sex: Hormones vs. Genes.

Saad, M. Saleh.

Biology Department /College of Education/Iraqi University/Baghdad

Summary:

In human hands, the relative lengths of the second (2D, or index) finger and fourth (4D, or ring) finger differ between males and females. The ratio of 2D length to 4D length known as the 2D:4D ratio, & its value is < 1 for most men and ≥ 1 for most women. This sexually dimorphic character of the limb was linked to sex steroids &genes. Fetal brain on the other hand develops in the male direction (during the intrauterine period) through a direct action of testosterone on the developing nerve cells, or in the female direction through the absence of this hormone surge. The objective of this study is to search whether there is any relationship between brain sex as determined by standard scientific brain sex tests & the 2D:4D ratio by measuring the length of index & ring fingers in human hands. A sample of 150 individual (80 male &70 female) aged 20-25 years old was tested in this study. The results showed a high significant difference in 2D:4D ratio between male & female(X^2= 42.75, P< 0.001, 1df.), & the masculine brain sex score was more obvious in males with low 2D:4D digit ratio in comparison with females (X2 = 6.653, P< 0.05, 1df.).The mean brain score in males with longer 2D than4D (10.33 ±2.000) is set near the lower border of the feminine brain score (10.70 ±2.115) with a significant statistical difference (X2=8.972,P<0.05, 1df.).

Keyword: *Brain Sex, hand finger, male, female*

Introduction:

The relative lengths of the 2nd & 4th finger in human hand differ between male & female (Fig-1). The 2nd digit (index finger, 2D) is usually shorter than the 4th digit (ring finger,4D) in males & the digit 2D:4D ratio for most men is <1, whereas in females the index finger is generally equal or longer than the ring finger& hence the 2D:4Dratio is ≥1. This sexually dimorphic character of the human forelimb were noticed before more than 120 years ago [1].

The subsequent studies & researches indicate that this sex difference exist in two years old children [2] & may be established prenatally by the 13th or 14th week post conception [3][4]. Sexual dimorphism in 2D:4D ratio is thought to be due to exposure to high prenatal androgens & low estrogens that produce a low 2D:4D ratio in males. These assumptions were supported by the studies of males & females with congenital adrenal hyperplasia (CAH) which is characterized by the overproduction of prenatal androgens.

Corresponding Address:
Saad, M. Saleh
Biology Department /College of Education/Iraqi University/Baghdad
Email: drsaadalobaidy@yahoo.com

Another evidence that (CAH) associate with lower 2D:4D ratio (more masculine) in both sexes was offered[5],[6] especially in the right hand [7].The above studies led to the hypothesis that a low 2D:4D ratio reflects embryonic exposure to a high levels of testosterone, whereas high 2D:4D ratio reflects a prenatal environment low in testosterone [8]. In mice this ratio is controlled by the balance of androgen to estrogen signaling during early digit development. Androgen receptors (AR) & estrogen receptor α (ER-α) activity is higher in digit 4 than in digit 2. Inactivation of (AR) decreases growth of digit 4 which leads to a higher 2D:24 ratio (as in females), whereas inactivation of (ER-α) increases growth of digit 4 which leads to a lower (2D:4D) ratio (as in males) . Androgen & estrogen differentially regulate the network of genes (such as Fgfr2,Sox9, Col10 a1,Col4 a2,& Col12 a1) that control chondrocyte proliferation in specific digits or even specific phalanges leading to a differential growth of digit4 in males & females[9].Human fibroblast growth factor receptors (FGFRs) exist as a gene family of 4 membrane bound receptor tyrosine kinases (FGFR1-4) that mediate signals of at least 22 fibroblast growth factors (FGF1-22).FGFs/FGFRs play important roles in multiple biological processes, including mesoderm induction and patterning, cell growth and migration, organ formation and

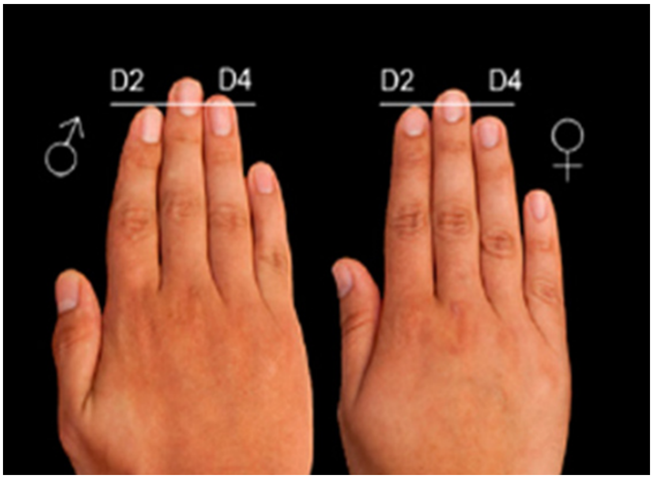

Figure-1: Human Hands,male(L) 2D:4D <1.female(R) 2D:4D≥ 1

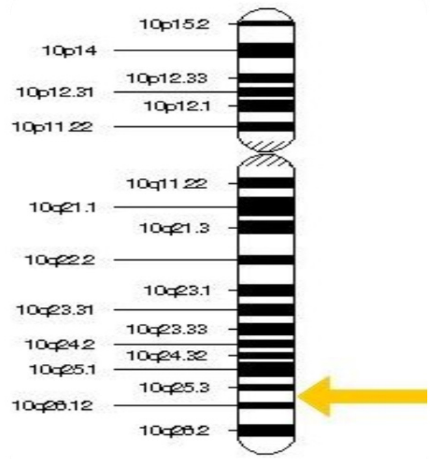

Figure 2: Cytogenetic Location of FGFR2 gene on the long (q) arm of chromo. 10 at position 26

bone growth (Figure-2) [10]. Another studies in the field of developmental neurology highlight the key role of testosterone as a major factor in determining brain sex [11],[12]. During the intrauterine period, the fetal brain develops in the male direction through a direct action of testosterone on the developing nerve cells, or in the female direction through the absence of this hormone surge [13]. The action of testosterone together with the genes responsible for sexual differentiation of the brain (such as PCD H11x) at different levels in the brains of male & female causing the decision of gender identity (the conviction of belonging to the male or female gender)[14],[15]. The global geneticist conduct 65 study on the role of testosterone in sex determination as these studies have given a decisive proof that this hormone is the key to the development of the brain sex to a male sex or female . In the sixth week of pregnancy which follows , is determined by the amount of the final gender male hormone testosterone in the womb .If the embryo is female (XX) & do not exposed to a considerable amount of this hormone in the womb the fetus will be female in terms of appearance and the brain together . If the female embryo exposed to a small amount of this hormone , the result would be female body with male brain . While the exposure of embryo to a large amount of the male hormone lead to a male body & male brain although they originally contain female chromosomes XX, with the launch of this hormone "instruction" to the body of the fetus not to develop a female genital[16].

Experimental studies on animals revealed that the human male neonate testosterone produced by testes prenatally takes the main role in the irreversible masculinization of the brain i.e. creation of the difference vs. female brain [17]. Sex determination is the commitment of an organism toward male or female & it's endpoint is reproductive structure. In fact there could be many different endpoints to sex determination leading to differences between the sex: brain sexual differences, behavioral differences,& susceptibility to disease [18].

The objective of this study is to search whether there is any relationship between brain sex as determined by standard scientific brain sex tests & the 2D:4D ratio by measuring the length of index & ring fingers in human hands.

Subjects & Methods:

This study was conducted among college students during the period from October through December 2013. A random sample of students from the College of Education-Iraqi University represented by 150 individual of both sexes (80 males , 70 females) aged between 20-25 years old were tested. The length of index finger and ring finger on both hands were measured using a small ruler starting from the line located at the base of the finger (in the palm of the hand) up to it's end (Fig-1). The data had been recorded in the questionnaire developed by the College of Mind fields /University of Nottingham/2010[19],[20],[21],&[22]. It contains information about: sex, age, handedness, name (optional), & the 2D:4D ratio. The participants after taking their permission to participate in the study were asked to answer twenty questions by yes or no (option) in the questionnaire for brain sex determination. Answers was given a numerical weight to each question, gives a whole which ranges (between 1-20 points).Those who have access (1-10) point have a male brain sex while those with(10-20) point have a female brain sex. The results were expressed as mean ± SD (standard deviation) or proportion (%).The categorical variables were compared by using Chi-square test.

Results & Discussion:

The results (Table-1) showed the number of individuals who have a shorter index finger than ring finger ; individual who have an equal (or longer) index to ring finger, and the mean brain sex score in each category for both sexes of the research sample.

Table 1: Summary rates along the index to ring finger & brain sex scores in the research samples.

	2D shorter than 4D				**2D longer(or equal)than 4D**			
	brain sex score				**brain sex score**			
Sex & No.	**No.**	**%**	**Mean ±**	**SD**	**No.**	**%**	**Mean ±**	**SD**
Male (80)	**71**	**88.75**	**8.55**	**2.285**	**9**	**11.25**	**10.33**	**2.000**
Female (70)	**23**	**32.86**	**10.13**	**2.007**	**47**	**67.14**	**10.70**	**2.115**
Total (150)	**94**	**62.67**			**56**	**37.33**		

2D= Index finger. 4D =Ring finger.

Three chi-square tests were conducted from this table as follow:

1-Sexual dimorphism in the 2D:4D ratio:

The percentage of males who had a shorter index finger are 88.75 % of the male sample, compared to32.86 % of the female sample . This result means that the shortness of the index finger compared to ring finger is more common in the males than in females with a highly significant statistical difference (X^2= 42.75,P< 0.001,1df.). This difference proves that there is a clear sex difference in the length of the index finger between male & female hands (Table1-a).

Table-1a : Result of comparison between 2D:4D ratio in male & female samples.

Sex	2D < 4D	2D ≥ 4D	Total
Male	71	9	80
Female	23	47	70
Total	94	56	150

(X^2= 42.75, P<0.001,1df.)

2-The Brain Sex Scores in individual with shorter Index finger (2D) than ring finger (4D):

The mean brain sex score (point) of males (8.55) was set within masculine brain sex limits (1-10 point),while in the females (10.13) set near the lower limits of the feminine brain sex (10-20 point).The Chi-square value (X2=6.653,P<0.05,1df.) showed significant difference & indicate that the relationship between brain sex score & shortness of ring finger in males is significantly higher than what is found in females (Table-1b).

Table-1b: Brain Sex Scores & Index Finger (2D) shorter than ring finger (4D).

sex	2D<4D	Brain Score	Total
male	71	8.55	79.55
female	23	10.13	33.13
total	94	18.68	112.68

(x2=6.653, P< 0.05,1df.)

3-The brain sex scores in individual with longer (or equal) index finger (2D) than ring finger (4D) :

The mean brain sex score in both, males (10.33) & females (10.70) of this category was set within feminine brain sex limits. Chi-square value also showed significant difference between longer index finger with brain sex in females & males (Table-1c).

Table-1c: Brain Sex Scores & Index Finger (2D) longer than ring finger (4D).

sex	2D>4D	Brain Score	Total
male	9	10.33	19.33
female	47	10.70	57.70
total	56	21.03	77.03

($x2=8.972$, $P< 0.05$, 1df.)

Search results are compatible with most current literature that mentioned over the literature's review of the prevalence of low 2D:4D digit ratio in males in comparison with that in females. The most plausible explanation for this situation (especially with the existence of significant statistical sex differences) is what is referred to the theory of hormones. Scientific studies had confirmed the role of the sexual hormones in the early stages of early embryonic capita in determining the length of the index finger. The finger bud affected by feminine hormone and not the male one's . The higher exposure of the fetus in the early stages to a larger amount of the masculine hormone the greater the length of the ring finger (with shorter index finger) and vice versa.

On the other hand masculine hormone plays a role in determining the features of anatomical and functional properties of the brain and thus determine the sex of the brain (as fore mentioned), and here we find that the degree of correlation between short index finger and brain sex of the males is higher than it was in females

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الثنائية الشكلية الجنسية للنسبة الاصبعية 4:2 وجنس الدماغ في الانسان: الهورمونات مقابل الجينات

سعد محمد صالح

قسم علوم الحياة – كلية التربية – الجامعة العراقية – بغـــداد

الخلاصة:

تتميز اليد البشرية بأن النسبة بين أطوال اصبعي السبابة (الثاني) والبنصر (الرابع) في اليد تختلف بين الذكور والأناث، ويشار الى النسبة بين طول السبابة الى البنصر اصطلاحا بالنسبة الاصبعية 4:2، وان اصبع السبابة يكون اقصر من اصبع البنصر عند اغلب الرجال و بهذا فان قيمة النسبة الاصبعية تكون (< 1) ، بينما يكون مساويا او أطول من البنصر عند اغلب النساء ،فتكون قيمتها لديهن (≥ 1). لقد عزي سبب هذه الثنائية الشكلية الجنسية الى الهورمونات الستيرويدية الجنسية والجينات الـــــــــوراثية، حيث أن نمو الدماغ في المرحلة الجنينية يتكشف بالاتجاه الذكري من خلال التأثير المباشر لهورمون التستوستيرون على الخلايا العصبية فيه ، أو بألاتجاه الانثوي عند غياب الوفرة من هذا الهورمون.

ان الهدف من الدراسة الحالية هو البحث عن وجود اية علاقة بين جنس الدماغ (ذكريا او انثويا) كما يحدده الاختبار القياسي لجنس الدماغ ، والنسبة الاصبعية 4:2 المحددة بقياس طول اصبعي السبابة والبنصر. لقد تم اختيار عينة عشوائية من الافراد تعدادها 150 فردا من كلا الجنسين (80 ذكور و 70 اناث) تتراوح أعمارهم بين 25-20 عاما، وتم اجراء قياس اطوال الأصابع واختبار جنس الدماغ لهم.

في مجال النسبة (X^2= 42.75, P< 0.001,1df.) لقد اظهرت النتائج وجود فـــــروق احصائية معنوية الاصبعيـــــــة بين الذكور والاناث، وان معدل درجات جنس الدماغ الذكري يكون اكثر وضوحا في الذكور ذوي (X2=6.653,P<0.05,1df.)اصبع السبابة الأقصر عما هو عليه في الاناث وبفرق معنوي

فانه يقـــــع (10.33 ±2.000) اما بالنسبة لمعدل درجات جنس الدماغ لدى الذكور ذوي السبابة الأطول ضمن الحدود الدنيا لدرجات جنس الدماغ الانثوي مع وجود فرق معنوي عند مقارنته بمعدل جنس الدمــــــاغ (X2=8.972,P<0.05,1df.) لدى الاناث ذوات السبابة الأطول.