ORIGINAL RESEARCH

Reverse Sexual Dimorphism in Digit Ratios Detected in Down Syndrome

Suresh Bidarkotimath,[1] Ramakrishna Avadhani,[2] Viveka S,[3] Arunachalam Kumar[4]

AbstractBackground: Down syndrome being the major common cause of mental retardation in children is most commonly studied for chromosomal anomalies. The sexual abnormalities in it include undescended testis, and late sexual maturity. It has been proven that the androgen levels in children and adults with this syndrome are low.

Study Purpose/Objectives: To establish the androgen levels in early perinatal period the digit ratio can be used. Digit ratio is the ratio between the length of 2nd finger and 4th finger as measured form the bases of digit to their tip. Digit ratios are shown to be sexually dimorphic.

Methods: We analyzed the digit ratios of 23 Down syndrome patients which included 13 males and 10 females and compared it with the age related control group of 50 children.

Results and Mean Findings: We found that the ratios are sexually dimorphic in Down syndrome patients [The mean of 2D:4D ratios of males right hand was 0.961 (SD 0.042) and left hand was 0.977 (SD 0.067). The mean of 2D:4D ratios of females right hand was 0.90 (SD0.053) and left hand was 0.939 (SD 0.075)] and they are statistically different from the control group. The ratios in females are found to be significantly lower than the males, which is contrary to the normal population.

Conclusions: It is hypothesized that the perinatal androgen levels is lower in the Down syndrome fetuses, which may intern responsible for the delayed sexual features in males.

Keywords: digit ratio (http://ijfpr.org/tag/digit-ratio), down syndrome (http://ijfpr.org/tag/down-syndrome), perinatal androgen levels (http://ijfpr.org/tag/perinatal-androgen-levels)

Contents

Current Issue (http://ijfpr.org/) 01
Volume 1, No. 1
June 2011

1 Introduction

The ratio of index finger (2D) to the ring finger (4D) length is referred as digit ratio (2D:4D). The digit ratio and its association to the human characteristics has been the focus of much research in recent years.

The digit ratios are determined by taking the lengths of the fingers from the proximal crease of the digit to their tip. [1] It has been widely accepted that the sex difference in 2D:4D ratio arises early in development and the ratios are slightly lower in males than females, making it – sexually dimorphic. This dimorphism arises due to the near equal lengths of 2nd and 4th fingers in males. [2]

Once established in early neonatal life digit ratio assumed to be stable in later life. The digit ratio has been reported to be associated with several characteristics such as fetal growth, congenital adrenal hyperplasia, developmental psychopathology, autism and Asperger's syndrome. [3] Little is known about 2D:4D ratio variations in Down syndrome patients.

Down syndrome (trisomy 21, Monglolism) is the most common chromosome disorder and single most common cause of moderate mental retardation. It is associated with impairment of cognition and characteristic facial and other dysmorphic features. It is also associated with undescended testis and delayed appearance of secondary sexual features in male children. [4]

Down syndrome children attain a significantly lesser height than their normal counterparts. [5] It has been confirmed that levels of circulating androgens as evidenced by urinary testosterone and epiandrosterone levels are low.

Though much is known about the adult androgen levels and related clinical problems, there is relative paucity of knowledge on the perinatal androgen levels in Down syndrome.

The Homeobox genes, Hox a and d control the differentiation of the urinogenital system, and may therefore indirectly influence the prenatal production of testicular androgen and development of the digits. [6] [7]

Prenatal testosterone comes from maternal testosterone, which may pass across the placenta and enter the fetal bloodstream, and from the fetus itself, which secretes increasing amounts from about 8 weeks (the time of Leydig cell differentiation) to mid-gestation. [8] [9]

From that point levels slowly decrease until a few months after birth when it has reached the low level characterizing childhood. [10] The fetal source is dependent on the differentiation of the testes. [11] Perinatal androgen levels attain maximum level at 3 – 6 months of intrauterine life and there is slight increase before delivery.

At puberty there is slow but sustained increase in the testosterone levels before attaining the adult levels. There is substantial evidence that digit ratio is established early in intrauterine life under the influence of androgens. Low androgen levels during the late intrauterine life around the time of delivery causes relative delay in the descending of testis. In this study efforts are made to find out any alterations in early perinatal androgen levels as depicted by digit ratio.

Identity from Skeletal Remains
(http://ijfpr.org/archives/192)

CASE REPORT
Homicidal Hanging – A Case Report
(http://ijfpr.org/archives/196)

MEDICAL EDUCATION
Skills of Compiling Scientific Paper for Journal Publication
(http://ijfpr.org/archives/177)

Book Reviews
(http://ijfpr.org/archives/491)

NFCFM Oration 2009
(http://ijfpr.org/archives/506)

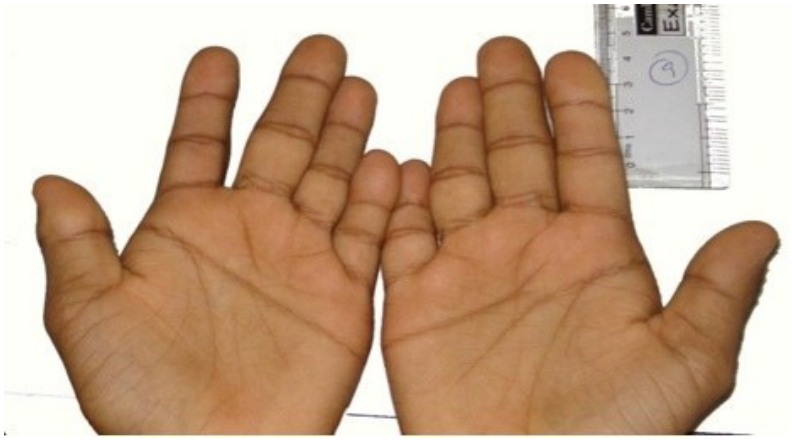
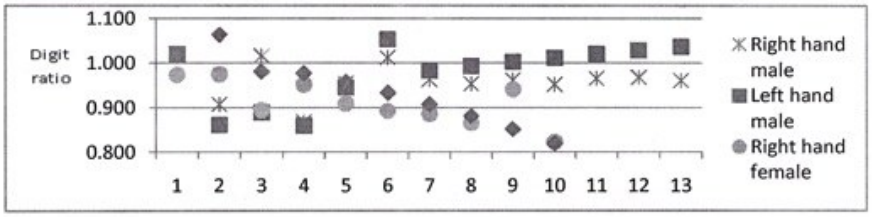
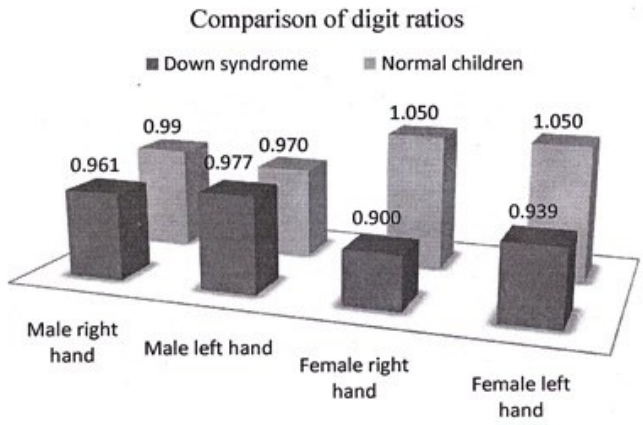


Figure 1: Hand photograph of Down syndrome patient



Graph 1: Scatter diagram showing the distribution of digit ratios of both hands of male and female Downs Syndrome patients



Graph 2: Comparison chart showing distribution of digit ratios of both hands of male and female Downs Syndrome patients

2 Materials and Method

We have selected 23 karyotypically diagnosed cases of Down syndrome (all having 21 trisomies) children from Saanidhya Center for disabled, Mangalore. All subjects were unrelated Caucasians. Their age ranged from 6 to 22 years. The digits lengths were determined by taking photographs of the hands of the selected children by using Digital camera (Sony India) with 8MP resolution, auto ISO having light background. The digit lengths were measured from the ventral proximal crease to the tip of the fingers both on ulnar and radial aspect (in order to account the sloppy proximal crease) by using 'measure tool' of Adobe Photoshop CS5. [12] Similar set of data was also taken from 50 age related normal children selected from the same school. The direct measures of digits using measuring tool like vernier calipers and measures from photocopies produce comparable 2D:4D ratios. [13] The data was tabulated and analyzed using student's t test.

3 Results

Out of 23 Downs cases selected, 13 were males and 10 were females. Repeatability of 2D:4D from all 23 hands were as follows: males (n=13) r1=0.86; females (n=10) r1= 0.92. There was significantly greater variance between subjects than within-subject error (repeated measures ANOVA: males, F=13.70, p=.0001; females, F= 23.22, p=.0001).We concluded that our

measurements represented real differences between subjects. The mean of 2D:4D ratios of males right hand was 0.961 (SD 0.042) and left hand was 0.977 (SD 0.067).

The mean of 2D:4D ratios of females right hand was 0.90 (SD0.053) and left hand was 0.939 (SD 0.075) as shown in Graph: 1 .In accord with previous workers males have statistically significant lower ratios than the females. The difference between the Down syndrome male and female patients were statistically significant (right hand $t = 42$, $p > 0.001$, left hand $t = 10$, $p > 0.001$).

The mean of 2D:4D ratios of males of age related control group was – right hand 0.990 (SD 0.020) and left hand 0.970 (SD 0.040). The mean of 2D:4D ratios of females of age related control group was – right hand 1.050 (SD 0.030) and left hand 1.050 (SD 0.030).

The difference between the males and females of control group were statistically significant (right hand $t = 8.37$, $p > 0.001$ and left hand $t = 7.94$, $p > 0.001$). There is statistical difference between the digit ratios of Down syndrome and control group in both males (right hand $t= 2.355$, $p > .001$) and females (right hand $t= 8.04$, $p > .001$).

The ratios in the right hands of Down syndrome patients are significantly lower in females (0.90) than in males (0.961). The same is true for the left hand as well. Whereas the ratios in age related normal children group is shows the opposite trend – males having significantly lower ratios than females.

4 Discussion

Digit ratio: It has been known for more than a century that males and females tend to differ in the relative lengths of their index (2D) and ring (4D) fingers. The concept of digit ratio is popularized by an evolutionary psychologist, Prof John Manning. He describes the digit ratio as a living fossil and a record of factors the fetus was exposed to at a critical time for the development of many other things. [1]

The digit ratios are sexually dimorphic and it has been proved that these ratios retain its dimorphism in infants, children and adults. A study has proved that this ratio is dimorphic even in fetuses, providing much needed support for the theory of establishment of the digit ratio in early neonatal period. [14] In males, the second digit tends to be shorter than the fourth, and in females the second tends to be the same size or slightly longer than the fourth, making 2D:4D ratios sexually dimorphic with mean male 2D:4D lower than, mean female 2D:4D. The dimorphism patterns are well recognized in laboratory animals as well as variations with different race and ethnicity. [13] [15] [16]

The differentiation of the digits is under the control of Homeobox or Hox genes (the posterior-most Hox-d and Hox-a genes), which also control the differentiation of the testes and ovaries. [17] [18]

This common control of the distal limbs and genital bud may be seen when progressive removal of posterior Hox gene results in loss of digits, genital bud derivatives, and fertility. [7] [17] It is suggested that the common control of the differentiation of the gonads and digits may mean that the functioning of the former may be reflected in the formation of the latter. [19]

Polymorphisms within Hox-d and Hox-a may therefore result in variation in gonad and digit formation and function. Patterns of 2D:4D ratios may therefore reflect aspects of gonadal function such as the production of testosterone and estrogen. [13]

Several studies have found a significant positive relationship between 2D:4D ratio and medical problems like attention deficit hyperactive disorder (ADHD) autism, aggression in males, sporting ability in females. In contrast to this, a

significant negative relationship has been found between 2D:4D ratio and physical competence. [20] [21] [22]

There is some evidence that 2D:4D ratio may also be indicative for human development and growth. Men who had an above average placental weight and a shorter neonatal crown-heel length had higher 2D:4D ratios in adult life. [23]

Moreover, studies about 2D:4D correlations with face shape suggest that testosterone exposure early in life may set some constraints for subsequent development.

Prenatal sex steroid ratios (in terms of 2D:4D) and actual chromosomal sex dimorphism were found to operate differently on human faces, but affect male and female face shapes by similar patterns. However, exposure to very high levels of testosterone and/or estrogen in the womb may have also negative effects. It has been also stated that, men with low 2D:4D ratios (indicating high testosterone) and women with high 2D:4D ratios (indicating high estrogen) express lower levels of facial symmetry. [24]

There is some evidence that testosterone facilitates the differentiation of the brain, both prenatally and postnatally. There have been many extensions of this, such as immune disease and autism are related to prenatal testosterone, this also explaining why more men are left-handed, autistic, etc. than women. [25] Prenatal exposure to testosterone is thought to promote the development of the right-hemisphere and increase the incidence of sinistrality. As such, a low 2D:4D was found to be associated with improved left-hand performance.

It has been showed that the 2D: 4D ratio in patients suffering from polycystic ovarian disease are not substantially decreased and in turn the perinatal androgen levels are not greatly elevated in them. [26]

Down syndrome hand characteristics: Among many phenotypic findings of Down syndrome the most important ones are the hand characteristics, physical traits (ear length and inter-nipple distance) and clinical findings (Brushfield spots, wide-spaced first toe, and excess back neck skin). Down syndrome is associated with many hand characteristics, which can be classified into three main categories namely hand lines, dermatoglyphics and hand morphology. [27]

Simian crease (single palmar distal transverse crease), extended proximal palmar transverse crease, single interdigital crease on 5th (and sometimes on 4th) finger are the more common hand crease characteristics. [14] [28]

Simian crease is found more than a quarter of Down syndrome patients. Other studies have indicated that the simian crease is also very significant when present only in the right hand; when present only in the left hand it is especially significant when combined with a Sydney line in the right hand. [29] [30] Simian crease incidence is increased in fetuses with Down syndrome and this Simian crease is reported in more than one third cases from India. [31]

Extended proximal transverse palmar crease (Sydney line) is again a significant sign of Down syndrome; incidence is more than 15%. Where they indicated that, the extended distal transverse crease is significant when observed in the left hand; in the right hand it is significant when combined with a simian crease in the left hand. There are reports of single flexion crease on 4th and 5th fingers. [28] [31]

Ulnar loops (especially the index finger), radial loops on the ring and index fingers, loops between the base of the index and middle finger, and/or the middle and ring fingers, hypothenar ulnar loops, whorls, or carpal loops and distally located axial triradii are the more common dermatoglyphic characteristics of Down syndrome. [14] [30]

The ulnar loops in Down syndrome tend to be vertically oriented and L-shaped with the 'open' side directed to the side of the little finger. Another common variant is, 8 or 9 ulnar loops combined with a radial loop on the ring finger or little finger.

Radial loop is most frequently seen on the ring finger (the radial loops are usually vertically oriented and L shaped – with the 'open' side directed to the side of the thumb).

A radial loop on the thumb, index finger or middle finger may not point towards Down syndrome. The 'palmar ridge line' starts in the triradius below the index finger.

In Down syndrome the path of the 'palmar ridge line' ends often just above or close to the point where the 'upper transverse crease' exits the palm. In the normal population the path of the 'palmar ridge line' is usually found completely below the 'upper transverse crease'. [26]

In Down syndrome the alignment of ridges over the distal palmar area is partly due to the short broad hand shape nearly always rather 'transverse'. This is usually indicated by the combination of a palmar ridge line which exits the palm above (or just below) the heart line, combined with another palmar ridge line which exits the palm between the pointer finger and the middle finger. Characteristic palmar axial triradius is also advocated as one of the features of this syndrome. [31] In Down syndrome quite often 3 or more triradii can be observed on the hypothenar due to the presence of various types of large loops, multiple loops, or whorls.

The morphological changes in the hand include short thumb, short and incurved little finger, brachydactyly (short fingers), broad short palm, hyper extensible joints. [29]

A low 2D:4D ratio has been reported to be correlated with an increased preference to use the left hand. Low 2D:4D ratio in children is associated with an increased risk of autism. [19]

This may be because 2D:4D ratio is itself related to high prenatal testosterone and also associated with measures of size at birth in males, sperm counts, family size, age at breast cancer presentation and age at myocardial infarction. [28] [29]

Current study of 2D:4D ratios showed that males have statistically significant lower ratios than the females, indicating the sexual dimorphism

The difference between the males and females digit ratio were substantial than compared with the difference of the same in the control group. 2D: 4D ratios in the Down syndrome group on an average are smaller in value (e.g. right hand ratios, males- 0.961 and females – 0.90) than the age related control group (right hand ratios, males – 0.99 and females 1.050) is statistically significant.

Sexual dimorphism is established in spite of brachydactyly in Down syndrome patients.

As the digit ratios of both males and females of Down syndrome patients varied significantly from the control group, it may be said that yet another factor determines the relative lengths of the digits in Down syndrome, apart from factors which decreases the lengths of all the fingers (resulting in brachydactyly).

5 Conclusions

From this study it is concluded that the digit ratio in Down syndrome is sexually dimorphic. As the digit ratios in the females with Down syndrome patients is significantly lower than the males, which is in contrast to the age related normal children and with the results of many previous works it can be stated that the perinatal androgen levels are significantly lower in Down syndrome.

The detection of the lowered digit ratio in the fetuses with suspected Down syndrome may be used as indicator of adult androgen levels and intern the secondary sexual maturity of the infant.

As the digit ratios in Down syndrome children are statistically different from the digit ratios of normal children it can also hypothesized that there can be yet another factor intervening the process of digit formation apart from the factors which brings about the uniform decrease in the digit lengths resulting in clinodactyly.

The findings in this study could help give clinical forensic scientists a better understanding of the syndrome with special relevance to the sexual dimorphic character in its presentation.

6 Acknowledgements

We thank Mr. Vasanth Kumar Shetty, Principal, Saanidhya Samarth Center, Mangalore for allowing us to conduct the study.

We extend our thanks to Dr. Ramesh Pai, Dean, A J Institute of Medical Sciences for allowing us to proceed with the study. Our thanks are also to all the children of Saanidhya Samarth Center.

7 References

1. Manning, John T. Digit Ratio: A Pointer to Fertility, Behavior and Health. New Jersey : Rutgers University Press 2002:24-40. [↩]

2. Frietson Galis, Clara M. A., Ten Broek, Stefan Van Dongen, Liliane C. D. Wijnaendts. Sexual Dimorphism in the Prenatal Digit Ratio (2D:4D). Arch Sex Behav 2010;39:57-62. [↩]

3. J.Manning, A.Stewart, P.Bundred, R.Trivers. Sex and ethnic differences in 2nd to 4th digit ratio of children. Early Human Development 2004;80(2):161-168. [↩]

4. Culley, Alvin Petersa and William. Urinary levels of testosterone and epitestosterone in down's syndrome (mongolism). Clinica Chimica Acta 1969;25(2):24-40. [↩]

5. Siegfried M. Pueschel. Adolescent Development in Males With Down Syndrome. Am J Dis Child 1985;139(3):236-238. [↩]

6. Kondo T, Zakany J, Innis J, Duboule D. Of fingers, toes and penises. Nature. 1997;390(29):10. [↩]

7. Mortlock DP, Innis JW. Mutation of Hoxa 13 in hand– foot– genital syndrome. Nat Genet 1997:179-180. [↩]

8. George FW, Griffin JE, Leshin M & Wilson JD. Endocrine control of sexual differentiation in the human. [book auth.] MJ Novy & JA Resko. Fetal endocrinology. New York : Academic Press, 1981. [↩]

9. Jamison CS, Meier RJ & Campbell BC. Dermatoglyphic asymmetry and testosterone in normal males. American Journal of Physical Anthropology 1993;90:185-198. [↩]

10. JM, Tanner. Foetus into man: Physical growth from conception into maturity. Cambridge : Harvard Press, 1990. [↩]

11. Lording DW, & Dekretser DM. Comparative ultrastructural and histochemical studies of the interstitial cells of the rat testis during fetal and postnatal development. Journal Reproduction and fertility 1972;29:261-269. [↩]

12. Christoph J. Kemper, Andreas Schwerdtfeger. Comparing indirect methods of digit ratio (2D:4D) measurement. American Journal of Human Biology 2008;21(2):188-191. [↩]

13. J.T. Manning, L. Barley, J. Walton, D.I. Lewis-Jones, R.L. Trivers, D. Singh, R. Thornhill, P. Rohde, T. Bereczkei, P. Henzi, M. Soler, A. Szwed. The 2nd:4th digit ratio, sexual dimorphism, population differences, and reproductive success:evidence for sexually antagonistic genes? Evolution and Human Behavior 2000;21:163–183. [↩]

14. Trent D.Stephens,Thomas H.Shepard.The Down syndrome in the fetus.Teratology1980;22(1):37-41. [↩]

15. Baker, F. Anthropological notes on the human hand. Am Anthropol 1888;1:51–76. [↩]

16. George, R. Human finger types. Anat Rec 1930;46:199–204. [↩]

17. Peichel, C. L., Prabhakaran, B., & Vogt, T. F. The mouse Ulnaless mutation deregulates posterior Hoxd. Development 1997;24:3481-3492. [↩]

18. Herault Y, Fradeau N, Zakany J & Duboule D. Ulnaless (Ul), a regulatory mutation inducing both loss-of-function and gain-of-function of posterior Hoxd genes. Development 1997;124:3493-3500. [↩]

19. Manning J T, Scutt D, Wilson J Lewis-Jones D I. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and levels of testosterone, LH and oestrogen. Hum Reprod 1998;13:3000-3004. [↩]

20. Manning JT, Trivers RL, Thornhill R, Singh D. The 2nd:4th digit ratio and asymmetry of hand performance in Jamaican children. Laterality 2000;5(2):121- 132 . [↩]

21. McFadden D, Westhafer JG, Pasanen EG, Carlson CL and Tucker DM. Physiological evidence of hypermasculinization in boys with the inattentive subtype of attention-deficit/hyperactivity disorder (ADHD). Clinical Neuroscience Research 2005:233–245. [↩]

22. a) Stevenson JC, Everson PM, Williams DC, Hipskind G, Grimes M, Mahoney ER. Attention deficit/hyperactivity disorder (ADHD) symptoms and digit ratios in a college sample. Am J Hum Biol 2007;19(1):41-50.b) G. Ronaldsa, D.I.W. Phillips, K.M. Godfreya, J.T. Manning. The ratio of second to fourth digit lengths:a marker of impaired fetal growth? Early human Development 2002;68(1):21-26. [↩]

23. B Fink, JT Manning, N Neave, K Grammer. Second to fourth digit ratio and facial asymmetry. Evolution and Human Behavior 2004;24(2):125-32. [↩]

24. Baron-Cohen S, Wheelwright S. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. Journal of Autism and Developmental Disorders 2004;34(2):163-175. [↩]

25. Marla E. Lujan, Terri G. Bloski, Donna R. Chizen, Denis C. Lehotay and

Roger A. Pierson. Digit ratios do not serve as anatomical evidence of prenatal androgen exposure in clinical phenotypes of polycystic ovary syndrome. Human Reproduction 2010;25(1):204-211. [↩]

26. A. Rex, M. Preus. A diagnostic index for Down syndrome. The Journal of Pediatrics 1982;100(6):903-906. [↩]

27. G, Purvis Smith S. The Sydney line: A significant sign in Downs syndrome. Journal of Paediatrics and Child Health 1972;8(3):198 – 200. [↩]

28. Plato, Chris C., Cereghino, James J. and Steinberg, Florence S. Palmar Dermatoglyphics of Down's Syndrome: Revisited. Pediatric Research 1973;7(3):111-118. [↩]

29. Maina P Kava, Milind S Tullu, Mamta N Muranjan, K.M Girisha. Down syndrome: Clinical profile from India. Archives of Medical Research 2004;35(1):31-35. [↩]

30. J.F.M. Deckers, A.M.A. Oorthuys & W.H. Doesburg. Dermatoglyphics in Down's syndrome II. Clinical Genetics. 1973, Vol. 4: 381-387. [↩]

31. T, Fogle. Using dermatoglyphics from Down syndrome and class populations to study the genetics of a complex trait. [book auth.] C. A. Goldman. Tested studies for laboratory teaching: ABLE, 1990:129-150. [↩]

Author Information

1. **Suresh Bidarkotimath,** Department of Anatomy, A. J. Institute of Medical Sciences, Mangalore 575 004, Karnataka (India) [↩]

2. **Ramakrishna Avadhani,** Professor and Head of Department of Anatomy, Yenepoya Medical College, Mangalore 575 018, Karnataka (India) [↩]

3. **Viveka S,** Department of Anatomy, A. J. Institute of Medical Sciences, Mangalore 575 004, Karnataka (India) [↩]

4. **Arunachalam Kumar,** Professor of Anatomy and Dean, K.S. Hegde Medical Academy, Mangalore 575 018, Karnataka (India); Corresponding Author Email: ixedoc@hotmail.com [↩]

Pharmacology, DNA Fingerprinting, Sexual Jurisprudence, Genetic Engineering, Environment Medicine etc.

Published by **National Foundation of Clinical Forensic Medicine,** India

or mail them to
Journal Office, IJFPR,
103 PG Woods, J.J. Road,
Vidyarathna Nagara,
Manipal 576104, Karnataka, India.

ISSN: 2231-6795 (Web) 2231-6787 (Print)