Association between the dopamine D4 receptor gene exon III variable number of tandem repeats and political attitudes in female Han Chinese

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Twin and family studies suggest that political attitudes are partially determined by an individual’s genotype. The dopamine D4 receptor gene (DRD4) exon III repeat region that has been extensively studied in connection with human behaviour, is a plausible candidate to contribute to individual differences in political attitudes. A first United States study provisionally identified this gene with political attitude along a liberal–conservative axis albeit contingent upon number of friends. In a large sample of 1771 Han Chinese university students in Singapore, we observed a significant main effect of association between the DRD4 exon III variable number of tandem repeats and political attitude. Subjects with two copies of the 4-repeat allele (4R/4R) were significantly more conservative. Our results provided evidence for a role of the DRD4 gene variants in contributing to individual differences in political attitude particularly in females and more generally suggested that associations between individual genes, and neurochemical pathways, contributing to traits relevant to the social sciences can be provisionally identified.

‘There’s not a liberal America and a conservative America—there’s the United States of America.’

—Barack Obama

1. Introduction

The liberal–conservative ideological divide has become pervasive in American politics viz., red and blue states, and understanding the determinants of this enduring gulf is of keen interest not only to political scientists and psychologists but also to the media and the public at large. Nor is the American liberal–conservative divide peculiar to the United States but characterizes political attitudes across the globe. Although the liberal–conservative distinction is by no means watertight, it remains one of the best ways to grade political attitudes since the French Revolution [1]. Two core dimensions have been suggested to underlie the liberal–conservative continuum: (i) attitudes towards inequality and (ii) attitudes towards social change versus tradition [2,3]. Indeed, it appears that ideology is doggedly salient in the life of nations and can be defined as an ‘interrelated set of moral and political attitudes that possesses cognitive, affective, and motivational components’ [1, p. 653].

Individual differences in political attitude have been attributed to both situational and dispositional factors [4]. Situational factors such as 9/11 produce a collective shift in political views [5] and are clearly relevant for understanding differences in attitudes. However, biology cannot be ignored. Starting with a study of Madsen [6] showing a role of serotonin in dominance behaviour, biology has increasingly become a focus of explanation in understanding ideas related to political and other social attitudes. Among
dispositional factors related to broad biological processes that have captured recent attention are neural structures [7–10] and cognitive processes [11] including physiological response to threats [12], facial expression processing [13] and sensitivity to disgust.

Accumulating evidence shows that social attitudes towards many contemporary issues are moderately heritable [14–17]. The total contribution of genetic factors to social attitudes such as ‘conservatism’ is significant. In the large twin study of Eaves et al. [15], ‘conservatism’ shows a heritability of 64.5% for men and 44.7% for women. Indeed, heritability of social attitudes is comparable to heritability of personality traits. A few studies have also reported association between specific genes and political attitudes and behaviour [18–23].

Dopaminergic neurons date back at least 600 million years to the stem metazoan, an archaic crawling annelid [24]. This ancient neurotransmitter has acquired over the course of evolution an important role in brain function including risk-based decision-making, reward prediction and punishment learning [25–27], as well as risky behaviours [28,29]. Animal models of the role of dopamine in cognition, learning and memory, have provided invaluable clues as to the role of dopamine in these same human behaviours [30–37].

A particular gene, encoding the dopamine D4 receptor (DRD4), that we first provisionally identified with the personality trait of Novelty Seeking [38–40], (but see [41–43]), was recently identified by Fowler and his group [18] as contributing to individual differences in political attitude but only contingent on number of friends. The DRD4 gene contains a variable number of tandem repeats (VNTR) locus in exon III, where a 48 bp sequence may be repeated two to 11 times [44]. Settle et al. [18] tested association between DRD4 exon III VNTR and political attitude using data from the ‘Add Health’ survey study [45]. Self-identified political attitude was ascertained from responses to a widely used survey questionnaire [46]. Settle et al. [18] used a family-based design to minimize population stratification in a group of young adults and found a significant interaction between self-reported number of friends and the DRD4 7 repeat (7R) allele. In short, the number of friends moderates an association between 7R and political attitude, and having more 7R alleles and more friends is associated with being more liberal.

By leveraging our ongoing investigation of decision-making [47–53], we were positioned to undertake an independent study of association between DRD4 and political attitude in 1771 Han Chinese university students in Singapore. We employed not only a similar self-report question as did Settle et al. [18] to measure political attitude, but an additional more detailed questionnaire [54] to further validate our first findings. Our aim was to test association between DRD4 exon III polymorphism and political attitude in a non-Caucasian population living in a different cultural and political milieu, characterized by distinct DRD4 allele frequencies [55] and using in addition a more detailed measure of political attitudes [54].

We further hypothesized that there would probably be a gender difference in political attitudes. Notably, in an East Asian study, a greater number of young men have outright support for democracy compared with young women. This corresponds to the view that more young women in East Asia support authoritarian rule and are more cynical towards whether the type of political system matters [56]. (See also [57] who showed that Japanese females were more conservative than Japanese males.) In another study, which is consistent with many others, traditional morality and attitudes prevail especially among women in China compared with the UK [58].

Finally, a replication in Singaporean Han Chinese would considerably strengthen the provisional role of the DRD4 in partially explaining individual differences in political attitude along the liberalism–conservatism continuum.

2. Material and methods
(a) Participants and questionnaires
Study subjects were recruited via email advertisement among students of the National University of Singapore (NUS). They participated in an incentivized laboratory economic experiment session, donated samples of blood or saliva for DNA extraction and then were invited to complete online surveys with psychological questionnaires. To minimize population stratification, we recruited only students with Han Chinese ancestry.

Political attitude was indexed by self-placement scores, as described in [18,54] (see the electronic supplementary material, table S1).

Number of friends was indexed by question: ‘how many close friends/confidants do you have?’ with options being: ‘none’, ‘1 or 2 friends’, ‘3 to 5 friends’, ‘6 to 9 friends’, ‘10 or more friends’.

(b) Genotyping
DNA was extracted either from blood samples using QIAamp DNA Blood Midi Kit (Quiagen), or from saliva samples, collected with Oragene DNA OG-500 tubes (DNA Genotek Inc., Ontario, Canada). The DRD4 exon III VNTR was analysed by PCR with 0.3 units of HotStar Plus DNA polymerase (Qiagen) per reaction, 1× Q-solution, 1× CoralLoad buffer, 200 μM of each dNTP, 200 nM of each primer and 10–20 ng of genomic DNA per reaction, in a volume of 10 μl. Primer sequences were: forward 5′-GGCAGCTACTGTGGTCTCCTG-3′, reverse 5′-AGGACCCTCATGGCCCTTG-3′ [61]. Thermal protocol comprised activation step—95°C for 5 min; 40 cycles of 94°C for 30 s, 55°C for 30 s, 72°C for 40 s; and final hold at 72°C for 5 min.

(c) Genotype classification scheme
The 7R variant of DRD4 exon III VNTR is present in very low frequencies in East Asian populations [55]. In East Asian groups, the second most common variant is the 2R which has been suggested to functionally ‘substitute’ for the 7R [62]. Recently, it was suggested that any allele other than most common (presumably ancestral) 4R probably confers decreased functionality of the DRD4 gene [63]. Molecular studies of DRD4 receptor synthesis [64,65] strengthen this notion and show that the folding efficiency is rate-limiting in the biogenesis of DRD4 and importantly, the receptor with only two repeats (2R) is less upregulated compared with the receptor with four repeats (4R). Importantly, the folding of DRD4 in the endoplasmic reticulum forms the bottleneck of receptor biosynthesis. Altogether, in East Asian groups, it therefore makes sense, to avoid losing any genetic information, to test association by comparing 4R/4R subjects against all others (mostly 2R carriers) as we do in this study.
(d) Statistics
Statistical analysis was performed with Stata/IC 11 (StataCorp LP, College Station, TX, USA). Deviations from Hardy–Weinberg equilibrium were tested with command -genhw- [66]. Associations with political attitude were tested using ordered logistic regression (OLR), associations with personality traits were tested using linear regression. In regression models, the DRD4 exon III VNTR 4R/4R genotype was coded as '1'; all other genotypes were coded as '0' (recessive genetic model). Sex was coded as '1' for males and '2' for females. All regressions used a robust variance estimator. Cliff’s deltas were calculated using the method from [67]. Permutation analysis on the basis of Monte Carlo simulations was conducted using command -permute- in Stata/IC 11. The values of dependent variable (political orientation) were permuted 1000 times and regression tests with several genetic models (4R additive, dominant, recessive, 2R additive, long alleles (more than 4R) dominant) were performed at each permutation.

3. Results
(a) Summary statistics
In this study, 1771 (883 males) NUS undergraduates indicated their political views on a 5-item Likert scale from ‘highly conservative’ to ‘highly liberal’ (higher scores correspond to more liberal attitude). The political attitude distribution is shown in the electronic supplementary material, table S2.

The mean age of these subjects was 21 years, s.d. = 1.4, range 18–28 (males: mean 21.7, s.d. 1.3, range 18–28; females: mean 20.2, s.d. 1.2, range 18–28). OLR indicated that the effect of age on political attitude in this student sample was not significant (odds ratio (OR) = 1.04, p = 0.22), but the distinction between sexes was evident, with females being less liberal than males (OR = 0.698, p = 6.3 × 10^{-5}) (see the electronic supplementary material, table S3).

(b) Association between personality traits and political attitude
Subjects were also inventoried with the NEO-PI-3 (Big Five model) and TCI-R (Temperament and Character Inventory). NEO-PI-3 scores were available for 1257 subjects (71% of the sample), and TCI-R scores—for 959 subjects (54%). Using OLR, we found that liberal political attitude was positively correlated with Openness (coeff. = 0.036, p = 3.5 × 10^{-10}), inversely with Agreeableness (coeff. = −0.33, p = 9 × 10^{-10}) and to a lesser degree with Neuroticism (coeff. = −0.018, p = 0.02) domains of the NEO (electronic supplementary material, table S4). Moreover, liberalism was positively associated with TCI novelty seeking (coeff. = 0.032, p = 1.7 × 10^{-9}), negatively related with self-transcendence (coeff. = −0.018, p = 0.0035) and to a lesser extent with reward dependence (coeff. = −0.013, p = 0.03) (electronic supplementary material, table S5).

(c) Association between political attitude and DRD4 exon III variable number of tandem repeats
Genotype and allele frequencies of DRD4 exon III VNTR are shown in the electronic supplementary material, table S6. As expected, the most common allele was the 4R followed by the 2R in this Han Chinese population in which the prevalence of the 7R allele is known to be low [55]. No deviation from Hardy–Weinberg equilibrium was detected (p > 0.05). Notably, the frequency of all alleles of more than six repeats were extremely rare as is typical of Chinese populations (less than 0.5%).

We initially examined the role of both DRD4 and sex for association with political ideology. As shown in table 1 (model a), a significant association was observed between the DRD4 exon III VNTR and political attitude (OR = 0.820, p = 0.027), the 4R/4R carriers were less liberal than other subjects. Comparison of 4R/4R with all other DRD4 genotypes is not an uncommon practice [68–73]. Additionally, presence of a single 7R trumps the effect of the 4R in many studies hence it is not surprising that the 4R/4R grouping has special significance. Moreover, the 4R/4R is the ancestral genotype [74], again suggesting its distinct status. Finally, the 4R/4R is more efficient in forming heterodimers than the 4R/7R [64], suggesting a possible biochemical mechanism underlying the grouping of the 4R/4R homozygote versus all others as we have herein done. The effect of sex on political attitude remained significant in the model including DRD4 (OR = 0.700, p = 7.7 × 10^{-15}) with females being less liberal. We next included the interaction term (DRD4 × sex) in the model and observed a significant interaction (OR = 0.675; p = 0.03) between DRD4 and sex (table 1, model 2); this implied that the effect of DRD4 was modulated by sex.

To have a closer look at the interaction effect, we next examined each sex separately. As shown in table 1, the association between political attitude and DRD4 was highly significant for females (OR = 0.658, p = 0.001), but not for males (OR = 1, p = 1). Cliff’s delta (effect size measure for ordinal data [67]) was 0.058 in the combined sample and 0.115 in the female group, indicating a small effect size is almost always observed for complex traits from diabetes [75] to educational achievement [76]. Among females in the highly conservative category 37.5% of subjects carried non-4R/4R genotypes, whereas this proportion was as high as 62.1% in the highly liberal group. We further examined the robustness of the association results by carrying out permutation analysis (1000 iterations) with several genetic models (4R additive, 4R recessive, 4R dominant, 2R additive and long alleles (more than 4R) dominant) towards minimizing the problem of multiple testing [77]. In the combined sample (males and females), the empirical p-value showed only borderline significance (p = 0.076), whereas the association remained highly significant in the female sample (p = 0.003).

(d) Association of DRD4 with a broader range of political attitudes
Whether people are liberal or conservative is an aggregate measure of political attitude, and individuals may have different views on specific economic, social and political issues. Hence, we also used an adapted version of the questionnaire in Benjamin et al. [54], which inventoried a broader range of such attitudes. The original version of the questionnaire had 34 questions, which focused on subjects living in Sweden. We modified the questionnaire and chose 22 questions, which were more relevant to attitudes on economic, social and political policies in Singapore.

We applied the OLR model to test the association between subject’s attitude on each question and DRD4, with sex as a covariate (electronic supplementary material, table S7).
Table 1. Effect of DRD4 exon III VNTR on political attitudes. (Ordered logistic regression: odds ratios indicate odds of being in higher political attitude category with one unit increase of independent variable. (a) Model without interaction term. (b) Model with DRD4 × sex interaction term. DRD4 = 1 if DRD4 exon III VNTR genotype is 4R/4R and DRD4 = 0 for all other genotypes. Sex = 1 for males and 2 for females. Higher values of political ideology scale correspond to liberal attitude. Minus sign at the coefficients, and odds ratios less than 1 imply that 4R/4R carriers were less liberal. p-values in parentheses. *p < 0.10; **p < 0.05; ***p < 0.01.)

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<td>DRD4</td>
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<td>1.482</td>
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<td>(7.7 × 10^{-5})</td>
<td>(0.32)</td>
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<td>DRD4 × sex</td>
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<td>0.675**</td>
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Among the 22 items, there were three which we judged were very relevant to our Singapore student population, and that appeared to strongly index Singapore political orientation (Question 13, ‘strengthen animal rights’; Question 15, ‘decrease carbon dioxide emissions’; Question 14, ‘invest more to prevent environmental damages’; see the electronic supplementary material, figure S1). The associations of these items with DRD4 polymorphism were significant (p < 0.05; electronic supplementary material, table S7). The coefficients’ signs were consistent with our main results: those subjects who have genotype 4R/4R tended to have less liberal views.

To minimize issues of multiple testing, we carried out a PCA analysis on all 22 questions of the broad political attitudes questionnaire. In model 1 of table 2, the main component from PCA was correlated with DRD4 (coeff. = 0.298, p = 0.003). When we further checked the loadings of the main component, we found that Question 13, Question 14 and Question 15 had the highest loadings (0.40, 0.47 and 0.47, respectively). These were all questions that were directly related with environmental problems. In Singapore, political discussion and activity is distinct from Western democracies [78], but students do care about environmental issues [79]. Broad concerns about the habitat in Singapore and beyond are as much of a social issue as an economic issue. People here suffer from forests burning in Indonesia fairly frequently, and hence the environment is naturally a hot button issue (e.g. [79]). Moreover, specifically at the NUS campus, the environment has a very high profile. Indeed, the NUS has an Office of Environmental Sustainability (http://www.nus.edu.sg/oes/prog/prog.html). The campus is also distinguished by a ‘Green Carnival’ (http://www.nus.edu.sg/oes/prog/envedu/green_carnival.html). The Cronbach’s α-value of these three questions is 0.8, which suggests that they are consistently measured. We group the three questions together, and add up the three responses of the questions into an aggregate score of attitude towards environmental protection. In table 2, the model 2 (environmental score) shows that the score is significantly associated with DRD4 genotype (p = 0.00069). This suggests that political attitude in Singapore may be indexed more accurately by attitude on environmental protection which has a high profile focus on campus that is unusually pervasive.

(e) Interaction between DRD4 and number of friends

As Settle et al. [18] reported a significant association between DRD4 and political attitude only as an interaction between gene and number of friends, we also examined the role of friendship in this study. Our subjects were asked to report their number of close friends. The distribution is shown in the electronic supplementary material, table S8.

As shown in the electronic supplementary material, table S9, the effect of number of friends, coded either as an ordinal or dichotomized variable, i.e. ‘number of friends’ into ‘0–5 friends’ and ‘more than 5’ friends categories, was not significant (electronic supplementary material, table S9, models 1 and 2). Nor was there any significant interaction between friendship and DRD4 genotype (electronic supplementary material, table S9, models 3 and 4). The only significant interaction term, after including DRD4, sex and friendship in the model, was the interaction between sex and DRD4 (electronic supplementary material, table S9, model 5). In short, we found no evidence for a role of friendship in the role of DRD4 in contributing to political attitudes in our Singaporean Han Chinese subjects.

4. Discussion

The main finding of this study was an association between DRD4 and political attitude along the liberal–conservative axis. Singapore is characterized by a distinct political culture compared with the United States and we further examined a homogeneous ethnic group of Han Chinese with distinct DRD4 exon III VNTR allelic frequencies. Despite these notable differences in the two samples, our results also indicated that variation in DRD4 affects variation in political attitudes.
However, we observed a main effect of DRD4 on political attitude, whereas Settle et al. [18] observed the effect of the gene in the context of a number of friends. Importantly, we further validated our findings with a more detailed political attitudes questionnaire adapted for Singapore’s unique political climate.

In this study, we observed a highly significant correlation between TCI novelty seeking and political attitude in the expected direction. Individuals high on novelty seeking tended to be more liberal politically. We however, observed highly significant correlations between NEO agreeableness (negative) and openness (positive) with political liberalism. We observed a weaker negative correlation between liberalism and neuroticism. Gerber et al. [80] provides a good discussion of personality and political attitudes. Some studies have examined political attitudes and agreeableness [81,82] with unclear results. Hirsh et al. [83] examined personality and political attitudes and observed that one key subpart of agreeableness (politeness) positively correlates with conservatism, while the other main subpart (empathy) positively correlates with liberalism. These results suggest that if agreeableness is reported as an aggregate score, then the two subscales would tend to cancel each other out perhaps explaining in part the discrepancies reported in the literature between this trait and political ideology.

Although we found that political attitude was strongly correlated with TCI novelty seeking, DRD4 was solely associated with political attitude and not with personality traits in the current sample (electronic supplementary material, tables S10 and S11). That being said, other work from our laboratory with this same group of subjects showed an association between financial risk attitude modelled in behavioural economic tasks and the DRD4 exon III VNTR (Y. Jiang, M. Monakhov, R. P. Ebstein, S. Zhong, S. H. Chew 2015, unpublished data) and notably, risk attitude is an important correlate of novelty and sensation seeking. We suggested the notion that risk attitude may not be easily captured by pencil and paper questionnaires and that behavioural economic tasks are perhaps a more efficient anyway captured by pencil and paper questionnaires and that behavioural economic tasks are perhaps a more efficient way to measure one’s risk attitude.

An important difference between Singapore and the United States that might offer some explanation of the difference between our results and the results reported by Settle et al. [18] regarding ‘friendship’ is that Singapore compared with the United States is a considerably more collectivist society. In Hofstede’s model [91], Singapore scores 20 on individualism, whereas the United States scores 91. In societies characterized as collectivist, connections with other people are long-term due to social bonds that are made more concrete by reciprocal commitments between members of the family, tribe or religion. Indeed, such connections are so relevant that the self is defined by them and self for members of a collectivist culture is fundamentally relational [92]. These cultural distinctions between Singapore and the United States suggested to us that the association between DRD4 and political attitude, not surprisingly, would be characterized by nuanced differences. After all, gene effects on behaviour are sometimes contingent on culture [93–95].

This study is especially important in the context of the Risch et al. [96] criticism, that warned against ‘attempts to rescue an unsuccessful candidate gene disease association, no matter how strong the candidate, by invoking an interaction with a common environmental exposure’, as our study showed a main effect (no need for interaction) of this gene and altogether give us some measure of confidence that the association will continue to be successfully extended in future studies.

### Ethics

Subjects gave informed written consent prior to participating. The Institutional Review Board of the National University of Singapore approved the study. Subjects were reimbursed for participation in the project (S$25 per hour on average).

### Data accessibility

Data can be downloaded from the Dryad Digital Repository: http://doi.org/10.5061/dryad.c5m95.
References


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Competing interests. We declare we have no competing interests.

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