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Influence of androgen receptor repeat polymorphisms on personality traits in men

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Background: Testosterone has been attributed importance for various aspects of behaviour. The aim of our study was to investigate the potential influence of 2 functional polymorphisms in the amino terminal of the androgen receptor on personality traits in men. **Methods:** We assessed and genotyped 141 men born in 1944 recruited from the general population. We used 2 different instruments: the Karolinska Scales of Personality and the Temperament and Character Inventory. For replication, we similarly assessed 63 men recruited from a forensic psychiatry study group. **Results:** In the population-recruited sample, the lengths of the androgen receptor repeats were associated with neuroticism, extraversion and self-transcendence. The association with extraversion was replicated in the independent sample. **Limitations:** Our 2 samples differed in size; sample 1 was of moderate size and sample 2 was small. In addition, the homogeneity of sample 1 probably enhanced our ability to detect significant associations between genotype and phenotype. **Conclusion:** Our results suggest that the repeat polymorphisms in the androgen receptor gene may influence personality traits in men.

Contexte : On a attribué de l'importance à la testostérone pour divers aspects du comportement. Notre étude visait à étudier l'influence possible de 2 polymorphismes fonctionnels de la terminaison amine du récepteur de l'androgène sur les traits de personnalité chez l'homme. **Méthodes :** Nous avons évalué et génotypé 141 hommes nés en 1944 recrutés dans la population générale. Nous avons utilisé 2 instruments différents : les échelles de la personnalité de Karolinska et le questionnaire sur le tempérament et le caractère. Pour la répétition, nous avons évalué de la même façon 63 hommes recrutés dans un groupe d'étude en psychiatrie médico-légale. **Résultats :** Dans l'échantillon recruté au sein de la population, on a établi un lien entre la longueur des répétitions du récepteur de l'androgène et les traits névrotiques, l'extraversion et l'autotranscendance. On a retrouvé le lien avec l'extraversion dans l'échantillon d'origine indépendante. **Limites :** La taille de nos 2 échantillons était différente : l'échantillon 1 était de taille modérée et l'échantillon 2, de taille modeste. En outre, l'homogénéité de l'échantillon 1 a probablement amélioré notre capacité de détecter des liens significatifs entre le génotype et le phénotype. **Conclusion :** Nos résultats indiquent que les polymorphismes répétés dans le gène récepteur de l'androgène peuvent avoir une influence sur des traits de personnalité chez l'homme.

Introduction

Testosterone influences the structure and function of the brain, both during development and in the adult organism, and is a key factor for the sexual differentiation of this organ.[1,2] Given this influence, it is reasonable to assume that testosterone may be of importance for interindividual differences in personality traits, not least those displaying sexual dimorphism, such as neuroticism, extraversion and proneness to aggression. Supporting this notion, studies suggest that androgen levels may correlate with such traits.[2–10]

The actions of androgens are mediated mainly by androgen

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receptors (ARs), which are widely distributed throughout the human brain. The AR gene (*AR*) is located on chromosome Xq11–12 and composed of 8 exons.[11,12] Exon 1, encoding the amino-terminal domain, contains 2 polymorphic trinucleotide repeats: one CAG repeat encoding a polyglutamine stretch[13] and one GGN repeat encoding a polyglycine stretch.[14]

The polymorphic polyglutamine stretch appears to be of importance in the function of the receptor as a transcription factor, tentatively by influencing the interaction between the receptor and various coactivators (relatively short fragments improving this interaction and hence increasing receptor responsiveness).[15–20] The importance of the polymorphic polyglycine stretch for AR function is less explored. Recent in vitro studies indicate that polyglycine repeat length is associated with receptor responsiveness, but the exact nature of these effects is not fully clarified.[21–25] In line with these data, a large number of studies have reported associations between short CAG or GGN repeats and increased risk of prostate cancer and benign prostate hyperplasia[26–29] and decreased risk of infertility in men.[30–32] Although investigations on the influence of *AR* repeat polymorphisms on human behaviour have been sparse, associations with personality,[33–37] externalizing behaviour[38] and depression[39] have been suggested.

In the present study, we investigated the extent to which the *AR* repeat polymorphisms are related to personality traits in 2 independent samples of men assessed with 2 personality questionnaires, the Karolinska Scales of Personality (KSP)[35,40,41] and the Temperament and Character Inventory (TCI).[42]

Methods

Participants

We recruited sample 1 from the general population, and we recruited sample 2 from a forensic psychiatry clinic. Sample 1 comprised men living in Gothenburg, Sweden, who were born during the first 6 months of 1944. They had previously been recruited by means of the population register for a study on metabolic risk factors and anthropometry; for details see a previous report by Rosmond and colleagues.[43] We assessed their personalities with the KSP and TCI. Sample 2 comprised perpetrators of severe violent and sexual crimes who had been consecutively referred by the court for pretrial forensic psychiatric investigation at the Department of Forensic Psychiatry in Gothenburg and who had accepted to participate in a research project.[44] In addition to lifetime file reviews and collateral information, the clinical workup for this group included the Structured Clinical Interview[45] for Axis I and Axis II DSM-IV[46] disorders, assessments for childhood-onset neuropsychiatric disorders, the KSP and TCI.

All participants provided written informed consent. The Ethics Committee, University of Gothenburg, Sweden approved our study protocol.

Personality assessments

The KSP consists of 135 items forming 15 subscales and measuring relatively stable personality traits.[35,40,41] These subscales are often classified into 4 factors covering different dimensions of temperament: neuroticism, psychoticism, nonconformity and extraversion.[35,47–49] Interindividual variations in several of the KSP scales have been shown to be partly hereditary.[50] To adjust for age and sex, we standardized the KSP personality test scores using normative data (T scores) to have an expected mean of 50 (standard deviation [SD] 10). The TCI is based on a self-administered true/false questionnaire and designed to assess personality along 4 dimensions of temperament (novelty seeking, harm avoidance, reward dependence and persistence) and along 3 dimensions of character (self-directedness, cooperativeness and self-transcendence).[51] In the present study, we used a Swedish 238-item translation of the TCI.[42] As with the KSP, we standardized the TCI scores using normative data (T scores).

Genotyping

We isolated genomic DNA using the QIAamp DNA Blood Mini Kit (QIAGEN). We amplified the 2 different regions by polymerase chain reaction (PCR).

We performed the PCR of the CAG repeat in the *AR* in a total volume of 15 µl containing about 50 ng DNA, 0.625 U AmpliTaq DNA polymerase (Applied Biosystems) and 0.2 µM each of the following primers: 5′-GTGCGCGAAGTGATCCAG A-3′ and 5′-GTTTCCTCATCCAGGACCAGGTA-3′.[52] We fluorescently labelled the forward primer with 6-FAM. We added nucleotides promoting the nontemplated addition of adenine by Taq DNA polymerase to the 5′ end of the reverse primer.[53] We performed thermal cycling in an Applied Biosystems GeneAmp PCR System 9700 with the following temperature profile: 95°C for 15 minutes followed by 35 cycles of 95°C for 30 seconds, 57°C for 30 seconds and 72°C for 30 seconds, with a final incubation at 72°C for 7 minutes.

We performed the PCR of the GGN repeat in the *AR* in a total volume of 15 µL containing about 50 ng DNA, 0.75 U ThermalAce DNA polymerase (Invitrogen) and 0.2 µM each of the following primers: 5′- TCCTGGCACACTCTCTTCAC -3′ and 5′- GCCAGGGTACCACACATCAGGT -3′.[14] We fluorescently labelled the forward primer with HEX. We performed thermal cycling in an Applied Biosystems GeneAmp PCR System 9700 with the following temperature profile: 98°C for 3 minutes followed by 35 cycles of 98°C for 30 seconds, 62°C for 30 seconds and 72°C for 30 seconds, with a final incubation at 72°C for 10 minutes.

We analyzed the fluorescently labelled DNA fragments by size with automated capillary electrophoresis using an ABI PRISM 310 Genetic Analyzer (Applied Biosystems).

Sequencing

To verify the actual number of repeats corresponding to a specific fragment length, we sequenced PCR products from 5 individuals. To this end, we amplified fragments containing the CAG or GGN repeats using the PCR primers described previously (with the exception of the forward primer for the CAG repeat being 5′- GTGCGCGAAGTGATCCAGA-3′) with 1U of HotStarTaq polymerase (QIAGEN)/20 µL

reaction and an annealing temperature of 58°C. We sequenced the PCR products using the BigDye Terminator Cycle Sequencing Kit (v3.1, Applied Biosystems). We then subjected samples to electrophoresis using an ABI 3730 genetic analyzer (Applied Biosystems).

Statistical analysis

Prompted by previous studies suggesting an inverse relation between the number of CAG repeats in the *AR* and receptor activity, we grouped all alleles into 2 groups of roughly equal size using the median as cut-off; we defined those with 21 repeats or fewer as short (S), whereas we defined those with 22 repeats or more as long (L). In the same way, we defined a short GGN repeat as 23 repeats or fewer and a long repeat as 24 repeats or more.

Based on previous studies,[48,49] we grouped the 15 subscales of KSP into 4 factors (extraversion, including impulsiveness and monotony avoidance; neuroticism, including somatic anxiety, psychic anxiety, muscular tension, psychasthenia, inhibition of aggression, guilt and socialization; nonconformity, including indirect aggression, verbal aggression, irritability and social desirability; and psychoticism, including detachment and suspicion). This grouping was undertaken by calculating the mean of all items within one factor, using 100-X for the 2 scales (socialization and social desirability) displaying negative loading in relation to the other scales within that factor.[49] In case a certain factor displayed a significant association with genotype, the possible relations between genotype and the different subscales within this factor were further analyzed.

We assessed associations between *AR* genotypes on the one hand and KSP and TCI scores on the other using 2-way analysis of variance (ANOVA) with CAG and GGN polymorphisms as categorical explanatory variables, each having 2 levels: S and L. To measure the proportion of variance in phenotypes explained by the combined effect of the 2 genetic variants, we calculated R^2 values for the 2-way ANOVA models. For all analyses on sample 1, we applied 2-sided tests. For the analyses on sample 2, aiming to replicate the findings observed in sample 1, we used 1-sided tests. We used SPSS software, version 15.0 (SPSS Inc.) for the 2-way ANOVA.

We corrected for multiple testing for the analyses of sample 1 by means of permutation tests (10 000 permutations), the 4 KSP factors and the 7 TCI dimensions. The reported *p* values are uncorrected.

We determined the extent of linkage disequilibrium between the *AR* repeat polymorphisms by means of χ^2 tests; the sum of squared D values divided by the product of the corresponding allele frequencies multiplied by the number of haplotypes in the sample is $\chi^2_{n-1,m-1}$, where *n* and *m* are the number of alleles for the 2 loci. We pooled alleles with frequencies less than 1%.

Results

Participants

Sample 1 comprised 275 men aged 59 years at the time of personality assessment. We obtained genotype data and useful KSP and TCI questionnaires from 141 of these men. Sample 2 comprised 100 perpetrators of severe violent and sexual crimes (92 men and 8 women). We obtained genotype data and useful KSP questionnaires from 63 of the men and TCI questionnaires from 50 men. The age of these participants varied from 17 to 76 (mean 35) years.

The allele distribution of the *AR* repeat polymorphisms, as displayed in Figure 1, was similar to that reported in other Swedish populations.[31,35] The 2 polymorphisms were not in linkage disequilibrium. The *AR* genotype (S/L) frequencies did not differ between sample 1 and sample 2 ($p > 0.1$ for both polymorphisms). The KSP and TCI scores in the 2 samples, divided by *AR* genotypes, are shown in Table 1 and Table 2, respectively.

Karolinska Scales of Personality data

In sample 1, 2-way ANOVA revealed associations between *AR* polymorphisms and neuroticism and extraversion, but not psychoticism or nonconformity (Table 3). Neuroticism was associated with the CAG repeat only (Fig. 2), whereas extraversion was associated with the CAG repeat and with the interaction between the 2 repeat polymorphisms (Fig. 3). The association with extraversion survived correction for multiple testing ($p_{corrected} = 0.009$), whereas that with neuroticism did not ($p_{corrected} = 0.15$).

Within the extraversion factor, the 2-way ANOVA

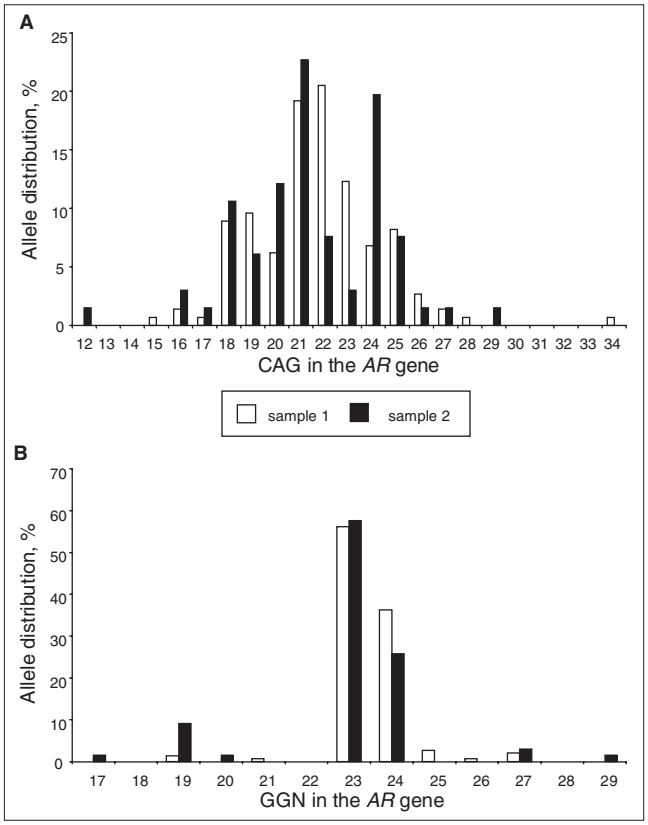

Fig. 1: Allele distributions of (**A**) CAG and (**B**) GGN alleles in the *AR* gene in samples 1 and 2.

revealed significant associations between the CAG × GGN interaction and both subscales, impulsiveness and monotony avoidance, carriers of the short CAG allele displaying higher scores when also carrying a long GGN repeat allele (Table 3). As shown in Table 3, the CAG main effect was also significant for the subscale monotony avoidance.

Although the results did not remain significant after correction for multiple testing, it is noteworthy that within the neuroticism factor 2-way ANOVA revealed significant associations for somatic anxiety and muscular tension. As shown in Table 3, the CAG repeat was associated with the neuroticism factor and the somatic anxiety, psychasthenia and muscular tension subscales. For the GGN repeat polymorphism, these associations did not reach significance; moreover, there was no significant interaction between the 2 repeats for any of these items. However, in contrast to the CAG repeat, the GGN repeat was significantly associated with the socialization subscale (Table 3). We observed no significant associations for the other neuroticism subscales (i.e., psychic anxiety, inhibition of aggression or guilt).

In sample 2, the effect of the interaction between the 2 repeats on the extraversion factor and the monotony avoidance subscale observed in sample 1 could be replicated, as could the associations between the CAG repeat and these traits (Table 4). Moreover, in sample 2 the 2-way ANOVA model showed significant associations between the CAG repeat and the impulsiveness subscale (Table 4).

On the other hand, analysis of association between *AR* genotypes and the neuroticism factor did not reach significance in sample 2 ($p = 0.06$). However, the significant associations observed in sample 1 between the CAG repeat and the somatic anxiety and muscular tension neuroticism subscales could be replicated (Table 4). With respect to the socialization subscale, the outcome differed from that observed in sample 1; whereas the effect of the CAG repeat and the interaction between the 2 repeats were significant in sample 2, the GGN main effect was not.

As in sample 1, we observed no associations in sample 2 between *AR* genotypes and psychoticism (2-tailed p values: CAG $p = 0.67$; GGN $p = 0.55$; CAG × GGN $p = 0.69$; $R^2 = 2.0\%$; model $p = 0.82$) or nonconformity (2-tailed p values: CAG $p = 0.06$; GGN $p = 0.68$; CAG × GGN = 0.27; $R^2 = 9.8\%$; model $p = 0.19$).

Temperament and Character Inventory data

When we performed 2-way ANOVA to assess possible associations between the 2 *AR* repeat polymorphisms and the 7 dimensions of personality assessed using TCI, we found that only the self-transcendence dimension was significantly associated with *AR* genotype (Table 3 and Fig. 4). The

Table 1: Karolinska Scales of Personality and Temperament and Character Inventory scores* in a normal population of men (sample 1) grouped into carriers of short and long alleles of the CAG and GGN repeat polymorphisms of the *AR*, respectively

Test measure	Polymorphism; mean (SD)			
	CAG-S	CAG-L	GGN-S	GGN-L
KSP	(*n* = 59–66)	(*n* = 72–75)	(*n* = 78–83)	(*n* = 53–58)
Neuroticism	50.57 (7.06)	47.43 (6.67)	47.85 (6.50)	50.32 (7.50)
Somatic anxiety	53.44 (9.00)	48.27 (8.36)	49.24 (8.39)	52.61 (9.55)
Psychic anxiety	48.90 (8.93)	45.85 (8.73)	46.48 (8.58)	48.32 (9.37)
Muscular tension	54.13 (9.74)	49.90 (9.74)	50.30 (9.49)	54.03 (10.23)
Psychasthenia	50.31 (11.47)	46.09 (10.51)	47.78 (11.09)	48.31 (11.25)
Inhibition of aggression	45.11 (9.43)	44.65 (10.48)	44.60 (10.12)	45.24 (9.87)
Guilt	48.49 (7.35)	45.94 (9.51)	45.78 (8.70)	49.02 (8.33)
Socialization	46.38 (10.93)	48.66 (10.53)	49.24 (9.80)	45.26 (11.66)
Psychoticism	46.93 (9.20)	47.93 (9.69)	47.96 (8.94)	46.78 (10.16)
Nonconformity	48.64 (6.30)	47.09 (6.39)	47.96 (6.58)	47.61 (6.13)
Extraversion	54.57 (9.69)	51.27 (8.05)	52.36 (8.18)	53.47 (10.04)
Impulsiveness	51.99 (10.77)	49.68 (8.74)	49.90 (8.37)	52.01 (11.45)
Monotony avoidance	57.15 (10.73)	52.86 (11.51)	54.83 (11.23)	54.93 (11.55)
TCI	(*n* = 67)	(*n* = 74)	(*n* = 82)	(*n* = 59)
Temperament				
Novelty seeking	51.52 (11.98)	52.00 (9.10)	52.01 (10.15)	51.44 (11.11)
Harm avoidance	49.70 (10.78)	47.70 (9.68)	48.34 (9.49)	49.08 (11.25)
Reward dependence	49.73 (10.76)	47.93 (10.69)	48.44 (10.55)	49.27 (11.02)
Persistence	52.43 (10.16)	49.89 (10.88)	51.20 (10.45)	50.97 (10.86)
Character				
Self-directedness	48.43 (10.78)	50.65 (10.56)	49.72 (10.52)	49.42 (10.99)
Cooperativeness	47.24 (8.52)	48.19 (10.92)	46.65 (9.94)	49.25 (9.56)
Self-transcendence	51.76 (9.31)	46.26 (9.29)	47.32 (8.62)	51.03 (10.68)
Self-transcendence 1	54.24 (11.99)	48.22 (10.11)	49.95 (10.14)	52.64 (12.90)
Self-transcendence 2	51.60 (9.28)	49.61 (9.84)	49.09 (8.99)	52.59 (10.11)
Self-transcendence 3	49.30 (8.96)	44.47 (9.15)	45.55 (8.96)	48.46 (9.68)

KSP = Karolinska Scales of Personality; L = long; S = short; SD = standard deviation; TCI = Temperament and Character Inventory.
*We standardized all personality test scores using normative data (T scores)

association between the CAG repeat and self-transcendence remained significant after correction for multiple testing ($p_{corrected} = 0.006$). Within this dimension, the CAG repeat was significantly associated with the self-transcendence 1 (self-forgetful v. self-conscious experiences) and self-transcendence 3 (spiritual acceptance v. material rationalism) subscales (Table 3), with participants carrying short CAG repeat alleles displaying higher scores. In contrast, the GGN repeat was significantly associated only with the self-transcendence 2 subscale. The interaction between the 2 repeats was neither significant for the dimension nor for the subscales (Table 3 and Fig. 4).

In sample 2, there was a tendency for an association between self-transcendence and the *AR* CAG repeat similar to that seen in sample 1; however, this association did not reach statistical significance ($p = 0.07$).

Discussion

Our data suggest that men recruited from the normal population carrying an *AR* with relatively short CAG repeats display higher scores on the personality factor extraversion (as assessed using KSP) than those carrying an *AR* with relatively long CAG repeats, and that this association is dependent on the length of the GGN repeat. That this observation is not a chance finding gains support from the fact that it could be replicated in an independent sample.

Our conclusion that androgens may contribute to interindividual differences in behaviour supports previous investigations that suggested testosterone levels[2,3,7,10] and *AR* variants[34,38] are related to personality traits such as sensation seeking, impulsiveness and other externalizing behaviours in men. With respect to associations between AR polymorphisms and personality traits related to extraversion, the literature is not unanimous. On the one hand, at least partly in line with our data, recent studies suggest that men displaying short CAG repeats are at higher risk for committing severe violent and sexual crimes than those with long CAG repeats.[54,55] On the other hand, 2 studies report associations between short CAG repeat alleles and psychoticism,[36,37] which we did not observe in our samples, and between short GGN repeats and high scores on scales related to aggression, hostility and impulsivity.[34] Moreover, a previous study assessing the possible influence of the CAG repeat in the *AR* on personality traits, as assessed using the KSP, failed to detect any associations that remained significant after correction for multiple comparisons.[35] Differences in outcomes among studies may, for example, be related to variations in race or other characteristics of the studied populations and to discrepancies in the assessments of the phenotype.

As described, there is a negative correlation between CAG repeat length and AR responsiveness. Although less established, several investigations show a positive correlation between GGN repeat length and AR activity or protein amount.[23–25] Since androgens promote extraversion-related traits, our observation that participants carrying a short CAG repeat and a long GGN repeat were those displaying the highest extraversion scores is thus in line with these functional data. Further studies on how these 2 polymorphisms interact with respect to AR activity in brain are warranted, as

Table 2: Karolinska Scales of Personality and Temperament and Character Inventory scores* in a forensic psychiatric population (sample 2) grouped into carriers of short and long alleles of the CAG and GGN repeat polymorphisms of the *AR*, respectively

Test measure	Polymorphism; mean (SD)			
	CAG-S	CAG-L	GGN-S	GGN-L
KSP	(*n* = 30)	(*n* = 20)	(*n* = 34)	(*n* = 16)
Neuroticism	63.08 (12.46)	57.35 (11.72)	59.87 (12.84)	62.72 (11.49)
Somatic anxiety	67.87 (18.85)	58.85 (14.77)	63.56 (17.99)	65.75 (17.70)
Muscular tension	70.23 (17.91)	58.35 (14.77)	66.44 (17.94)	63.44 (17.19)
Psychasthenia	62.27 (14.69)	55.35 (12.92)	57.35 (12.69)	64.06 (16.73)
Socialization	21.63 (17.28)	34.20 (17.64)	27.15 (18.96)	25.63 (17.45)
Psychoticism	56.73 (9.74)	54.43 (12.60)	55.18 (11.79)	57.16 (8.94)
Nonconformity	53.28 (9.04)	49.04 (7.25)	50.77 (9.15)	53.31 (7.09)
Extraversion	60.70 (13.70)	50.73 (12.51)	55.81 (12.52)	58.63 (17.02)
Impulsiveness	63.70 (17.04)	55.15 (14.03)	58.24 (16.09)	64.63 (16.41)
Monotony avoidance	57.70 (13.86)	46.30 (13.09)	53.38 (12.25)	52.63 (19.02)
TCI	(*n* = 36)	(*n* = 27)	(*n* = 45)	(*n* = 18)
Temperament				
Novelty seeking	52.08 (10.31)	50.48 (10.54)	52.36 (10.27)	49.00 (10.47)
Harm avoidance	61.06 (14.22)	59.85 (15.18)	58.73 (14.99)	65.06 (12.59)
Reward dependence	47.67 (10.27)	48.67 (10.31)	48.22 (10.57)	47.78 (9.55)
Persistence	47.86 (9.64)	50.00 (9.98)	49.73 (10.34)	46.39 (7.90)
Character				
Self-directedness	38.50 (15.25)	40.37 (13.38)	40.56 (15.66)	36.17 (10.32)
Cooperativeness	42.58 (17.85)	45.19 (13.85)	43.51 (15.14)	44.17 (19.02)
Self-transcendence	58.97 (15.01)	53.41 (14.49)	57.04 (14.73)	55.44 (15.82)

KSP = Karolinska Scales of Personality; L = long; S = short; SD = standard deviation; TCI = Temperament and Character Inventory.
*We standardized all personality test scores using normative data (T scores)

are studies of sufficient sample size to permit an analysis of the effect of different allele combinations on behaviour.

In our sample recruited from the general population, the CAG polymorphism was associated with neuroticism (as assessed using KSP). This association did not remain significant after correction for multiple testing, but there was a similar tendency in the sample from the forensic psychiatry group. With respect to 2 of the KSP neuroticism subscales (somatic anxiety and muscular tension), the findings obtained in sample 1 could be replicated in sample 2: short CAG repeats were significantly associated with high scores in both populations. These data support previous reports suggesting that CAG repeat length may affect interindividual variation in anxiety traits[35] and indirectly influence the risk for depression in men.[39]

The significant association between CAG genotype of the *AR* gene and self-transcendence in sample 1 is noteworthy. The self-transcendence dimension consists of 3 subscales representing different aspects of religious behaviour, subjective experience and individual world view. This dimension is reported to be the most stable TCI dimension over time, and it is 1 of the 2 TCI dimensions showing the largest interindividual variability.[42] In the initial presentation of the TCI, self-transcendence — as well as the other character traits — was thought to be influenced mainly by environmental factors.[51] However, recent twin studies challenge this view.[56,57] Also supporting genes to be of importance for the TCI character traits are previous studies revealing associations between various polymorphisms and these traits, including self-transcendence.[33,58–60] The notion that *AR* may influence religious behaviour and self-transcendence is reasonable in view of the fact that these aspects of the phenotype display marked sex differences.[42,57] Moreover, this notion is supported by a previous report by Comings and colleagues[33] in which a multivariate analysis comprising 59 different genes revealed an association between the *AR* repeat polymorphisms and TCI-assessed self-transcendence.

Table 3: Results* from 2-way analyses of variance of the effect of the CAG and GGN repeat polymorphisms on Karolinska Scales of Personality and Temperament and Character Inventory scores in a normal population of men (sample 1)

Test measure	*p* value; polymorphism			R^2, %	ANOVA *p* value
	CAG	GGN	CAG × GGN		
KSP					
Neuroticism	0.015	0.08	0.44	7.6	0.018
Somatic anxiety	0.001	0.06	0.14	12.0	0.001
Psychic anxiety	0.07	0.35	0.90	3.6	0.20
Muscular tension	0.02	0.06	0.54	7.3	0.02
Psychasthenia	0.04	0.99	0.98	3.6	0.20
Inhibition of aggression	0.82	0.74	0.93	0.1	0.98
Guilt	0.16	0.06	0.98	4.9	0.09
Socialization	0.23	0.04	0.14	5.7	0.06
Psychoticism	0.61	0.53	0.98	0.6	0.85
Nonconformity	0.13	0.55	0.77	1.8	0.49
Extraversion	0.01	0.7	0.004	9.1	0.004
Impulsiveness	0.12	0.29	0.04	5.1	0.07
Monotony avoidance	0.006	0.74	0.006	8.8	0.005
TCI					
Temperament					
Novelty seeking	0.94	0.78	0.06	2.7	0.29
Harm avoidance	0.34	0.80	0.40	1.5	0.55
Reward dependence	0.44	0.76	0.36	1.4	0.59
Persistence	0.12	0.74	0.44	2.0	0.44
Character					
Self-directedness	0.22	0.99	0.88	1.1	0.68
Cooperativeness	0.44	0.10	0.91	2.2	0.38
Self-transcendence	0.001	0.06	0.44	10.8	0.001
Self-transcendence 1	0.002	0.33	0.19	8.8	0.005
Self-transcendence 2	0.39	0.05	0.64	4.0	0.13
Self-transcendence 3	0.003	0.15	0.49	8.4	0.007

KSP = Karolinska Scales of Personality; TCI = Temperament and Character Inventory.
*p values are 2-sided. For p values corrected for multiple testing, see the Results section. Cell sizes for analysis of **neuroticism**: CAG-SxGGN-S: 31, CAG-SxGGN-L: 28, CAG-LxGGN-S: 47, CAG-LxGGN-L: 25, **nonconformity**: CAG-SxGGN-S: 31, CAG-SxGGN-L: 33, CAG-LxGGN-S: 49, CAG-LxGGN-L: 24, **etxraversion**: CAG-SxGGN-S: 33, CAG-SxGGN-L: 33, CAG-LxGGN-S: 50, CAG-LxGGN-L: 25, **all TCI dimensions**: CAG-SxGGN-S: 34, CAG-SxGGN-L: 33, CAG-LxGGN-S: 48, CAG-LxGGN-L: 26.

Limitations

When interpreting our observation that certain associations were significant in sample 1 but only close to significant in sample 2, it should be taken into consideration that sample 2 was small and that, being a forensic psychiatry population, this sample probably differs in various aspects from the population-based sample. Moreover, sample 2 was less

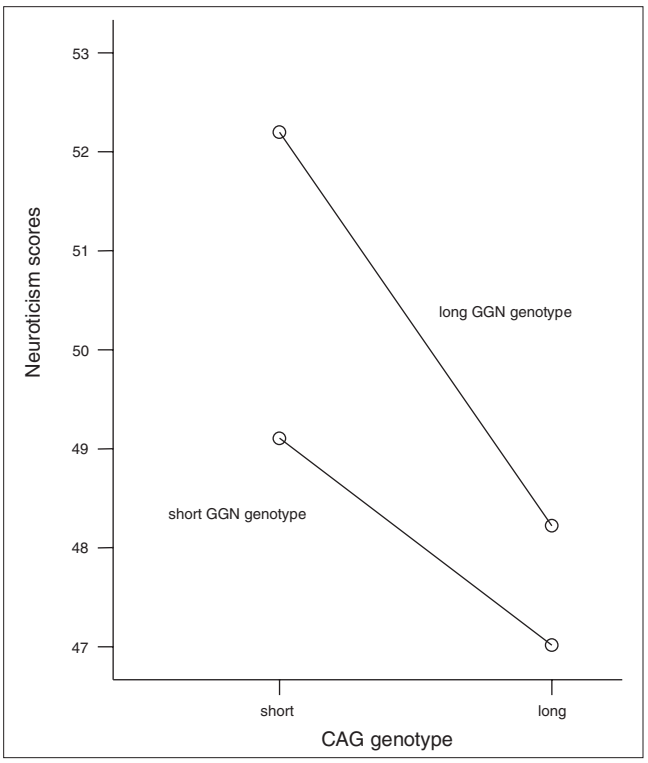

Fig. 2: Carriers of short CAG alleles display higher neuroticism scores than carriers of long CAG repeat alleles in men recruited from the general population (sample 1). No significant interaction between the repeat polymorphisms is seen. For cell sizes, see Table 3.

homogeneous than sample 1 in terms of age. Indeed, the homogeneity with respect to sex, age and race characterizing sample 1 probably enhanced our ability to detect significant associations between genotype and phenotype, thereby compensating for the fact that this population was also moderate in size.

Conclusion

Our study lends support to the notion that the CAG repeat of the *AR* is associated with KSP-assessed extraversion and that this association is influenced by the GGN repeat in the same gene. We also provide preliminary evidence of an association between the CAG repeat and KSP-assessed neuroticism and between the same repeat and TCI-assessed self-transcendence.

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Contributors: Drs. Westberg, Rosmond, Anckarsäter and Eriksson designed the study. Drs. Westberg, Landén, Annerbrink, Melke, Rosmond, Holm, Anckarsäter and Eriksson acquired the data, which Drs. Westberg, Henningsson, Melke, Nilsson, Anckarsäter and Eriksson analyzed. Drs. Westberg and Eriksson wrote the article. All authors reviewed the article and gave final approval for publication.

Table 4: Results* from 2-way analyses of variance of the effect of the CAG and GGN repeat polymorphisms on Karolinska Scales of Personality and Temperament and Character Inventory scores in a forensic psychiatric population (sample 2)

Test measure	*p* value; polymorphism			R^2, %	ANOVA *p* value
	CAG	GGN	CAG × GGN		
KSP					
Neuroticism	0.6	0.35	0.30	6.5	0.19
Somatic anxiety	0.02	0.45	0.15	8.7	0.12
Muscular tension	0.003	0.10	0.09	16.0	0.02
Psychasthenia	0.07	0.11	0.41	9.6	0.1
Socialization	0.001	0.24	0.01	20.4	0.07
Extraversion	0.001	0.38	0.01	21.5	0.005
Impulsiveness	0.007	0.34	0.01	18.2	0.01
Monotony avoidance	0.0005	0.15	0.04	21.0	0.006
TCI					
Character					
Self-transcendence	0.07	0.27	0.37	4.1	0.24

KSP = Karolinska Scales of Personality; TCI = Temperament and Character Inventory.
*Only items yielding significant associations in sample 1 are included; *p* values are 1-sided. Cell sizes for the for the analysis of **neuroticism and extraversion**: CAG-SxGGN-S: 19, CAG-SxGGN-L: 11, CAG-LxGGN-S: 15, CAG-LxGGN-L: 5, **self-transcendence**: CAG-SxGGN-S: 24, CAG-SxGGN-L: 12, CAG LxGGN-S: 21, CAG-LxGGN-L: 6.

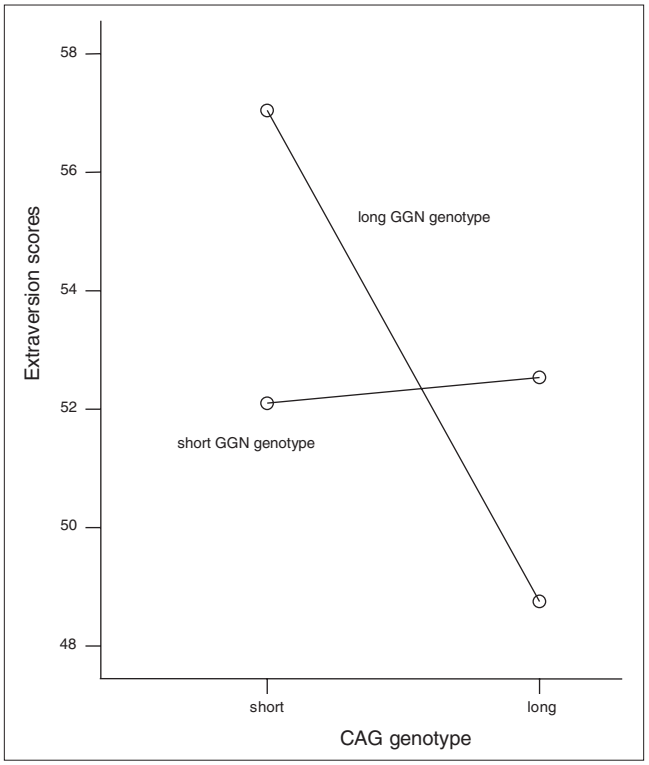

Fig. 3: Two-way interaction effect between the CAG and GGN repeat polymorphisms on extraversion scores in men recruited from the general population (sample 1); carriers of a short GGN allele show no effect of the CAG repeat on extraversion scores, whereas carriers of a long GGN allele show higher extraversion scores when also carrying a short CAG repeat allele. For cell sizes, see Table 3.

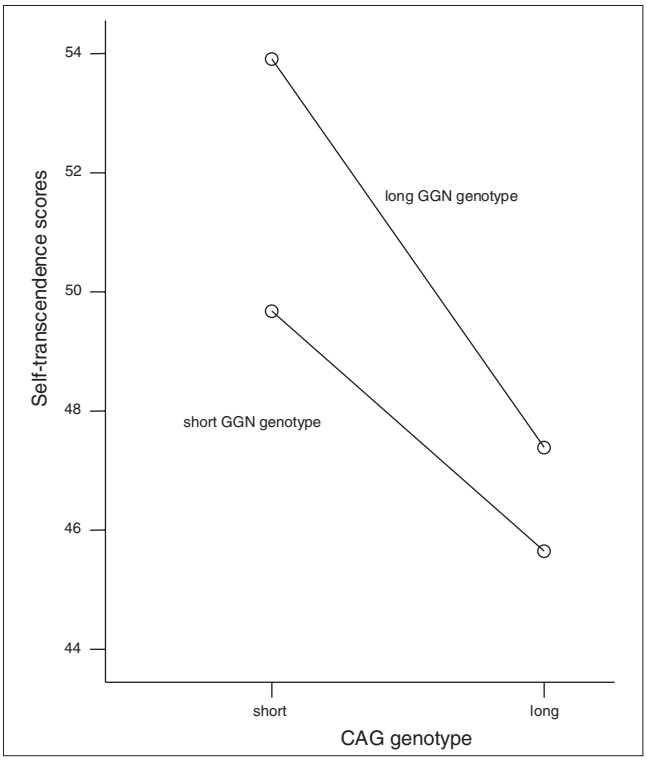

Fig. 4: Carriers of a short CAG allele display higher self-transcendence scores than do carriers of a long CAG repeat allele in men recruited from the general population (sample 1). There is no interaction between the 2 *AR* repeat polymorphisms. For cell sizes, see Table 3.

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