

Association analysis of 15 polymorphisms within 10 candidate genes for antisocial behavioural traits

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This study sought to test 15 simple sequence repeat polymorphisms within 10 candidate genes for association with antisocial behavioural traits. Genes included were those known to regulate dopamine synthesis and transmission in the brain (*DBH*, *DRD2*, *MAOA*, *TFAP2B*, *NR4A2*, *LMX1B*) and those involved in the differentiation of social and sexual behaviour in men and women (*AR*, *ESR1*, *OXTR*, *AVPR1A*). Participants were Caucasians (men = 1007, women = 1089) aged 20–24 years who were assessed for indicators of antisocial traits such as pseudo-maturity, substance misuse and unstable lifestyle. Significant associations for antisocial traits were found with *AR* and *ESR1* polymorphisms in men, and with polymorphisms within *NR4A2* and *TFAP2B* in women. The association with *TFAP2B* remained significant after correction for multiple testing. This pattern of associations suggests that genetic variation within transcription factors may in part explain the

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Introduction

Adoption and twin studies have established that variation in antisocial behaviour has a significant genetic component (Rhee and Waldman, 2002), hence research in behavioural genetics is now aimed at identifying the variation within specific genes responsible for the observed heritability of these traits. Externalizing or antisocial traits such as substance abuse, impulsivity, criminality and precocious sexuality are common in the population, although only a fraction of individuals exhibit the full range of antisocial traits with sufficient severity to warrant a diagnosis of antisocial personality disorder (ASPD). In line with recent research, this study sought to identify genetic variation contributing to antisocial traits present in the general population. The most likely candidate genes are those involved in brain development differentiation and function. Consequently, research to date has included genes responsible for neurotransmitter synthesis, reception, hormone regulation and more recently, transcription factors (Damberg *et al.*, 2001). Genes selected for this study were those involved in development of dopamine neurons (Lim Homeobox transcription factor 1B, *LMX1B*), dopamine synthesis (dopamine-β-hydroxylase, *DBH*), dopamine neurotransmission (dopamine receptor D2, *DRD2*), dopamine metabolism (monoamine oxidase A, *MAOA*) and transcriptional regulation of dopamine-related genes (nuclear receptor 4A2, *NR4A2* and transcription factor AP2B, *TFAP2B*). Owing to the established role of insecure attachment in antisocial behavioural outcomes

(Zeanah and Zeanah, 1989), and the preponderance of antisocial traits in men (Moffitt, 2003), polymorphisms in genes involved in steroid hormone regulation (androgen receptor, *AR* and estrogen receptor α, *ESR1*) and social or attachment-related behaviours (vasopressin receptor, *AVPR1A* and oxytocin receptor, *OXTR*) were also tested for association with antisocial traits.

Methods

Participants

This research involved participants in the 20+ age cohort of the PATH Through Life Project, a large Australian longitudinal study of three age cohorts that commenced in 1999. The participants were drawn from the Australian Electoral Rolls, where enrolment is compulsory for all Australians over 18. The participants were aged 20–24 years at first contact and are to be followed up every 4 years over a period of 20 years. For this age group, cheek swab DNA samples and two waves of data have been collected. The analyses reported here are based on the first wave of interviews. Further information about sampling (Parslow *et al.*, 2004), and characterization of the participants in terms of psychological functioning (Jorm *et al.*, 2004; Jorm *et al.*, 2005) have been described elsewhere. The Australian National University Human Research Ethics Committee approved this study, and informed consent was obtained from all participants.

Genotyping

Caucasian participants ($N = 2096$, men = 1007, women = 1089) were genotyped at 15 variable sequence repeat loci [*AR* (GCA), *AVPR1A* (TG)_x(TC)_y, *AVPR1A* (AGAT), *DBH* (TG), *DRD2* (GA), *DRD2* (GT), *ESR1* (TG), *LMX1B* (TG), *LMX1B* (CA), *MAOA* 30 bp repeat, *NR4A2* (CGG), *NR4A2* (AC), *OXR* (CA), *TFAB2B* (ACAA), *TFAB2B* (TC)] using a multiplex design where all 15 loci were amplified by PCR and separated by capillary electrophoresis simultaneously, using an ABI 3730 genetic analyser (Biomolecular Resource Facility, JCSMR, ANU; Biomolecular Resource Facility, John Curtin School of Medical Research, Australian National University, Canberra, Australia, SPSS version 12, Chicago, USA). Primer sequences, reagents, details of each polymorphism, and genotyping methods have been reported elsewhere (Prichard and Easteal, 2006).

Measurement of antisocial traits

As there is no scale in PATH designed specifically to measure antisocial behavioural traits, a scale was created comprised of known indicators of antisocial traits. This follows from the work of McGue and Iacono (2005), who demonstrated, using a population-based longitudinal study of 1252 males and females, that nicotine dependence at an early age (< 15 years), alcohol and substance abuse/dependence, police problems and sexual intercourse all predicted externalizing psychopathology at age 20. The presence of multiple problem behaviours before age 15 substantially increased the subsequent risk for substance abuse, clinically defined ASPD and major depressive disorder in both men and women, however, men were more likely to exhibit ASPD, whereas women were more likely to exhibit major depressive disorder.

This study relied on a parallel antisocial behavioural or antisocial traits measure using early onset problem behaviour indicators on the basis of the, where possible, McGue and Iacono (2005) study together with other established indicators of antisocial behaviour (Pedersen *et al.*, 2003; Hare and Neumann, 2005). This is a defensible approach given the apparent generality of risk for externalizing psychopathology in the population and the intercorrelation of indicators of problem behaviour. Indicators selected for inclusion in the factor analysis which established the measure properties of the scale were pseudo-maturity variables [early age of first sex (< 15 years), early age of leaving home (< 18 years), early age of living with partner (< 18 years) and early age of childbirth (< 18 years)], substance use/abuse variables [current smoking status, past hazardous/harmful drinking, early marijuana use (< 16 years), frequent marijuana use (weekly or more)], and unstable lifestyle indicators: frequent financial problems, low educational attainment (< 5 years of secondary school education), current unemployment, and problems with the police with a court appearance in the last 6 months (c.f. McGue and

Iacono, 2005). The unstable lifestyle indicators were selected on the basis of their similarity to items in the *Diagnostic and Statistical Manual of Mental Disorder-IV* criteria for ASPD. Frequency data for each variable are given in Table 1.

Factor analysis of these indicators coded as binary variables (present/absent) was undertaken using MPLUS Version 3.12 (Muthén and Muthén, 2004). This program is suitable for the factor analysis of binary data. All 12 indicators loaded substantially on a single factor (range of factor loadings; 0.318–0.891), which provided a good fit to the data. Therefore, this measure was used to assess antisocial traits in subsequent analyses. As would be expected, participants' scores on this antisocial measure were highly correlated with the unweighted sum of the original binary indicators of the trait ($r = 0.88$).

Genotype coding and statistical analysis

Statistical analyses were conducted using two methods. Firstly, each locus was recoded by grouping several alleles of similar size together to render statistical analysis more manageable. This was necessary as low frequency variants were found at all loci, and reasonable as simple sequence repeat polymorphism length variation has been found to correlate with transcriptional efficiency (Sabol *et al.*, 1998; Hammock and Young, 2002; Sharma *et al.*, 2003).

Depending on the number of alleles and the frequency distribution at each locus, alleles were categorized by size

Table 1 Indicators of antisocial behaviour in PATH recoded for inclusion in factor analysis

Antisocial trait	Variable coding (codes, N) ^a
Age of first sexual intercourse	≤ 14 years (1, $N = 97$) > 14 years (0, $N = 1873$)
Age of first living away from home	≤ 17 years (1, $N = 384$) > 17 years (0, $N = 1665$)
Age of first living with a romantic partner	≤ 17 years (1, $N = 78$) > 17 years (0, $N = 2007$)
Age of parenting first child	≤ 17 years (1, $N = 20$) > 17 years (0, $N = 2065$)
Past alcohol misuse	Hazardous or harmful (1, $N = 558$) Abstinent or moderate (0, $N = 1529$)
Current smoking status	Smoker (1, $N = 659$) Nonsmoker (0, $N = 1435$)
Age of first marijuana use	≤ 15 years (1, $N = 453$) > 15 years (0, $N = 1641$)
Marijuana use frequency	Weekly or more (1, $N = 204$) < Weekly (0, $N = 1892$)
Financial problems	Frequent (1, $N = 118$) Occasional or sometimes (0, $N = 1976$)
Educational attainment	≤ 4 years secondary school (1, $N = 179$) > 4 years secondary school (0, $N = 1917$)
Current employment status	Unemployed (1, $N = 284$) Employed (0, $N = 1812$)
Recent police problems	Court appearance in past 6 months (1, $N = 59$) No problems in past 6 months (0, $N = 2036$)

^aCoding for indicators of problem behaviour: 1 = trait present; 0 = trait absent.

into either two or three groups with the cutpoint chosen to give the comparable numbers of alleles in each group. Hence, loci with small numbers of alleles were divided in to two groups and relabelled 'short' or 'long' giving three possible genotypes: short/short, short/long, long/long. Loci with more alleles were divided into three groups and relabelled according to size 'short', 'medium' and 'long' with six possible genotypes: short/short, short/medium, short/long, medium/medium, medium/long and long/long. An exception to this classification system was the *MAOA* locus, which was recoded according to transcriptional efficiency directly assessed and recorded in the literature (Sabol *et al.*, 1998). Rare *MAOA* (30 bp rpt) alleles; 3.6 and 6, observed only once each in the sample were included in the low activity group as they are closer in size to the alleles in that group (Caspi *et al.*, 2002). One individual who was null at the *MAOA* locus was excluded from subsequent analysis. The *AR* (GCA) locus was additionally recoded by categorizing alleles into short and long groups only despite the many alleles present. This was done to enable replication of previous association studies in behavioural and personality traits that grouped the data in this way (Comings *et al.*, 1999).

All analyses were carried out separately for men and women. Mean scores for antisocial behaviour for grouped genotypes at each locus were compared using analysis of variance in Statistical Package for the Social Sciences (SPSS, Version 12). When a significant difference was observed ($P < 0.05$), post-hoc least significant difference (LSD) tests were examined. A second analysis was also performed where each of the two alleles detected at the 15 loci genotyped for each individual were treated as continuous variables. Linear regression was used to test for association between allelic length and scores for antisocial traits.

Correction for multiple testing was performed using the Holm method (Aickin and Gensler, 1996). This method controls type I error rate but has substantially greater power than the Bonferroni method. Sixteen tests were performed for men and women (15 loci and alternate *AR* allele grouping) in the first set of analyses, with the second set of analyses involving 15 tests, hence the adjusted significance criteria were based on an alpha of 0.05, corrected for 16 and 15 tests, respectively.

Results

Only very small differences were noted between results for analyses using grouped genotypes with the results obtained using ungrouped alleles as continuous variables. Table 2 shows mean scores for antisocial traits for grouped genotypes at each locus together with the unadjusted P value resulting from testing between group differences using one-way analysis of variance. In men, the only

positive association was found at the *AR* (GCA) locus, where men with the medium genotype scored higher for antisocial traits ($P = 0.039$). Very little difference was found when the same locus was tested using ungrouped alleles, although this result marginally escaped significance ($P = 0.053$). Conversely, men at the *ESR1* (TG) locus did not show significant differences between grouped genotypes ($P = 0.074$); however, a significant association resulted when using ungrouped alleles as independent variables in the analysis ($P = 0.034$). In women, two significant results were observed with identical P values resulting from each analysis method. Those with the long/long *NR4A2* (CA) scored significantly higher for antisocial traits ($P = 0.008$), as did those with the short/long genotype of *TFAP2B* (TC), ($P = 0.002$), a result that remained significant after Holm correction for multiple testing.

Discussion

This study tested 15 genetic loci for association with antisocial traits in male and female Caucasians. Although most of the loci tested were negative, two positive associations were observed in men – at the *AR* (GCA) and *ESR1* (TG) loci – and two positive associations – at the *NR4A2* (CA) and *TFAP2B* (TC) loci – were observed in women. These results will be discussed in the context of prior literature findings.

AR (GCA) and *ESR1* (TG)

The *AR* and *ESR1* genes encode proteins that function as steroid-hormone activated transcription factors that control several processes, including the maintenance of sex-specific behaviours (Gobinet *et al.*, 2002; Sisk *et al.*, 2003). This study found an association of the *AR* (GCA) medium allele with antisocial traits in men. It is, however, difficult to interpret the finding owing to the absence of prior reports comparing short, medium and long alleles. The marginally significant P value ($P = 0.039$) must also temper any confidence in the association. Negative or sporadic findings have been reported in the literature for this polymorphism in which genotypes comprised of short and long alleles were compared. For example, the long form was found to be associated with higher scores for muscular tension (measured as part of the Karolinska Scales of Personality Inventory, KSP) and lower scores for lack of assertiveness in Swedish male Caucasians. In their study, the authors suggested the result could be due to chance as the results were no longer significant after correction for multiple testing (Jonsson *et al.*, 2001). In another study of Australians, males with the short form of the polymorphism were found to score significantly higher for psychoticism, a trait correlated with antisocial behaviour (Turakulov *et al.*, 2004). Our results support the conclusions of other researchers who have stated that if this polymorphism is related to psychological traits at all, the relationship is a weak one (Loehlin *et al.*, 2003),

Table 2 Mean scores (standard deviations) for antisocial traits when grouping for genotypes at each locus in males and females

Locus	Short/short	Short/medium	Short/long	Medium/medium	Medium/long	Long/long	P-value
Males – antisocial traits scale							
AR (GCA) ^a	0.094 (0.503)	–	–	0.113 (0.501)	–	0.022 (0.461)	0.039 ^b
AR (GCA) alternate ^a	0.102 (0.498)	–	–	–	–	0.058 (0.484)	0.160
AVPR1A (TG) x (TC) _y	0.077 (0.475)	0.068 (0.501)	0.038 (0.471)	0.137 (0.487)	0.117 (0.526)	0.067 (0.479)	0.499
AVPR1A (AGAT)	0.113 (0.488)	0.058 (0.491)	0.109 (0.501)	0.111 (0.510)	–0.007 (0.453)	0.065 (0.539)	0.269
DBH (TG)	0.084 (0.516)	–	–	0.067 (0.477)	–	0.100 (0.480)	0.726
DRD2 (GA)	0.077 (0.495)	–	–	0.078 (0.473)	–	0.110 (0.598)	0.940
DRD2 (GT)	0.085 (0.504)	0.070 (0.488)	0.121 (0.475)	0.076 (0.485)	0.061 (0.487)	0.127 (0.574)	0.885
ESR1 (TG)	–0.013 (0.421)	0.083 (0.480)	0.025 (0.491)	0.072 (0.489)	0.136 (0.515)	0.158 (0.529)	0.074
LMX1B (TG)	0.106 (0.459)	0.090 (0.476)	0.073 (0.491)	0.086 (0.513)	0.047 (0.491)	0.101 (0.538)	0.886
LMX1B (CA)	0.077 (0.492)	–	–	0.088 (0.474)	–	0.020 (0.800)	0.955
MAOA 30 bp rpt ^a	0.066 (0.484)	–	–	–	–	0.087 (0.495)	0.513
NR4A2 (CGG)	0.087 (0.550)	–	–	0.086 (0.486)	–	0.070 (0.483)	0.868
NR4A2 (AC)	0.094 (0.461)	–	–	0.068 (0.488)	–	0.082 (0.533)	0.762
OXTR (CA)	0.094 (0.492)	–	–	0.060 (0.478)	–	0.063 (0.543)	0.567
TFAP2B (ACAA)	0.105 (0.523)	–	–	0.087 (0.490)	–	0.060 (0.479)	0.575
TFAP2B (TC)	0.206 (0.612)	–	–	0.073 (0.478)	–	0.077 (0.491)	0.556
Females – antisocial traits scale							
AR (GCA)	0.131 (0.528)	0.147 (0.515)	0.038 (0.491)	0.099 (0.503)	0.085 (0.499)	0.086 (0.567)	0.308
AR (GCA) alternate	0.121 (0.511)	–	–	0.079 (0.489)	–	0.119 (0.035)	0.415
AVPR1A (TG)x(TC) _y	0.105 (0.535)	0.054 (0.490)	0.122 (0.497)	0.094 (0.521)	0.115 (0.531)	0.125 (0.519)	0.689
AVPR1A (AGAT)	0.110 (0.519)	0.102 (0.505)	0.111 (0.495)	0.041 (0.502)	0.045 (0.516)	0.272 (0.603)	0.326
DBH (TG)	0.076 (0.491)	–	–	0.113 (0.510)	–	0.103 (0.544)	0.569
DRD2 (GA)	0.107 (0.507)	–	–	0.089 (0.520)	–	0.046 (0.529)	0.663
DRD2 (GT)	0.037 (0.465)	0.118 (0.521)	0.106 (0.548)	0.114 (0.517)	0.077 (0.495)	0.054 (0.471)	0.789
ESR1 (TG)	0.122 (0.525)	0.104 (0.499)	0.130 (0.539)	0.102 (0.534)	0.092 (0.494)	–0.004 (0.471)	0.639
LMX1B (TG)	0.163 (0.586)	0.063 (0.501)	0.120 (0.524)	0.122 (0.478)	0.095 (0.516)	0.047 (0.466)	0.477
LMX1B (CA)	0.103 (0.508)	–	–	0.086 (0.539)	–	–0.051 (0.363)	0.682
MAOA 30 bp rpt	0.066 (0.499)	–	–	0.126 (0.513)	–	0.080 (0.513)	0.265
NR4A2 (CGG)	0.158 (0.547)	–	–	0.082 (0.494)	–	0.104 (0.520)	0.370
NR4A2 (AC)	0.093 (0.517)	–	–	0.064 (0.490)	–	0.185 (0.540)	0.008 ^c
OXTR (CA)	0.121 (0.516)	–	–	0.058 (0.497)	–	0.174 (0.551)	0.058
TFAP2B (ACAA)	0.025 (0.478)	–	–	0.128 (0.533)	–	0.095 (0.496)	0.090
TFAP2B (TC)	–0.170 (0.270)	–	–	0.188 (0.529)	–	0.082 (0.507)	0.002 ^d

^aMales are hemizygous at this locus inheriting only one copy of the polymorphism, short, medium or long for AR (GCA), short or long for AR (GCA) alternate and MAOA 30 bp rpt.

^bMedium genotype significantly different from long ($P=0.01$) by least significant difference criteria.

^cLong/long genotype significantly different from short/short ($P=0.03$) and short/long ($P=0.002$) by least significant difference criteria.

^dShort/long genotype significantly different from short/short ($P=0.004$) and long/long ($P=0.006$) by least significant difference criteria.

particularly considering that the alternative analysis performed in this study using ungrouped alleles as continuous variables did not yield a significant association.

To date no studies have reported an association between the 5' flanking region polymorphism of *ESR1* with behavioural traits. When genotypes were grouped for length no significant association was observed. In the second analysis, however, using ungrouped allele length it was found that longer alleles of the *ESR1* (TG) polymorphism were significantly associated with higher scores for antisocial traits in men ($P=0.034$). This result did not remain significant after Holm correction for multiple testing, and given the relatively high P value, it may be that this result arose due to chance.

NR4A2 (AC)

The *NR4A2* gene encodes a member of the steroid-thyroid hormone-retinoid receptor superfamily (Jankovic *et al.*, 2005). The encoded protein may act as a transcription factor involved in dopamine neuron devel-

opment and gene-regulation involving dopamine-related processes in the brain (Sacchetti *et al.*, 2001). No association of *NR4A2* (AC) genotypes with antisocial traits was found in men, however, women with the long/long genotype scored higher for antisocial traits ($P=0.008$). This result, however, while highly significant in isolation, was no longer significant after correction for multiple testing. Although there is some indication of this gene influencing individual differences in personality (Carmine and Buervenich, 2003), there have been very few reports of its associations. Thus, replication of the result reported here is required before firm conclusions about its role can be drawn.

TFAP2B (TC)

TFAP2B is a transcription factor involved in neural gene expression and in the development of midbrain structures including monoaminergic neurons (Takeuchi *et al.*, 1999). It is expressed in the hippocampus, midbrain and cerebral cortex, influencing regulation of monoaminergic-related genes thought to be due to *TFAP2B* binding sites in their regulatory sequences (Damberg *et al.*, 2000).

Although one group has reported an association of the *TFAP2B* (ACAA) polymorphism with personality traits (Damberg *et al.*, 2000), this study is the first to report an association of the *TFAP2B* (TC) locus with behavioural traits, in which women with the short/long form of the polymorphism were found to score higher for antisocial traits. Interestingly, the *TFAP2B* (ACAA) locus, which was found to be in strong linkage disequilibrium with the *TFAP2B* (TC) polymorphism in this sample (Prichard and Eastaale, 2006) also showed a similar nonsignificant trend ($P = 0.09$) in which women with the short/long *TFAP2B* (ACAA) genotype also scored higher for antisocial traits. The consistency of the result across the two loci in linkage disequilibrium, and its survival after correction for multiple testing suggests that this association may be genuine.

In summary, this study reports positive associations between genetic polymorphisms and antisocial traits, although replication is necessary before any firm conclusions can be drawn. If the results withstand replication, a great deal about the nature of the association remains to be understood. This includes the biological mechanism by which these genetic differences confer vulnerability to antisocial traits, and why the patterns of association differ between men and women. Coming from a large well-ascertained community sample, the results reported here offer a starting point for further investigation.

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