Medical Hypotheses (2002) **59**(3), 334–336

doi: 10.1016/S0306-9877(02)00181-0, available online at http://www.idealibrary.com

The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene?

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Summary The androgen receptor gene (AR) contains a domain which includes a variable number of CAG sequences and alleles with low numbers of CAG repeats show high transactivation activity when complexed with testosterone. The ratio of 2nd and 4th digit length (2D:4D) is negatively correlated with phenotypic effects of testosterone. Low numbers of CAG repeats and low 2D:4D are both associated with high sperm numbers and protection against breast cancer. This suggests that CAG number and 2D:4D are correlated i.e. low CAG number and low 2D:4D indicate high activation of androgen-responsive genes. Findings from AR studies predict that low 2D:4D will be associated with prostate and hepatocellular cancer, urolithiasis, ADHD, ankylosing spondylitis, spontaneous abortion, and polycystic ovaries, while high 2D:4D will be associated with motor neuron diseases and endometrial cancer. Findings from 2D:4D studies predict that short CAG length will be common in autism and Asperger's syndrome, while high numbers of CAG repeats will be found in men who are prone to early myocardial infarction. © 2002 Elsevier Science Ltd. All rights reserved.

The effect of androgen is likely to be dependent on the amount of hormone produced and the activity of the androgen receptor gene (AR). The AR codes for a protein that has three functional domains (1), one of these, the N-terminal domain, has a polymorphic CAG microsatellite encoding variable-length glutamine repeats. The CAG repeat length ranges normally from *6* to *39* repeats, shorter length correlates with greater transactivational activity and variation in CAG repeat length has been reported to be associated with the aetiology of a number of important diseases including prostate and breast cancer (2,3).

Characterisation of the AR gene requires that DNA be prepared and that sequencing services are available. It would therefore be of value to have a simple correlate of AR polymorphism which is readily measured. We suggest that variation in the ratio of the length of the 2nd and 4th digits (2D:4D) maps on to variation in CAG length. 2D:4D differs between the sexes (males have lower 2D:4D, i.e. longer 4th digits relative to 2nd, than do females), it is fixed early in development (4) and it is likely that 2D:4D is negatively related to in utero testosterone because (a) the waist:hip ratio of mothers (a positive correlate of testosterone) is negatively related to the 2D:4D of their children (5) and (b) individuals with congenital adrenal hyperplasia (a condition associated with high prenatal androgen) have low 2D:4D compared to controls (*6*).

Received 21 January 2001
Accepted 13 February 2002

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SIMILARITIES IN DIGIT RATIO AND ANDROGEN RECEPTOR STUDIES

2D:4D ratio and CAG repeal length are normally distributed variables (2,4) and recent studies suggest that the 2D:4D ratio and CAG repeat lengths are positively correlated, thus: (a) The 2D:4D shows marked ethnic

differences (7), Caucasian samples from England. Spain, Poland, Germany, and Hungary have high values of 2D:4D, but black samples from Jamaica and South Africa show significantly lower 2D:4D. CAG repeat length also shows ethnic variation with Caucasian-Americans having higher mean repeat lengths than African-Americans (8). (b) Studies of spermatogenesis and ovarian function have also revealed that 2D:4D and CAG length are both negatively related to male fertility parameters such as ejaculate size (4,9) and positively associated with female fertility parameters such as polycystic ovarian syndrome (10) and family size (7). (c) High 2D:4D and long CAG repeats may also indicate susceptibility to breast cancer (11). A comparison of 2D:4D ratios in women with breast cancer and controls showed no significant differences in digit ratio. However, within the cancer group women with high 2D:4D presented with their tumour before participants with low 2D:4D (10). Similarly high CAG number has been found to reduce age at presentation of breast cancer in BRCA1 carriers (12) and to increase susceptibility to breast cancer in the general population (12).

PREDICTED DIGIT RATIO FINDINGS FROM ANDROGEN RECEPTOR STUDIES

If variation in 2D:4D ratio is a phenotypic proxy for CAG repeat length this means that associations between AR and disease may predict correlations between 2D:4D and disease. Reports of disease associations with short CAG sequences indicate that low 2D:4D will be correlated with: (a) prostate cancer (2); (b) hepatitis B-related hepatocellular carcinoma (13); (c) urolithiasis in men (14); (d) male rheumatoid arthritis (15); (e) ADHD, conduct disorder and oppositional defiant disorder (16); (f) spontaneous abortion of female foetuses (17); and (g) ankylosing spondylitis (18). An association with long CAG sequences suggests that high 2D:4D will be found in (a) neurodegenerative disorders e.g. Kennedy disease (19) and (b) endometrial cancer (20).

PREDICTED ANDROGEN RECEPTOR FINDINGS FROM DIGIT RATIO STUDIES

In comparison with population norms low 2D:4D ratios have been found in children with autism and Asperger's syndrome, in their siblings and in their fathers and mothers (21). This suggests that short CAG repeat lengths may be found in such families and that children with autism and Asperger's have alleles with particularly low CAG repeat numbers.

Low testosterone predisposes men to myocardial infarction (MI) and high 2D:4D ratios have been found to be associated with early MI (22). This suggests that high CAG repeat number will be found to be a marker for heart disease in men.

CONCLUSION

The strength of the association between 2D:4D and CAG repeat length can only be established empirically. We have argued here that the association is strong. If so 2D:4D could be used as a simple proxy for AR variation. However, 2D:4D may also be related to polymorphisms in the oestrogen receptor (ER). 2D:4D ratio could therefore correlate with both testosterone and oestrogen related risk factors for disease. For example low testosterone and high oestrogen may both be associated with risk for breast cancer (23) and heart disease (24). High 2D:4D ratios could therefore be a stronger predictor of risk for breast cancer in women or MI in men than polymorphisms in the AR or ER alone.

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