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BRIEF COMMUNICATION

Lack of association between dopamine D4 receptor gene and personality traits

E. G. JÖNSSON,[1] M. M. NÖTHEN, J. P. GUSTAVSSON, H. NEIDT, K. FORSLUND, M. MATTILA-EVENDEN, G. RYLANDER, P. PROPPING AND M. ÅSBERG

From the Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institute, Stockholm, Sweden; and Institute of Human Genetics, University of Bonn, Germany

ABSTRACT

Background. Personality traits have shown considerable heritable components. Association between alleles of a polymorphism in the third exon of the dopamine D4 receptor gene (DRD4) and the personality trait Novelty Seeking has been reported. Recently, in a sample of Swedish non-psychiatric subjects we could not detect any significant relationships between the same polymorphism and Novelty Seeking related scales in the Karolinska Scales of Personality (KSP). However, there was a tendency in the direction of the proposed association. There were also tentative associations between an exon I 13 bp deletion polymorphism and the personality traits Socialization and Guilt.

Methods. We investigated a new Swedish population-based sample ($N = 167$) investigated with the KSP for three DRD4 polymorphisms.

Results. Neither of the previous results were replicated. Combining the previous and the present samples did not give rise to any significant association between DRD4 polymorphisms and personality scales.

Conclusions. The dopamine D4 receptor gene is probably not of importance to the different personality dimensions as measured by the Karolinska Scales of Personality.

INTRODUCTION

Family, twin and adoption studies indicate that genetic mechanisms underlie individual differences in personality traits (Loehlin, 1992). It has been hypothesized that certain personality traits may correlate with activity in different neuronal systems. The personality trait of Novelty Seeking (Cloninger *et al.* 1993), characterized by impulsivity, explorative behaviour, fickleness, excitability, quick-temperedness and extravagance, is one of several putative dopamine-connected traits, which all seem to represent different aspects of the higher-order Extraversion dimension (Eysenck & Eysenck, 1985). Recently Ebstein *et al.* (1996, 1997), using the tridimensional personality questionnaire (TPQ; Cloninger, 1987), and Benjamin *et al.* (1996), using the NEO personality inventory (NEO-PI-R; Costa & McCrae, 1992), reported an association between the presence of long alleles in a variable number tandem repeat (VNTR) polymorphism in the third exon of the dopamine D4 receptor gene (DRD4) and higher scores in Novelty Seeking in samples of Israelis and Americans. Using the Karolinska Scales of Personality (KSP; Schalling *et al.* 1987) we did not find any significant relationship to the Novelty Seeking related KSP scales, i.e. Monotony Avoidance and Impulsiveness, in a sample of Swedish comparison subjects (Jönsson *et al.* 1997). However, in the latter study there was a non-significant tendency in the direction

[1] Address for correspondence: Dr Erik G. Jönsson, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institute, SE-171 76 Stockholm, Sweden.

suggested by previous studies. Moreover, tentative associations were found between an exon I 13 bp deletion polymorphism and the KSP scales Socialization and Guilt. To evaluate further relationships between DRD4 genotypes and personality traits we investigated a second sample of Swedish volunteers from the general population for the same DRD4 polymorphisms.

METHOD

Subjects

Subjects ($N = 261$) from the general population in the northwestern part of Stockholm County were asked to participate. One hundred and seventy-one (66%) of the subjects gave informed consent and completed the investigation. The subjects were semi-structurally interviewed by a psychiatry resident (M.M.E., K.F., or G.R.) to obtain lifetime DSM-IV psychiatric diagnosis, data on current alcohol consumption, neuropsychological symptoms during childhood and adolescence, history of neurotraumata, family history of psychiatric and neurological disorders, and birthplace of biological parents. In addition, they were asked to complete a number of self-report questionnaires assessing current psychopathology and personality traits. Four of the interviewed subjects were omitted as they were either non-Caucasians or of non-European ancestry.

Of the 167 final comparison subjects 81 were men and 86 women. The age range was 21 to 76, with a mean $\pm$ S.D. of $56{\cdot}7 \pm 15{\cdot}8$ years. Genealogical reports implicated that 80% of the chromosomes originated in ancestors born in Sweden, 9% in Finland and the remaining 11% were distributed among nine European countries.

Personality questionnaire

Subjects completed the Karolinska Scales of Personality (KSP; Schalling *et al.* 1987; Gustavsson, 1997). The KSP consists of 135 items forming 15 different subscales. Four of these were of particular interest in the present study, i.e. the Novelty Seeking related scales Impulsiveness (high scores: acting on the spur of the moment, non-planning, impulsive and Monotony Avoidance (high scores: avoiding routine, need for change and action, 'sensation seeking') and the scales previously giving results tentative of association with DRD4 genotypes (Jönsson *et al.* 1997) i.e. Socialization (high scores: positive childhood experiences, good school and family adjustment) and Guilt (high scores: remorseful, ashamed for bad thoughts).

Molecular genetics

Venous blood was drawn from all participants. After DNA isolation three different DRD4 polymorphisms were analysed: a DRD4 exon III 48 bp repeat polymorphism (Van Tol *et al.* 1992), an exon I 12 bp repeat sequence (Catalano *et al.* 1993), and an exon I 13 bp deletion (Nöthen *et al.* 1994), predicted to result in a truncated non-functional protein. Genotyping of the different polymorphisms was performed as previously described (Catalano *et al.* 1993; Lim *et al.* 1994; Nöthen *et al.* 1994).

Statistical methods

The allele and genotype frequencies among different groups of subjects were compared using χ^2 tests of homogeneity. Associations between DRD4 genotypes and KSP scale scores, standardized to have a mean $\pm$ S.D. of 50 ± 10, were compared by two-tailed *t* tests. The exon III 48 bp genotypes were clustered in three ways (Benjamin *et al.* 1996; Ebstein *et al.* 1996): genotypes containing alleles with two to five repeats (short) *v.* six repeats and more (long), genotypes with the 7 allele *v.* all other genotypes, and genotype 4,4 *v.* 4,7. To adjust for multiple testing Boniferroni's correction was used. A P value $< 0{\cdot}001$ was considered to be significant. However, for the calculations between DRD4 genotypes and personality scales previously suggested to be associated, no corrections for multiple testing were performed. Power was estimated in accordance with Cohen (1988).

RESULTS

The allele and genotype frequencies did not deviate significantly from those in two previously investigated Scandinavian samples (Malhotra *et al.* 1996; Jönsson *et al.* 1997) (data not shown). There was no significant association between the DRD4 exon III 48 bp repeat polymorphism and any personality trait (Table 1). Neither was there any significant association between DRD4 exon I genotypes and any KSP scale (data not shown). When the present and previous Swedish samples (Jönsson *et al.* 1997) were pooled no

Table 1. *KSP personality scores in subject groups sorted by dopamine D4 receptor gene polymorphisms*

		Impulsiveness		Monotony avoidance		Socialization		Guilt	
Genotype	*N*	Mean ± S.D.*	*t*† *P*	Mean ± S.D.*	*t*† *P*	Mean ± S.D.*	*t*† *P*	Mean ± S.D.*	*t*† *P*
Exon III 48 bp repeat									
Short	97	51·8 ± 9·3	$t = -0{\cdot}09$	53·2 ± 10·5	$t = 0{\cdot}18$	49·4 ± 10·9	$t = -0{\cdot}18$	47·5 ± 9·6	$t = -0{\cdot}38$
Long	70	52·0 ± 10·4	$P = 0{\cdot}93$	52·9 ± 10·7	$P = 0{\cdot}86$	49·7 ± 11·5	$P = 0{\cdot}86$	48·1 ± 9·8	$P = 0{\cdot}70$
7 allele absent	99	52·1 ± 9·6	$t = -0{\cdot}90$	53·1 ± 10·4	$t = 0{\cdot}06$	49·0 ± 11·6	$t = -0{\cdot}74$	47·3 ± 9·6	$t = -0{\cdot}71$
7 allele present	67	51·5 ± 10·1	$P = 0{\cdot}37$	53·0 ± 10·9	$P = 0{\cdot}96$	50·3 ± 10·5	$P = 0{\cdot}46$	48·4 ± 9·8	$P = 0{\cdot}48$
4,4	67	50·1 ± 9·4	$t = -1{\cdot}18$	53·1 ± 10·3	$t = -0{\cdot}31$	49·7 ± 11·9	$t = -0{\cdot}22$	48·0 ± 9·4	$t = -1{\cdot}44$
4,7	49	52·3 ± 10·3	$P = 0{\cdot}24$	53·8 ± 11·7	$P = 0{\cdot}76$	50·3 ± 11·0	$P = 0{\cdot}83$	50·6 ± 9·6	$P = 0{\cdot}15$
Exon I 12 bp repeat									
1,1 + 1,2	24	52·1 ± 8·6	$t = 0{\cdot}12$	51·8 ± 11·4	$t = -0{\cdot}62$	52·3 ± 9·5	$t = 1{\cdot}28$	46·9 ± 8·4	$t = -0{\cdot}43$
Others	143	51·8 ± 10·0	$P = 0{\cdot}90$	53·3 ± 10·4	$P = 0{\cdot}53$	49·1 ± 11·4	$P = 0{\cdot}20$	47·9 ± 9·9	$P = 0{\cdot}67$
Exon I 13 bp deletion									
Absent	157	52·0 ± 9·8	$t = 0.90$	53·3 ± 10·7	$t = 0{\cdot}95$	49·4 ± 11·3	$t = -0{\cdot}33$	47·8 ± 9·7	$t = 0{\cdot}56$
Present	10	49·2 ± 7·6	$P = 0{\cdot}37$	50·0 ± 7·4	$P = 0{\cdot}35$	50·7 ± 9·6	$P = 0{\cdot}74$	46·1 ± 9·6	$P = 0{\cdot}58$

* Personality test scores are given as *t* scores, which are standardized using normative data to have a mean ± S.D. of 50 ± 10.
† *t* value by unpaired two-tailed *t* test. For one-tailed *t* test: $P/2$.

significant association emerged (data not shown).

DISCUSSION

In the present study no consistent associations could be found between DRD4 gene polymorphisms and different personality traits. This is at variance with four previous reports (Benjamin *et al*. 1996; Ebstein *et al*. 1996, 1997; Ono *et al*. 1997) but in accordance with five other investigations (Malhotra *et al*. 1996; Gelernter *et al*. 1997; Jönsson *et al*. 1997; Vandenbergh *et al*. 1997; Pogue-Geile *et al*. 1998). Thus, the finding of an association between DRD4 genotypes and Novelty Seeking related scales was not replicated. Neither were the tentative associations between DRD4 genotypes and KSP Socialization and Guilt (Jönsson *et al*. 1997), respectively, replicated in the present study.

One possibility of the inability to detect association between DRD4 polymorphisms and Novelty Seeking in the present sample may be that KSP does not adequately measure the traits of Novelty Seeking. However, like Novelty Seeking in the TPQ the KSP Monotony Avoidance and Impulsiveness are partly derived from the Solidity dimension of the Sjöbring system of personality dimensions (Sjöbring, 1973). Thus, empirically it has been shown that KSP Monotony Avoidance and Impulsiveness are correlated to Novelty Seeking (Cloninger, 1988; Curtin *et al*. 1995). It may also be noted that studies using either TPQ and/or NEO PI-R were unable to detect the proposed association (Malhotra *et al*. 1996; Gelernter *et al*. 1997; Vandenbergh *et al*. 1997; Pogue-Geile *et al*. 1998).

The exon III 48 bp repeat polymorphism gives rise to variable numbers of 16 amino acid repeats in the DRD4 protein. However, even if the number of repeats is the same the 16 amino acid repeats may consist of different amino acids (Lichter *et al*. 1993). This gives a possibility that a different 7-repeat length allele could be more frequent in Israelis and certain samples of US citizens than in Swedes, Finns (Malhotra *et al*. 1996), or other American samples (Gelernter *et al*. 1997; Vandenbergh *et al*. 1997; Pogue-Geile *et al*. 1998). As the two most common haplotypes account for more than 80% of the DRD4 4- and 7-repeat length alleles, respectively (Lichter *et al*. 1993) and no major differences in this respect has been shown between Caucasians, this possibility seems less plausible, although it cannot be excluded. Another possibility is that the DRD4 exon III 48 bp 7 repeat allele is in linkage disequilibrium with another functional DRD4 polymorphism in the Israeli and the first investigated US samples, but not in the Swedish, Finnish, or other American samples.

The power to detect an association (two-tailed $P < 0{\cdot}05$, effect size $d = 0{\cdot}5$ as reported by Ebstein *et al*. (1996)) between the DRD4 48 bp polymorphism and Monotony Avoidance and Impulsiveness, the subscales comprising traits described in Novelty Seeking, ranged from 0·75 to 0·89 in the present study. Similarly calculated power of the combined Swedish samples was 0·94 to 0·98. Using the effect size ($d = 0{\cdot}39$) estimated from Benjamin *et al*. (1996) reduces the power to 0·55–0·70 (0·79–0·90) in the present (combined) samples. The power for the analyses regarding the DRD4 exon I 13 bp polymorphism and the previous suggested associations to Socialization and Guilt (two-tailed $P < 0{\cdot}05$, effect size $d > 0{\cdot}9$) was 0·79 to 0·86. However, the power with regard to both DRD4 exon I polymorphisms was neither in the present nor in the combined sample sufficient to detect relationships of medium or minor effects.

In situ hybridization studies have demonstrated the expression of DRD4 mRNA in human post mortem tissue (Meador-Woodruff *et al*. 1994). However, the functional relevance of the DRD4, which is likely to be a receptor for not only dopamine but also norepinephrine and epinephrine (Lanau *et al*. 1997), is still unclear. This may call for careful interpretation of results involving the DRD4 gene. These proposals together with the six reports that were unable to replicate the proposed association suggest that DRD4 may require re-evaluation as a candidate gene for personality variation.

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