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Eysenck's Psychoticism and the X-linked androgen receptor gene CAG polymorphism in additional Australian samples

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Abstract

Data from existing Brisbane samples of adult women, and of adolescents of both sexes, were examined in an effort to replicate the Canberra finding of Turakulov, Jorm, Jacomb, Tan, and Easteal (2004); namely, an association between scores on Eysenck's Psychoticism (*P*) scale and short CAG sequences on the androgen receptor gene. They found a significant association in this direction in males, and a similar (although nonsignificant) one in females. Some support was found for a relationship between *P* scores and short CAG sequences in the Brisbane female samples, but the adolescent boys showed differences which, although small, tended to lie in the opposite direction. Correlations of CAG sequence length with *P* suggested that the sequence length, at best, accounted for only a very small proportion of the variance of *P*.

Keywords: Androgen receptor; Psychoticism; Eysenck; Testosterone; CAG repeats

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1. Introduction

Turakulov, Jorm, Jacomb, Tan, and Easteal (2004) examined the association between several testosterone-related genes and Eysenck's *P* scale, a scale originally intended to measure psychotic tendencies, but often associated more broadly with externalizing behavior problems, including impulsivity, aggression, and nonconformity to social rules (Zuckerman, 1989). One of the genes Turakulov and his colleagues studied was the X-linked androgen receptor (AR) gene, and one aspect assessed was the length of a repeated sequence of CAG triplets, which varies between 11 and 31 repeats in normal populations (Edwards, Hammond, Jin, Caskey, & Chakraborty, 1992). Short CAG sequences have been shown in vitro to be more effective in transcribing testosterone (Chamberlain, Driver, & Miesfeld, 1994), and have been linked to a number of androgen-related conditions, such as higher sperm concentrations (von Eckardstein et al., 2001), pattern baldness (Ellis, Stebbing, & Harrap, 2001), an elevated risk of prostate cancer (Giovanucci et al., 1997), and a lower ratio of the length of the index finger to the length of the ring finger (Manning, Bundred, Newton, & Flanagan, 2003)—although not all of these associations have proved to be easily replicable.

Turakulov et al. (2004) genotyped a large community sample in Canberra, Australia, using saliva from cheek swabs. Participants were administered the Eysenck Personality Questionnaire (EPQ), among other scales. Approximately 781 male and 890 female Caucasian adults had both Eysenck *P* scores and AR gene CAG sequence assessments. On the basis of earlier studies by Comings, Chen, Wu, and Muhleman (1999), the investigators divided CAG sequences into short ($\leqslant$22 repeats) and long (>22 repeats). This yielded two genotypes (Short and Long) for men, with one X chromosome, and three genotypes (Short/Short, Short/Long, and Long/Long) for women, with two X chromosomes.

The study found a modest but statistically significant association for men in the expected direction (higher *P* scores went with short sequences). Women showed an effect in the same direction (mean *P* for Short/Short > Short/Long > Long/Long). However, the effect fell short of conventional levels of statistical significance (the obtained *p*-value was 0.152).

Studies by Martin and his colleagues in Brisbane using samples of Australian twins also obtained data on AR gene CAG repeats and scores on Eysenck scales, and thus permit replication of Turakulov et al.'s (2004) comparisons. That is the purpose of the present paper.

2. Method

One of the Brisbane samples provided 294 adult female monozygotic (MZ) twin pairs who had had one member genotyped in a study of ovarian cancer (Spurdle et al., 2000), and who were part of a large national twin sample that had been administered the Eysenck Personality Questionnaire (EPQ) by mail. Since MZ twins have identical genotypes, this implied 588 women for whom both AR gene sequence length and Eysenck *P* score were known. In practice, of course, some error of assessment exists, so that measured AR sequence lengths would not be perfectly correlated between MZ twins. But for overall relationship to a third measure, it does not make an essential difference whether the same measurement error is attached to both twins' scores in each pair (as is done in effect here) or if a different measurement error is assigned to each.

A second study involved adolescent twins of both sexes tested in person at ages 12, 14, and 16 (Wright and Martin, 2004). Some twins were tested at all three ages, some at two out of the three, and some at just one age. The twins received AR gene CAG assessments based on a blood sample taken at one of their visits, plus *P* scale scores from the Junior Eysenck Personality Questionnaire (JEPQ) from testings at one or more of the three ages. Altogether, there were 457 boys and 445 girls tested at age 12 for whom an AR CAG score and *P* score were available, 345 boys and 336 girls tested at age 14, and 341 boys and 355 girls tested at age 16. Some of these represented repeated testings of the same individuals, and most were members of twin pairs (a few siblings close in age to the twins were also included in the studies). Precise statements of statistical probabilities would require taking into account this complex structure of the data. Here, however, we are concerned with whether the differences in *P* scores for individuals of different genotypes do or do not correspond in direction to those obtained in the Canberra study. Thus, for present purposes, we can largely ignore the complications presented by the nonindependences among the scores.

We classified the CAG repeat scores for the Brisbane samples into the same short and long categories used in the Canberra study. The EPQ and JEPQ *P* scales were used as scored in the respective studies. For most of the adult women, both long (25 item) and short (12 item) *P* scales were available, from different testings. The short scale was comparable with that used by the Canberra study. The JEPQ, although constructed to measure the same dimensions as the EPQ, uses different, age-appropriate, items, and has a 17-item *P* scale in contrast to the 12-item *P* scale used in most of the adult studies; thus the mean *P* scores for the adolescents and the adults will not be directly equivalent. However, it is the differences among *P* scores for different genotypes on the same questionnaire that is our basic datum, not the absolute level of scores, so this provides no serious difficulty.

3. Results

Table 1 shows mean *P* scores by genotype for the various samples: the Canberra adult males and females, the Brisbane adult MZ twin females (for both short and long versions of the *P* scale), and the Brisbane adolescent twin and sib 16-, 14-, and 12-year-olds.

Differences among the means across different samples are evident. Some of these reflect differences among the *P* scales used, others age and sex differences in *P* scores. These cross-sample mean differences may largely be ignored for our purposes, since it is the differences within samples among the different AR genotypes that are our principal concern. Also evident are differences in the relative frequencies of the different genotypes. The ''long'' gene (over 22 repeats) occurs 39% and 41% of the time for the Canberra adults, 52% of the time for the Brisbane adult women, and 24–31% of the time for the Brisbane adolescents. We suspect that these largely reflect differences in the precision and sensitivity of the assay procedures used by the different laboratories. (The Brisbane adult females and the adolescents were genotyped in different labs.) In the case of the Brisbane adolescent samples, AR assessments were also made of many of their fathers and mothers. (These are not included in the table, because the parents did not receive the Eysenck questionnaire.) The assessments were done by the same laboratory as those of the children, and gave frequencies for the long gene of 30% and 25% for fathers and mothers, respectively, essentially the same as those of the children. Again, the fact that the principal comparisons of interest are within

Table 1
Mean Eysenck *P* scores for different androgen receptor genotypes, and correlations of *P* with androgen receptor CAG sequence length

Sample	Genotype means			Correlation
	Short	Long		
Males				
Canberra adult	2.33 (477)	2.09 (302)		−0.038[a] (781)
Brisbane age 16	3.79 (248)	4.24 (93)		0.044 (341)
	3.73 (210)	4.20 (131)		
Brisbane age 14	4.26 (260)	4.35 (85)		−0.019 (345)
	4.26 (221)	4.31 (124)		
Brisbane age 12	3.59 (346)	4.08 (111)		.038 (457)
	3.50 (294)	4.09 (163)		
	S/S	S/L	L/L	
Females				
Canberra adult	1.90 (323)	1.77 (397)	1.63 (164)	−0.058[a] (890)
Brisbane adult (short *P*)	1.39 (122)	1.52 (288)	1.39 (150)	−0.015 (560)
	1.38 (173)	1.55 (283)	1.36 (104)	
Brisbane adult (long *P*)	2.51 (128)	2.69 (306)	2.80 (154)	−0.018 (588)
	2.62 (182)	2.67 (300)	2.80 (106)	
Brisbane age 16	2.47 (175)	2.44 (153)	2.04 (27)	0.006 (355)
	2.52 (130)	2.40 (174)	2.29 (51)	
Brisbane age 14	2.73 (158)	2.07 (146)	1.56 (32)	−0.088 (336)
	2.69 (121)	2.19 (154)	1.95 (61)	
Brisbane age 12	2.26 (210)	1.93 (194)	1.66 (41)	−0.037 (445)
	2.28 (160)	2.01 (213)	1.75 (72)	

Notes: Numbers of individuals shown in parentheses. For Canberra means, *N*s may vary slightly; minimum *N* is shown. Main tabulations: Short = ⩽22 CAG repeats, Long = >22 CAG repeats. Alternate tabulations for Brisbane data: division at 21 repeats for male and female adolescents, at 23 repeats for adult females. S/S, S/L, L/L = Short/Short, Short/Long, Long/Long. Adults: *P* score from Eysenck Personality Questionnaire (12 items; 25 for long *P*); adolescents: *P* score from Junior Eysenck Personality Questionnaire (17 items). Canberra data from Turakulov et al. (2004). Correlations for females are with the mean sequence length for their two chromosomes.

[a] Courtesy of A. Jorm and P. Jacob.

samples, and thus within groups genotyped in the same laboratory by the same procedures, makes these differences of less concern.

However, in view of the observed differences in "short" and "long" frequencies between samples, data for the Brisbane samples are also presented in Table 1 using dividing points between "short" and "long" that bring the frequencies into better agreement with the Canberra sample. The use of 23 repeats as a cutting point between "short" and "long" for the Brisbane adult females, and 21 for the adolescents, renders the frequencies of "short" and "long" alleles reasonably consistent across the several samples. Also shown in Table 1 is a direct correlation between CAG sequence length and *P* score. If one assumes that the division into "short" and "long" genotypes is a convenient fiction, and that the efficacy of the gene is continuously and monotonically related to the number of CAG repeats, this should provide a better indication of the strength of relationship between the gene and the behavioral trait.

To return, then, to the comparisons of interest: For adolescent females, the Brisbane mean differences (for either dividing point at every age) are consistent with the Canberra results and with theoretical expectations. The highest *P* scores are for the S/S genotype and the lowest for the L/L genotype, with the S/L genotype intermediate. The adult MZ females show small and inconsistent differences. However, on the whole, the Brisbane results for females may be considered supportive of the Canberra findings, suggesting a weak tendency for higher *P* scores to go with short CAG sequences among females.

The males are a different matter. The adolescent males with short CAG sequences tend to have lower, not higher, *P* scores. Although the differences are not large, they are at all three ages in the opposite direction from that observed for the Canberra adult males, and from that predicted on the assumption that *P* is related to testosterone. Again, the use of different cutting points makes little or no difference in the results.

Table 1 also presents for the various Brisbane samples the Pearson correlation between CAG sequence length and *P* score. If sequence length is linearly related to *P*, this should be more powerful than the dichotomizing or trichotomizing implicit in the Canberra approach, and give a better sense of effect sizes. As is evident from the final column in the table: although the correlations are mostly negative for the females—the expected direction if short sequences go with higher *P* scores—they are small at best; and for two of the three male groups they lie in the opposite direction. Obviously, short AR CAG sequences are not very strong predictors of high *P* for any of the groups—not at all for the adolescent males.

4. Discussion

Existing adult and adolescent data from the Brisbane twin studies were analyzed in parallel with the results for the Canberra community sample of adults. For the most part, the direction of differences for the Brisbane female samples agreed with that observed in Canberra, as well as with theoretical expectation: short CAG sequences went with higher average *P* scores. The adolescent males, however, did not show the same pattern. Among the Canberra adults, both men and women showed the same tendency: short CAG sequences were associated with higher *P* scores: but the Brisbane adolescent boys showed a (slight) tendency in the opposite direction. Those with short CAG sequences had slightly lower, not higher, mean *P* scores. In any case, the associations in both sexes, as measured by correlations, were weak ones.

There have been some previous attempts to link AR CAG sequence lengths with personality traits. In a study involving 340 Swedish adults, 186 men and 154 women, modest correlations were found between AR CAG sequence length and several scales of the Karolinska Scales of Personality, although none were high enough to be considered as constituting unequivocal evidence of a relationship (Jönsson et al., 2001). The strongest associations were with neuroticism subscales—muscular tension and lack of assertiveness for men and psychasthenia for women—and they were in the expected direction of longer sequence lengths going with higher neuroticism. There was also a tendency for men with short sequences to score higher on a verbal aggression scale. In a different analysis of these data, focusing on masculinity–femininity, a subscale called "Breaks Rules" which had been derived in the Australian sample and bears some conceptual resemblance to *P*, showed a very small correlation (−0.06) with CAG repeats for women in the expected direction (Loehlin,

Jönsson, Gustavsson, Schalling, & Stallings, 2003). In another study of Swedish women, however, AR CAG sequence lengths were found to be longer, not shorter, for personality characteristics deemed more masculine (Baghaei et al., 2003). These included independence, dominance, leadership, determination, and lack of insecurity. However, although traditionally masculine, it should be noted that these are not *P*-scale type traits.

Several studies have examined second-to-fourth finger ratios (2D:4D ratios) in relation to personality traits. This is a sexually dimorphic trait—men tend to have lower ratios than women—and is thought to be related to the prenatal organizational effects of androgens (see Manning, 2002 for a review). As noted earlier, it has been studied in relation to AR CAG sequence length, with shorter sequences being associated with more masculine 2D:4D ratios (Manning et al., 2003). Manning and his colleagues have shown relationships of 2D:4D ratios with personality traits among college students and preschool children. Among the preschoolers, more masculine finger-length ratios were indicative of hyperactivity among girls and more feminine ratios predicted emotional symptoms in boys (Williams, Greenhalgh, & Manning, 2003). For the college students, *P* scores were related to digit ratios in the expected (negative) direction in two samples of girls—although the individual correlations did not achieve statistical significance in the fairly small samples involved—but the results for the boys were mixed (Austin, Manning, McInroy, & Mathews, 2002). Another study of University students (Fink, Manning, & Neave, 2004) obtained a negative correlation between 2D:4D ratio and Agreeableness, for females (significant for the right hand only). No significant relationship was found for males. The samples were small ($N = 50$ females, 30 males), but the obtained result was in the opposite direction from that expected on an androgen/*P* hypothesis: a feminine 2D:4D ratio did not go with high Agreeableness (a low-*P* trait).

Does the length of AR gene sequences predict personality via its prediction of androgen levels? In general, as noted earlier, short AR CAG sequences go with a number of androgen-related characteristics. In a sample of Swedish women, shorter sequences were associated with higher serum levels of androgens (Westberg et al., 2001). But in another study involving 274 Swedish young male military recruits (mean age 18.1 years), a *positive* correlation was found between AR CAG sequence length and levels of free testosterone (Giwercman et al., 2004). Could this explain the anomalous relationship of AR sequence length and *P* obtained for the adolescent males in the present study? Only further research in new samples will tell. Males at differing ages would be particularly informative.

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