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Number of X-linked androgen receptor gene CAG repeats and femininity in women

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Abstract

Two studies used a sample of 300 female Australian monozygotic twins who had been genotyped for the X-linked androgen receptor gene and scored for the number of repeats of the triplet CAG. (A low number of repeats is associated with greater risk of prostate cancer in males and more effective transcription of androgens). In the first study, three measures of masculinity–femininity were constructed from the items of two personality questionnaires that had been taken by the members of a large twin sample (~3000 pairs). Two of the three measures, admitting to fears and worries and a willingness to break rules, were not significantly correlated with number of CAG repeats in the genotyped subsample. The third measure, confiding in others versus reserved, showed a small but significant correlation with CAG repeats in this female sample: fewer repeats went with scores in the reserved (i.e. masculine) direction. In the second study, CAG repeat scores were correlated with 90 questionnaire items related to female reproductive functions. Three items were associated with fewer repeats: age, having had a hysterectomy and length of labor at the birth of a second child. Because many items were screened, this was regarded as suggestive but not conclusive evidence of an association of CAG repeats with these reproduction-related traits.

Keywords: Androgen receptor gene; Twins; Femininity; Testosterone; Masculinity–femininity scales; Hysterectomy

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1. Introduction

There has been much recent interest in the identification of individual genes related to behavioral traits. One focus of attention has been on genes that contain repeated nucleotide sequences of various lengths. For example, the claim has been made that men with a longer repeat sequence in the dopamine D4 receptor gene are higher in sensation-seeking than men with a shorter version of the gene (Ebstein et al., 1996; Benjamin et al., 1996) — although this finding remains in dispute (e.g. Vandenbergh, Zonderman, Wang, Uhl, & Costa, 1997). The present paper focuses on another gene, called the androgen receptor (AR), which resides on the X chromosome, and is involved in mediating the effects of androgens such as testosterone on specific body tissues. The AR gene contains a sequence of repeated occurrences of the nucleotide triplet CAG, which varies in length in normals in the range of 11–31 repeats (Edwards, Hammond, Jin, Caskey, & Chakraborty, 1992).

One basic function of androgens is in normal male sex differentiation and development, in which they exert their effects in a tissue-specific manner via interaction with the AR DNA transcription factor. Classical abnormalities of AR function cause complete or partial Androgen Insensitivity Syndrome, with phenotypes ranging from total failure of normal male differentiation (patients, although genotypically male, are phenotypically female) to varying degrees of ambiguous genitalia (reviewed by MacLean, Warne, & Zajac, 1995). A role for the AR gene in other tissues has been highlighted by the discovery of AR mutations in male breast cancer patients, prostate cancer patients and in cases with spinal and bulbar muscular atrophy (MacLean et al., 1995). The atropy patients were shown to have an expansion of the AR CAG repeat beyond the normal range to above 40 repeats (La Spada, Wilson, Lubahn, Harding, & Fischbeck, 1991); the biological significance of this CAG repeat length expansion has been demonstrated by in vitro studies, in which larger CAG repeat lengths exhibited decreased transactivation capabilities (Chamberlain, Driver, & Miesfeld, 1994).

There is evidence that variation within the normal range of 11–31 repeats may influence the function of the androgen receptor molecule. The CAG repeat in AR has been linked to prostate cancer predisposition, with several reports of an association between prostate cancer risk and shorter CAG repeat lengths (Irvine, Yu, Ross, & Coetzee, 1995; Giovanucci et al., 1997; Hakimi, Schoenberg, Rondinelli, Piantadosi, & Barrack, 1997; Ingles et al., 1997; Stanford et al., 1997). In addition, CAG repeats have been found to correlate with androgenic characteristics in Hispanic females in a fertility clinic, with an inverse relationship between the Ferriman–Galway score of androgenism and CAG repeat number in a small sample of women with normal androgen levels (Legro, Shahbahrami, Lobo, & Kovaks, 1994).

In view of the last-mentioned finding, we wondered whether the number of CAG repeats in the AR gene might also be associated with psychological femininity in women: fewer repeats would be expected to go with more active transcription of androgen and hence with more masculine traits. This was the object of the first study described below. The various investigations that have linked CAG repeats to hormonal effects (and the availability of the necessary data) suggested examining another question as well: a second study explored the relationship of CAG repeats to a variety of female reproduction-related traits.

2. Study 1 — method

2.1. Subjects

Prompted by the association of prostate cancer with CAG repeat number in males, one of us (A.S.) had undertaken a similar study in ovarian cancer patients and controls. As the control sample for that study, 300 females were drawn from a sample of 3348 twin individuals for whom DNA was already available. For most of these women, extensive personality, reproductive and lifestyle data had been collected in previous surveys of the Australian National Health and Medical Research Council Twin Registry (Martin, & Jardine, 1986; Heath, Cloninger, & Martin, 1994). The only criteria for further selection into the control sample for the cancer study were that (i) subjects were selected on the basis of date-of-birth to match as closely as possible the date-of-birth distribution observed for the ovarian cancer patients screened, namely tertiles from 1900–1925, 1926–1938 and 1939–1970 and (ii) the subjects should be monozygotic females (whose cotwin was not also selected) so that two, replicate phenotypes were available for every genotype.

A number of the analyses to be reported were done separately for the first- and second-listed twins of each pair (hereafter 'twin 1' and 'twin 2'). For the purposes of this paper, we have treated these as if they were random replicates. This is not strictly true. The first-listed twin was most frequently the first-born twin (about 75% of the time) and, in the group of opposite-sex twin pairs, the female was more often listed first (about 60% of the time). Birth order effects on personality variables in twins tend to be slight at best (Loehlin & Nichols, 1976). The order difference for the opposite-sex pairs has an effect on *N*s in one or two of the tables, but is irrelevant for the analyses involving CAG repeats, as these are based on female MZ pairs only.

2.2. CAG repeats

The androgen receptor exon 1 CAG trinucleotide repeat was PCR-amplified using primer sequences detailed by La Spada et al. (1991), with inclusion of a 5′TET-labelled forward primer to generate a fluorescent product. The 10-μl reaction mix contained 30 ng DNA, primers (10 pmol each), dNTPs (200 nM), 1X Perkin-Elmer Taq polymerase buffer, 1 U Taq polymerase, 1.5 mM $MgCl_2$ and 7% deionized formamide. Amplification conditions were: 2 min at 94°C, 34 cycles (94°C 20 s/62°C 20 s/72°C 20 s), followed by a 10-min extension at 72°C. Amplified samples were diluted 1 in 12 in formamide loading buffer, denatured 2 min at 95°C and size-separated on a 6% denaturing polyacrylamide gel. The ABI Prism 377 genescan and genotyper systems were used for detection and sizing of fluorescent products. Separation of the ABI TAMRA-350 size standard in each lane allowed for genescan automated sizing of TET-labelled PCR products. In addition, control samples of known size were separated at different positions across each gel, and used to generate a gel-specific sizing correction factor. Consistent sizing of samples was indicated by the independent generation of matching size results for a random subset of samples separated on more than one gel.

For most of the analyses in this paper, the sum of the CAG repeats on the woman's two X chromosomes was used, assumed the same for both MZ twins of a pair. Some analyses were

also carried out in which repeat numbers for the longer and shorter alleles were considered separately, on the grounds that the dominance relationship between the alleles is unknown, and may differ from phenotype to phenotype.

2.3. Construction of masculinity–femininity (M–F) personality scales

Men differ from women along a number of psychological dimensions which also show variation within each sex (Lippa, 1995). Measures of three such dimensions were constructed from a pool of items from two personality questionnaires given to a large Australian volunteer adult twin sample (Heath, Cloninger, & Martin, 1994), of which the 300 genotyped female MZ twins are a subset. These questionnaires were short versions of the Eysenck Personality Questionnaire (Eysenck, Eysenck, & Barrett, 1985) and the Cloninger Tridimensional Personality Questionnaire (Cloninger, Przybeck, & Svrakic, 1991). They were identified simply as 'Personality I' and 'Personality II' in the mail questionnaire filled out by the respondents. The two questionnaires consisted, respectively, of 56 and 54 'yes–no' or 'true–false' self-descriptive items.

As a first step, the 110 items were correlated with sex separately for the first and second twins of the pairs ('twins 1' and 'twins 2'). These correlations were based on *N*s of around 2900, varying somewhat from item to item because of differing numbers of omissions. Items were selected that had an absolute correlation with sex of 0.10 or higher in both samples. With the sample sizes involved, a correlation of about 0.05 in one sample would be nominally significant at the 0.01 level, so there is little risk of a chance selection when requiring a correlation of 0.10 in both samples, even allowing for some nonindependence across twins (the twin item correlations, across all pairs, averaged only about 0.17). There were 33 items with sex differences that met the specified criterion, representing 30% of the item pool.

The selected items were then factor-analyzed within each sex separately for the sample of twins 1 and this was repeated for twins 2. Principal factors were extracted, with communality

Table 1
'Worried' scale items; factor loadings in four subsamples

Item	Female 1	Male 1	Female 2	Male 2
(E6) 'Just miserable' for no reason	0.37	0.39	0.29	0.38
(E20) Feelings easily hurt	0.49	0.49	0.43	0.50
(E28) Are you a worrier?	0.53	0.62	0.54	0.59
(E44) Like to act quickly	−0.38	−0.38	−0.34	−0.30
(E46) Worry after embarrassment	0.56	0.59	0.53	0.58
(C6) Relaxed when others fearful	−0.43	−0.52	−0.42	−0.46
(C10) Tense when do something new	0.62	0.63	0.64	0.61
(C11) Worried when others not	0.70	0.69	0.71	0.70
(C13) Tense when others see no danger	0.64	0.65	0.68	0.65
(C16) Calm where most see danger	−0.37	−0.38	−0.29	−0.30
(C43) More confident than most	−0.39	−0.42	−0.42	−0.35
(C46) Get over embarrassment quickly	−0.52	−0.48	−0.48	−0.56

estimates iterated from squared multiple correlations. Inspection of the factor loadings suggested that the first three unrotated factors agreed well across the four factorings, with a sufficient number of salient items on each to allow the construction of three approximately orthogonal scales. These factor loadings are given in Table 1 through 3. In each table are given the item number in the questionnaire (E for Eysenck, C for Cloninger), a brief characterization of the content of the item, and factor loadings in the four twin and sex subsamples. In general, a factor loading of 0.30 or above was considered useful in defining a factor — in a few cases a loading in the 0.20s was admitted in one of the subsamples. In a few other instances (not shown) item loadings elsewhere slightly exceeded 0.30, but in only one or two subsamples.

2.4. Characteristics of the M–F scales

The 12 salient items for factor 1 (Table 1) contrast an emotional, fearful person with a calm and confident one. For brevity, this factor is labeled 'Worried'. The six salient items for factor 2 (Table 2) contrast individuals who freely express their feelings with those who tend to be reserved and detached. Since most of the items are stated in the reserved direction, this factor is called 'Reserved'. The six items for factor 3 (Table 3) describe an individual who is inclined to break or bend social rules. We call this factor 'Breaks rules'.

Scales were scored by simple summation of the keyed responses, reflected where necessary. If a respondent omitted more than one-third of the items for a given scale, it was scored as missing. Because items were coded on a 1–3 scale (with 2 for uncertainty), this gave a possible score range of 8–36 for Worried and 4–18 for the other two scales. Means and standard deviations over the full twin sample are given for males and females for twins 1 and 2 in Table 4; intercorrelations among the scales for males and females are given in Table 5. From Table 4 it appears that the typical sex difference on these scales is slightly over half a standard deviation. Thus, while the scales do discriminate between the sexes — males averaged higher on Reserved and Breaks rules, females on Worried — there remains ample variation on all three scales within sexes, which is the focus of this investigation.

Table 5 shows that the three scales, as scored, are reasonably independent of one another within sexes. With these large *N*s, the negative correlations between Reserved and Breaks rules and the positive correlations between Worried and Reserved differ significantly from zero, but they are not large enough to create substantive problems.

Table 2
'Reserved' scale items; factor loadings in four subsamples

Item	Female 1	Male 1	Female 2	Male 2
(C3) Discuss experiences with friends	−0.50	−0.51	−0.48	−0.49
(C7) Seldom tell friends thoughts	0.61	0.65	0.63	0.67
(C18) More reserved than most	0.45	0.41	0.47	0.34
(C21) Practical, don't act on emotion	0.31	0.31	0.33	0.23
(C47) Keep problems to self	0.61	0.59	0.62	0.61
(C51) Stay cool and detached	0.42	0.57	0.45	0.46

Table 3
'Breaks rules' scale items; factor loadings in four subsamples

Item	Female 1	Male 1	Female 2	Male 2
(E9) Ever take more than your share?	0.44	0.46	0.43	0.44
(E17) Go own way rather than by rules	0.36	0.46	0.41	0.34
(E23) Ever take anything not yours?	0.50	0.50	0.49	0.47
(E27) Ever take advantage of someone?	0.49	0.51	0.46	0.60
(E52) Ever cheat at a game?	0.44	0.53	0.45	0.51
(C14) Break rules if get away with it	0.37	0.49	0.43	0.46

3. Study 1 — results

Correlations between twins 1 and 2 are given in Table 6 for monozygotic male and female pairs, same-sex dizygotic male and female pairs and opposite-sex dizygotic pairs.

The correlations are fairly typical of those observed for personality traits in twin studies and suggest a moderate degree of heritability for all three dimensions. Were there none, it would hardly be sensible to examine the relationships of the scales to number of CAG repeats.

The relations to CAG repeats are shown in Table 7. The table suggests at most a weak positive relationship of the Worried scale with number of repeats — a relationship that would require much larger samples than the present one to establish convincingly. Rule-breaking shows essentially no relationship. The third scale, Reserved, shows modest but consistent negative correlations for both twins 1 and twins 2. The consistency between twins 1 and twins 2 represents only a partial replication, because these are MZ twins. The CAG repeats score is identical for both twins of a pair, but the M–F scores are not — for Reserved the two twins are correlated 0.38 in the genotyped sample (0.35 for all female MZ pairs — Table 6). Thus the results for twin 1 and twin 2 are by no means constrained to be identical.

To obtain a better estimate of the CAG-Reserved correlation, plus a single overall significance test for it, a latent variable model was fit to the covariance matrix among the CAG repeat and Reserved scores for both twins. A dummy latent variable for CAG repeats was

Table 4
Means and standard deviations of M–F scales

Group	Worried		Reserved		Breaks rules		Ns
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Males							
Twin1	22.52	6.61	13.14	3.62	11.02	3.52	948–951
Twin2	22.36	6.42	13.22	3.53	10.97	3.43	1076–1078
Females							
Twin1	26.43	6.43	11.33	3.63	9.20	3.06	2031–2038
Twin2	26.26	6.32	11.40	3.74	9.16	3.04	1818–1824

Table 5
Intercorrelations among M–F scales (females above diagonal, males below). Ns 3842–3846 for females, 2021–2025 for males

	Worried	Reserved	Breaks rules
Worried	1.00	0.05	−0.01
Reserved	0.06	1.00	−0.08
Breaks rules	−0.00	−0.05	1.00

assigned a fixed 1.0 path to the pair's CAG score. Equal paths led from a latent Reserved variable to the observed scores for twins 1 and 2. N was taken as the average for the two (=280). The correlation between the latent CAG and Reserved variables was the parameter of primary interest. With this parameter allowed to be free, the model fit well ($\chi^2=0.271$, 2 df, $p=0.873$) and the correlation was estimated as −0.21. With the parameter fixed to zero, χ^2 increased to 6.917. The difference between these two χ^2 s, with 1 df, provides an overall significance test for the correlation of CAG repeats and Reserved. This difference χ^2 was 6.646, 1 df, $p=0.010$. One could apply a Bonferroni allowance for the fact that three M–F variables were tested. This can be done by using a criterion α of 0.0167 (one-third of 0.05). Thus one would still judge this result to be legitimately significant at the 0.05 level.

The correlations in Table 7 represent linear relationships. As a check on the possibility of nonlinear relationships, the sample was split approximately into thirds on number of CAG repeats and means calculated for the three M–F variables, separately for twins 1 and 2. There was no very compelling evidence for nonlinearity, although there was some tendency towards higher means on the Worried scale for women with high and low numbers of CAG repeats (p-values of 0.227 and 0.020 for twins 1 and 2, respectively, based on an analysis of variance test of departure from linearity — all other p-values for this test lay in the range 0.150–0.819).

In a different sort of test for possible nonlinear relationships, e.g. genetic dominance or the like, the M–F scales were correlated separately with repeat scores for the allele having the smaller and the one having the larger number of CAG repeats. With one trivial exception, the correlation with the shorter- and longer-sequence alleles had the same sign as that with the total score and the few differences in magnitude of correlation failed to replicate across twins 1 and 2, so again there was no strong evidence for nonlinear relationships.

Table 6
Twin pair correlations for M–F scales. Single entry Pearson correlations between twin 1 and twin 2 of a pair

Group	Worried	Reserved	Breaks rules	Ns
MZ females	0.46	0.35	0.40	934–940
MZ males	0.40	0.35	0.31	398–400
DZ females	0.22	0.14	0.32	535–540
DZ males	−0.05	0.12	0.16	223–224
DZ opp.-sex	0.02	0.03	0.10	566–567

Table 7
Correlations of CAG repeats with three M–F variables, for 1st and 2nd twins of female MZ pairs — (probability value given in parentheses)

	Worried	Reserved	Breaks rules	*N*
Twins 1	0.05 (0.389)	−0.13 (0.030)	−0.02 (0.720)	283
Twins 2	0.07 (0.224)	−0.13 (0.036)	0.02 (0.746)	276–277

4. Study 2 — method

In a second study in a more exploratory mode, the CAG repeat score was correlated with the 90 reproductive variables examined in a previous study comparing same-sex and opposite-sex twin pairs (Loehlin & Martin, 1998). These were items from a questionnaire covering menstruation, premenstrual symptoms, menopause, contraceptive practices, pregnancies, births, infant feeding and the like. The *N*s varied considerably from item to item — for example, only respondents who had had children answered the items on births and only the fraction of the sample past menopause could give the age at which menopause occurred. In addition, item responses were often dichotomous or skewed, so that caution in statistical interpretations is appropriate.

5. Study 2 — results

There were three variables out of the 90 that met a criterion of being significantly correlated at the 0.05 level with the CAG repeat score, separately for both the first and second twins. These variables were respondent's age, whether or not the respondent had had a hysterectomy and length of labor at the birth of the second child. (Length of labor at the birth of the first child was correlated in the same direction in both groups but only significantly so for twins 1).

Table 8 shows the correlations for the three qualifying variables. In all cases the correlations are negative: that is, women with fewer CAG repeats tended to be older, more likely to have had a hysterectomy and longer in labor at the birth of their second child. The consistency of the correlation of CAG repeats with age across twins 1 and 2 is artifactual, since both variables are correlated essentially 1.0 across pairs. However, the correlation itself was

Table 8
Correlations between CAG repeats and reproductive variables, for variables where this correlation was significant at the 0.05 level for both twins. Ns for the hysterectomy item represent the total responding — of these, 61 and 69 women, respectively, said 'yes'

Item	Twin 1	Twin 2	Ns
Age	−0.17	−0.17	291–292
Had a hysterectomy	−0.14	−0.19	274–278
Length of labor, second birth	−0.17	−0.22	146–149

somewhat unexpected, as genotypes presumably do not vary through life. Logically, it could represent a result of selection, if having a large number of CAG repeats were detrimental to survival. In this case, one would expect the correlation of CAG repeats with age to be less among younger women, for whom the effects of mortality should be relatively slight. This was not the case in these data: the correlation of age with number of repeats among women under age 45 was −0.08; for those 45 or above it was also −0.08, failing to provide support for this hypothesis.

Nor are the three variables independent. Both having had a hysterectomy and long labor at a second birth are positively correlated with the respondent's age (0.30 and 0.35 for the former, 0.18 and 0.18 for the latter, for twins 1 and 2, respectively). It is not absolutely clear that partialling age out of the other two correlations is theoretically appropriate, but if it is done the partialled correlation in each case remains statistically significant for one twin but not for the other. Doubts about the theoretical appropriateness of partial correlation reflect uncertainties about the causal relationships involved. For example, the association between age and hysterectomy might reflect in part changes over time in the use of this procedure rather than being a simple effect of age as such.

Hysterectomy has been previously studied in the larger twin sample from which the present 300 pairs were drawn and liability to it shown to be substantially influenced by genetic factors (Treloar, Martin, Dennerstein, Raphael, & Heath, 1992). In a follow-up study (Treloar et al., in press), information was obtained on two specific conditions that often are a basis for hysterectomy, the presence of endometriosis and fibroids. These diagnoses were derived from a combination of medical records and self-reports. It was thus possible to relate these two predisposing conditions to CAG repeats. Table 9 shows the results, in the form of mean numbers of CAG repeats for women with and without the respective diagnoses. (The two diagnoses are only weakly correlated with each other, with phi coefficients of 0.18 and 0.13 for twins 1 and twins 2, respectively, in the present sample).

Table 9 provides no evidence of an association of endometriosis with CAG repeats. There is a suggestion that a diagnosis of fibroids may be associated with a lower CAG repeat score, but this is appreciable only for the twin 2 subsample. Thus the reasons why hysterectomy should

Table 9
Means and S.D.s of CAG repeats among women with and without endometriosis and fibroids. *p*-values are for tests of differences between mean CAG repeats for 'yes' and 'no' groups

Diagnosis	Twins 1		*p*	Twins 2		*p*	Ns
	Mean	S.D.		Mean	S.D.		
Endometriosis							
Yes	46.40	3.07		46.39	3.62		18–20
No	46.17	4.23	0.811	46.32	4.15	0.944	254–255
Fibroids							
Yes	46.17	4.58		45.21	4.28		60–71
No	46.30	4.05	0.832	46.63	4.00	0.012	205–216

be associated with low CAG repeats remain far from clear, although fibroids would seem to be a stronger candidate than endometriosis as a mediator of this relationship.

Overall, one must be cautious in interpreting the results of this study as strong evidence for any association between CAG repeats and reproductive variables. Using a Bonferroni approach, a scan of 90 traits would call for a p-value of approximately 0.00055 for individual traits in order to yield assured overall significance at the 0.05 level (Loehlin, & Martin, 1998). Applying the model-fitting strategy described earlier, which takes into account the correlations in the two separate samples and the correlation between samples, the estimated probabilities of no correlation for the three individual selected traits lie in the range 0.0017–0.0032, i.e. well short of the required level.

6. Discussion

The first study looked for a relationship between the number of CAG repeats and psychological femininity. Three scales, orthogonal within sex, were constructed from the items of two personality questionnaires to measure dimensions of femininity. One of the three scales contrasted a willingness to express feelings to others, more characteristic of females, with a reserved attitude, more characteristic of males. Within the female sample, this scale showed small but consistent negative correlations with the number of CAG repeats, for both first and second twins. A model-fitting approach estimated a true correlation of about -0.21 for this relationship and judged it to be dependable at the 0.05 significance level, allowing for the fact that three scales were initially tested. The direction of the relationship was such that the women who scored in a relatively masculine direction on the scale showed fewer CAG repeats. Fewer CAG repeats are associated with enhanced risk for prostate cancer among males and more active transcription of androgens. Fewer CAG repeats within the normal range were found in one study of Hispanic women to be associated with masculine characteristics (Legro et al., 1994).

One might wonder if the physical characteristics were primary and the psychological ones merely a reflection of the women's self-conceptions about their femininity resulting from their perception of the physical traits. However, if this were so, one would expect differences in the masculine direction on all three behavioral dimensions. Therefore, it seems simpler to assume some specific effect in the brain that affects some but not other aspects of femininity. If such a finding of specificity is borne out in future studies, it should be helpful in the pursuit of the physiological and developmental mechanisms involved. It would also seem desirable in future studies to supplement measures based on self-report with other types of personality measurement, such as peer or spouse ratings — and, of course, to study males as well.

The second study looked at a battery of self-report items dealing with characteristics related to reproduction, ranging from premenstrual symptoms to child-rearing practices. Three items passed an initial screen by exhibiting correlations with CAG repeats that were individually significant at the 0.05 level in both the twin 1 and twin 2 samples. The items were age, having had a hysterectomy and length of labor at the second birth. (Length of labor at the first birth was similarly correlated, but met the 0.05 criterion only in one sample). Given the number of

items screened and the nonindependence of the twin 1 and twin 2 samples, one could not confidently reject the hypothesis that one or more of these results might be due to chance. Model-fitting procedures to the joint data yielded individual item probabilities in the 0.002–0.003 range for these three items, which suggests that further speculation about them may be appropriate, even though firm conclusions will need to await replication in new samples.

The correlation with age suggests selective factors of some kind, since genotypes presumably do not change with age. One such factor — selective mortality — would predict stronger effects among the older than among the younger women in the sample, but the correlation of CAG repeats with age in these two age groups proved to be essentially equal.

Another possible source of correlation between age and CAG repeats would involve differential selection into the sample. If younger women were preferentially selected for some trait positively associated with CAG repeats, or older women for some trait negatively associated, a negative correlation between age and CAG repeats would follow. For example, if the participation decision of older women depended on how reserved they were, whereas the participation of younger women depended on other factors unrelated to CAG repeats, age in the sample could become negatively associated with number of repeats.

This particular explanation is unlikely to constitute the whole story in this case, unless the differential selection by age were extreme, because the observed correlation between Reserved and CAG repeats is a weak one. This mechanism could, of course, operate along with other factors. The possible role of such selective factors in creating correlations suggests the value of including dizygotic twins, both genotyped, in future studies of this kind. An association within such pairs between CAG repeats and another trait would be largely immune to these sorts of selection effects.

The presence in the second study of an association between age and number of CAG repeats also raises the question of whether the relationships observed in the first study could have been mediated by age. All three of the M–F traits were, in fact, correlated with age: the tendencies to worry and to break rules diminished with age (correlations with age of −0.13 and −0.12 for the former, for twins 1 and 2 and −0.25 and −0.25 for the latter); whereas the tendency to be reserved increased with age (correlations of 0.13 and 0.18). As a check on the possibility of a spurious correlation, an expanded latent variable model was fit with age added as a third latent variable and the correlation between CAG repeats and the latent trait tested as before. The results for Reserved did not change materially: the increase in χ^2 when the correlation was constrained to zero was 6.670 — if anything, a trifle larger than when age was not included in the model — and the estimate of the underlying correlation between Reserved and CAG repeats remained −0.21, as before. Thus the correlation between Reserved and CAG repeats is not attributable to an age artifact. (The other two traits, Worried and Breaks rules, already nonsignificant, remained so).

Having had a hysterectomy appeared to be associated with fewer CAG repeats. For many of the twins in the sample, data were available on two conditions often leading to hysterectomy. One, the presence of endometriosis, appeared to be unrelated to CAG repeats. The other, the diagnosis of fibroids, showed a relationship, but only for one sample of twins. Thus it remains unclear whether the relationship of CAG repeats to hysterectomy (if real) is mediated in part by fibroids. It seems likely that other factors are involved as well, but unlikely that endometriosis is one of them.

We have little to say about length of labor. It is not altogether implausible that short labor would be associated with more feminine endocrinological characteristics, but this finding (again, if replicable) provides at best only a rough signpost for future investigations.

A final comment concerns the strength of the relationships observed in these two studies. All the correlations with CAG repeats were small. This means that the relationships involved are not of any immediate predictive value: Knowledge of the number of CAG repeats in a woman's AR gene would barely dent one's uncertainty about how reserved she is, or whether she is likely to have a hysterectomy one day. Nevertheless, even weak relationships, if replicable, may provide clues to directions of future research which could prove profitable in untangling the web of processes underlying human development.

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