DOI: 10.7860/JCDR/2016/21952.9000

Short Communication

Physiology Section

2D:4D Ratio and its Implications in Medicine

SARAVANAKUMAR JEEVANANDAM[1], PRATHIBHA K MUTHU[2]

ABSTRACT

Digit ratios, especially 2D:4D ratio, a potential proxy marker for prenatal androgen exposure shows sexual dimorphism. Existing literature and recent research show accumulating evidence on 2D:4D ratio showing correlations with various phenotypic traits in humans. Ratio of 2D:4D is found to correlate negatively to testosterone and positively to oestrogen in the foetus. Interestingly, it is constant since birth and not influenced by the adult hormone levels. Usually, males have lower ratios when compared to females. Prenatal androgen exposure and therefore, digit ratios have been reported to be associated with numerical competencies, spatial skills, handedness, cognitive abilities, academic performance, sperm counts, personalities and prevalence of obesity, migraine, eating disorders, depression, myopia, autism etc. The authors have attempted to write a brief account on the digit ratios and the dimorphism observed in various physiological, psychological and behavioural traits. Also, the authors have discussed the relevant molecular basics and the methods of measurement of digit ratios.

Keywords: Digit ratio, Prenatal androgen, Testosterone, Vernier calipers

INTRODUCTION

Digit ratio is the ratio of length of different digits or fingers typically measured from the mid-point of bottom crease where the fingers join the hands to the tip of the fingers. However, most commonly, digit ratios indicate only 2D (index finger):4D (ring finger) ratios [1]. Digit ratio is a sexually dimorphic trait found in a variety of species ranging from humans and mice to zebra finches and is constant since birth [2]. Variations have been reported in different ethnic and geographic groups. The ratios vary among different ethnic groups which is far larger than different between the sexes [3]. Measures of 2D:4D from various ethnic groups were done by Manning et al., and it was shown that in addition to the significant sexual dimorphism in 2D:4D, the mean ratios varied between the English, Scottish, Uygur, Han and Jamaican children [3,4]. Another study on children showed higher ratios among the Caucasians when compared to the Blacks and the Hans ethnicity of China [5]. Studies in South Indian Population have also identified the sexual dimorphism in 2D:4D ratios [6].

Digit ratio is reported to be influenced by the prenatal androgen exposure to the foetus. Analysis of amniocentesis samples have shown that the digit ratio is negatively correlated to prenatal testosterone, but positively to oestrogen exposure [7]. In other words, a foetus with more exposure to testosterone is expected to have lower (masculine) digit ratio. Usually, the male foetuses have a higher testosterone exposure and hence, the males always have lesser digit ratios when compared to females. Likewise, the females have lesser testosterone exposure and therefore, higher (feminine) ratios.

Evidence in support of this view comes from the presence of masculine or lower digit ratios in children with Congenital Adrenal Hyperplasia (CAH) who have higher androgen exposure and females suffering from CAH [8]. Likewise, in Klinefelter's syndrome, higher or feminine digit ratios, attributable to a low testosterone exposure have been reported [9]. Few studies have reported that maternal smoking during pregnancy elevates the prenatal testosterone and in turn is associated with low or masculine 2D:4D ratios in the children [10].

Ratio of 2D:4D (Index finger: Ring finger) has been shown to be more sensitive, despite other digit ratios (3D:5D) displaying sexual dimorphism and relationship to various human phenotypic traits [11]. Existing literature also shows accumulating evidence on 2D:4D ratio showing correlations with various traits in humans. It is thus considered to be a proxy marker of prenatal androgen exposure [12]. A longer index finger will result in a ratio higher than 1, while a longer ring finger will result in a ratio of less than 1. The second digit is typically shorter in both males and females, while the difference in length of the two digits is greater in males than females. The normal range of 2D: 4D ratios among males and females have been reported to be 0.947±0.029 and 0.965±0.026, respectively [13].

Molecular level studies have observed that prenatal testosterone is related to HOX A and HOD A gene expression. HOX A genes are highly conserved in mammals and they influence the differentiation of digits and toes. Hox A genes have also been implicated in sex determination, morphogenesis of urinogenital system, fertility and haematopoiesis [14]. This explains the sexual dimorphism pertaining to digit ratios. Further, studies have shown the influence of variations in the X- linked androgen receptor gene on the digit ratios. Ratio of 2D:4D is also affected by increased DNA replication of Cysteine-Adenine-Guanine (CAG) in the androgen receptor gene. If the alleles in the Androgen Receptor (AR) genes have more CAG, then it makes the AR gene insensitive to the testosterone while it is compensated by producing more testosterone in the embryo [15]. Interestingly, there is no correlation between digit ratio and adult sex hormone levels. It appears to be a function of androgen sensitivity, rather than the androgen concentration. This reiterates the fact that digit ratio is fairly constant from birth or late infancy onwards.

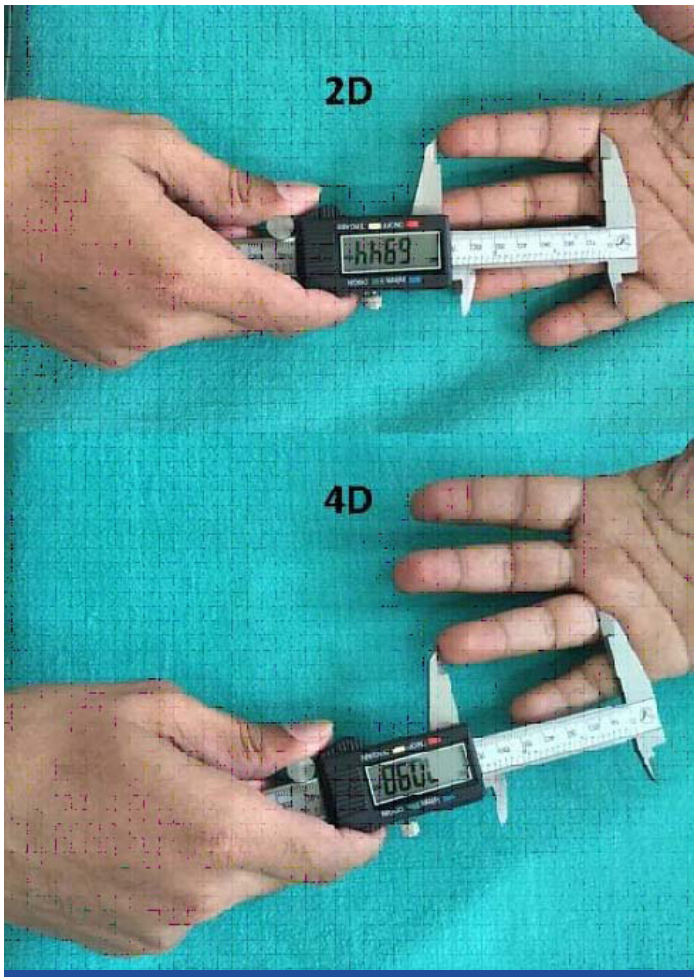
CORRELATION BETWEEN DIGIT RATIOS AND VARIOUS HUMAN TRAITS:

Inter sexual and intra sexual variations in 2D:4D ratio in humans have been observed and reported pertaining to various traits, abilities and disorders. Higher testosterone levels in utero facilitate the development of male typical characteristics and in turn inhibit the female typical characteristics. The authors have tabulated a list of sexually dimorphic traits that have shown correlation with the digit ratios [Table/Fig-1] [16-24].

Traits ranging from musical abilities, numerical and spatial skills and sporting capabilities have been reported to be associated with the digit ratios in different populations [16]. Lower or masculinised 2D:4D

Parameters	Low Digit Ratios (Masculine Ratio)	High digit Ratios (Feminine Ratio)
Physiological	Left handed preference [21-23]	Lowered sperm counts [23] Increased risk for heart disease [17] Increased risk of obesity and metabolic syndrome [17]
Pathological	Increased risk for anxiety [18]	Increased risk of depression and eating disorders [18]
Behavioural	Assertiveness in females [19-21] Aggression in males [19-21]	Numerical skills [16]
Sexual Orientation	Hetero sexual Preference [24]	Homosexual preference [24]

[Table/Fig-1]: Correlation between the digit ratios and various traits in humans [16-24].



[Table/Fig-2]: Measurement of 2D:4D ratio using digital vernier calipers.

ratios showed a relationship with better arithmetic, visual and spatial skills [16]. Males with higher or feminine digit ratio personalities are more prone to have low sperm counts, increased risk of heart disease, obesity and metabolic syndrome [17]. Also, prenatal testosterone levels have been implicated in migraine, autism, dyslexia, infertility and breast cancer [17].

Higher ratios as in females or feminine digit ratios in males showed correlation with eating disorders, anxiety and depression [18]. Low digit ratio is associated with certain characteristics like aggression in males and assertiveness in females [19]. Michelle et al., reported male vulnerability to behaviour disorders in childhood and female vulnerability to emotional disorders in adolescence [20]. It has been reported that prenatal testosterone may modulate striatally – based dopaminergic circuits and place boys at greater risk of disruptive behavioural disorders. Further, oestrogen at puberty may have certain effects on the serotoninergic pathways and place girls at greater risk for mood disorders. Men with lower (masculine) 2D:4D ratios showed lower aggression scores while men with higher (feminine) ratios scored higher on a test for depression [2,10].

Hand dominance or handedness has also been suggested to be a marker of in utero testosterone exposure and therefore few studies have explored the relationship between the 2D:4D ratio and the handedness of an individual. Nevertheless, the data has no consensus with reports showing inverse, null and direct associations with left hand dominance [21,22]. It has also been hypothesized that left hand dominance is associated with high in utero estrogen exposure, as evidenced by the increased number of left handed individuals in diethylstilbestrol (DES) exposed populations. On the contrary, research from Manning and colleagues have linked the lower right hand 2D:4D ratio and left hand writing preference, which supports an association between high prenatal testosterone and left hand dominance [23].

MEASUREMENT OF DIGIT RATIOS

Digit ratios have been measured by different techniques - by using vernier calipers, photographs of the hands and scanning the hands. The authors have briefly summarized the techniques, advantages and disadvantages of each of the above mentioned methods.

Digital Calipers

The lengths of second digit (index finger) and fourth digit (ring fingers) are measured from the fingertip to the midpoint of the basal crease, on the ventral surface of the hand, using digital vernier calipers [Table/Fig-2]. The 2D:4D ratio is obtained by dividing these values. Usually, two or more measurements are taken to ensure reliability [25]. The mean of the multiple measurements are taken for right and/or left hand and divided for the calculation of 2D:4D ratio of the right and left hands separately. It has been argued that the right digit ratio is more differentiated and sensitive to prenatal testosterone exposure, while others report an averaged 2D:4D ratio across both hands [26,27].

Role of X-Rays

X-rays have also been used for the measurement of the digit ratio in few studies. But there is always an ethical consideration with regard to exposure to radiations.

Using Photographs

Digit ratio can also be measured by indirect techniques such as photographs of the hands. Photographs are taken using a digital camera with the hand held in supination and fingers completely extended [28]. The length of the fingers can be subsequently measured directly or by using image editing software [27].

Using Photocopies

Digit ratios can also be measured by taking the photocopies of the hands. Few studies have reported that the 2D:4D ratio obtained from the photocopies tend to be lower than the values obtained from direct measurements [29]. The differences in the lengths of 2D tend to be shorter or equal in length when compared to direct measurements; whereas, the values of 4D will be longer or equal in length in comparison to the direct measurements. Digit ratio values obtained from the photocopies and direct measurements cannot be used in comparative trials or in one single study. The difference in values from these two techniques could be attributed to the shapes of the fat-pads at the tips of the fingers.

Using Scanners

Direct measurement and photocopies are reported to be of lesser accuracy and therefore, use of digital scanners came into vogue (e.g., Visioneer One Touch 9220 Scanner) [29,30]. Flat-bed scanners are appropriate tools in terms of precision, practicality and costs involved. The subject is asked to place both the hands on the scanner with all the fingers in both the hands, straight and visible. Prior to scanning, small marks are drawn on the basal creases of the index and ring finger, in order to increase the accuracy. Using

image editing softwares (e.g., Adobe Photoshop) the adjustment of contrast, brightness and size can be done. It can also be measured by using GNU Image Manipulation Program (GIMP) measure tool [25]. Also, prints of the scanned images can be taken; on which direct measurements are made using calipers [30]. The major disadvantage of this technique is improper placement of hands on the scanner (e.g., pressing too hard - there should be some gap between the scanner and the hands) or show their finger prints. Moving the hands also result in blurred images.

CONCLUSION

Digit ratio is sexually dimorphic and can be used as window for in utero exposure to androgens, especially testosterone. 2D:4D ratio has been shown to differ in all sexually dimorphic traits. However, there is no consensus on the intra-sexual and inter-sexual variations in digit ratios and traits across various ethnic groups. The recent surge in the number of studies on digit ratios, especially in India may open more avenues to be explored in this regard. More robust studies on large samples can help us establish meaningful associations between digit ratios, prenatal androgen exposure and sexually dimorphic traits.

REFERENCES

[1] Mayhew TM, Gillam L, McDonald R, Ebling FJ. Human 2D (index) and 4D (ring) digit lengths: their variation and relationships during the menstrual cycle. *Journal of Anatomy.* 2007;211(5):630-38.

[2] Bailey Allison A, Hurd PL. Depression in men is associated with more feminine finger length ratios. *Personality and Individual Differences*. 2005;39(4):829-36.

[3] Manning JT, Stewart AG, Bundred P, Trivers R. Sex and ethnic differences in 2nd to 4th digit ratio of children. *Early Human Development.* 2004;80(2):161–68.

[4] Knickmeyer RC, Woolson S, Hamer RM, Konneker T, Gilmore J. 2D:4D ratios in the first 2 years of life: stability and relation to testosterone exposure and sensitivity. *Hormones and Behavior*. 2011;60(3):256–63.

[5] Xi H, Li M, Fan Y, Zhao L. A comparison of measurement methods and sexual dimorphism for digit ratio (2D: 4D) in Han ethnicity. *Archives of Sexual Behavior*. 2014;43(2):329-33.

[6] Jacob M, Avadhani R, Nair B, Nallathamby R, Soman MA. Cross sectional study of second and fourth digit ratio with physical attributes in South Indian population. *Int J Anat Res*. 2015;3(2):1133-37.

[7] Rebecca B, Benson PJ. Digit ratio (2D: 4D) and the spatial representation of magnitude. *Hormones and Behavior*. 2006;50(2):194-99.

[8] Ciumas C, Lindén Hirschberg A, Savic I. High fetal testosterone and sexually dimorphic cer-ebral networks in females. *Cereb Cortex*. 2009;19(5):1164–72.

[9] McAnulty RD, Michele Burnette M. (2006) Sex and sexuality, Volume 1, *Greenwood Publishing Group*, pp.165

[10] Coyne SM, Manning JT, Ringer L, Bailey L. Directional asymmetry (right–left differences) in digit ratio (2D: 4D) predict indirect aggression in women. *Personality and Individual Dif-ferences*. 2007;43(4):865-72.

[11] Trivers R, Manning J, Jacobson A. A longitudinal study of digit ratio (2D: 4D) and other fin-ger ratios in Jamaican children. *Hormones and Behavior*. 2006;49(2):150-56.

[12] Milagros E, Alexander GM. Anxiety, sex-linked behaviors, and digit ratios (2D: 4D). *Archives of Sexual Behavior*. 2009;38(3):442-55.

[13] Loehlin JC, Medland SE, Martin NG. Is CAG sequence length in the androgen receptor gene correlated with finger-length ratio? *Personality and Individual Differences*. 2012;52(2):224-27.

[14] Zhang C, Dang J, Pei L, Guo M, Zhu H, Qu L, et al. Relationship of 2D: 4D finger ratio with androgen receptor CAG and GGN repeat polymorphism. *American Journal of Human Biology*. 2013;25(1):101-06.

[15] Romano M, Leoni B, Saino N. Examination marks of male university students positively correlate with finger length ratios (2D:4D). *Biological Psychology*. 2006;71(2):175-82.

[16] Luxen MF, Buunk BP. Second-to-fourth digit ratio related to verbal and numerical intelli-gence and the Big Five. *Personality and Individual Differences*. 2005;39(5):959-66.

[17] Oyeyemi BF, Iyiola OA, Oyeyemi AW, Oricha KA, Anifowoshe AT, Alamukii NA. Sexual dimorphism in ratio of second and fourth digits and its relationship with metabolic syndrome indices and cardiovascular risk factors. *Journal of research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*. 2014;19(3):234.

[18] Manning JT, Kilduff LP, Trivers R. Digit ratio (2D: 4D) in Klinefelter's syndrome. *Andrology*. 2013;1(1):94-99.

[19] Hampson E, Sankar JS. Re-examining the Manning hypothesis: androgen receptor polymor-phism and the 2D: 4D digit ratio. *Evolution and Human Behavior*. 2012;33(5):557-61.

[20] Martel MM, Klump K, Nigg JT, Breedlove SM, Sisk CL. Potential hormonal mechanisms of attention-deficit/hyperactivity disorder and major depressive disorder: a new perspective. *Hormones and Behaviour*. 2009;55(4):465-79.

[21] Trabert B, Graubard BI, Erickson RL, Zhang Y, McGlynn KA. Second to fourth digit ratio, handedness and testicular germ cell tumors. *Early Human Development*. 2013;89(7):463-66.

[22] Lust JM, Geuze RH, Van de Beek C, Cohen-Kettenis PT, Bouma A, Groothuis TG. Differential effects of prenatal testosterone on lateralization of handedness and language. *Neuropsychology*. 2011;25:581–89.

[23] Manning JT, Peters M. Digit ratio (2D:4D) and hand preference for writing in the BBC Internet Study. *Laterality*. 2009;14:528–40.

[24] Galis F, Ten Broek CM, Van Dongen S, Wijnaendts LC. Sexual dimorphism in the prenatal digit ratio (2D: 4D). *Archives of Sexual Behavior*. 2010;39(1):57-62.

[25] Bailey AA, Hurd PL. Finger length ratio (2D: 4D) correlates with physical aggression in men but not in women. *Biological Psychology*. 2005;68(3):215-22.

[26] Brown WM, Hines M, Fane BA, Breedlove SM. Masculinized finger length patterns in hu-man males and females with congenital adrenal hyperplasia. *Hormones and Behavior*. 2002;42(4):380-86.

[27] Mathangi K, Mathangi DC, Shyamala R. Finger Digit Ratio as a Predictor of Motor Skill in Children. *Journal of Clinical Research Letters*. 2012;3(1):24-6.

[28] Krishnakumar M, Atheeshwar S, Chandrasekar MD. Myopia and digit ratio in medical college students. *PloS one*. 2014;9(2), http://dx.

[29] Manning JT, Fink B, Neave N, Caswell N. Photocopies yield lower digit ratios (2D: 4D) than direct finger measurements. *Archives of sexual behavior*. 2005;34(3):329-33.

[30] Evardone M, Alexander GM. Anxiety, sex-linked behaviors, and digit ratios (2D: 4D). *Archives of sexual behavior*. 2009;38(3):442-55.

PARTICULARS OF CONTRIBUTORS:

1. Student, Saveetha Medical College and Hospital, Thandalam, Chennai, India.
2. Associate Professor, Department of Physiology, Saveetha Medical College and Hospital, Thandalam, Chennai, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Prathibha K Muthu,
E 25, Staff Quarters, Sri Ramachandra Medical College, Porur- 600116, Chennai, India.
E-mail: drmuthuprathi@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 09, 2016**
Date of Peer Review: **Jul 25, 2016**
Date of Acceptance: **Sep 20, 2016**
Date of Publishing: **Dec 01, 2016**