

Lack of Evidence for Allelic Association Between Personality Traits and the Dopamine D₄ Receptor Gene Polymorphisms

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Objective: Personality traits in human subjects have shown considerable heritable components. Recently, two research groups reported associations between dopamine D₄ receptor genotypes and the personality trait known as novelty seeking. This study was an attempt to replicate these findings. **Method:** Three different exonic dopamine D₄ receptor polymorphisms were genotyped in 126 healthy Swedish subjects. Personality traits of the subjects were assessed with the Karolinska Scales of Personality. **Results:** Although there was a tendency in the direction hypothesized, no significant association between genotype constellations and personality traits was found. **Conclusions:** The previously reported association between dopamine D₄ receptor alleles and novelty seeking was not replicated. Possible reasons for this include differences in personality inventories, ethnicity, and type I or type II errors.
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Personality traits in human subjects have shown considerable heritable components (1). It has been proposed that genetically determined variance in dopamine transmission underlies individual differences in the personality trait called novelty seeking (2), which is characterized by impulsiveness, exploration, changeableness, excitability, hotheadedness, and extravagance. Recently, two independent investigations (3, 4) reported an association between dopamine D₄ receptor genotypes and novelty seeking. In the present study we attempted to replicate these results in a group of healthy Swedish subjects.

METHOD

The study was approved by the Ethics Committee of the Karolinska Hospital, Stockholm. All subjects participated after giving informed consent. One hundred twenty-six unrelated Caucasians (76 men and 50 women) living in Sweden, whose mean age was 41 years (SD=8, range=25–61), had previously served as comparison subjects.

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Nine months to 21 years after the first investigation, they were reinvestigated and given a self-report questionnaire, the Karolinska Scales of Personality (5). The 135 items of this questionnaire form 15 subscales. Two of the subscales, monotony avoidance (high scores on avoiding routines, need for change and action) and impulsiveness (high scores on acting on the spur of the moment, lack of planning, impulsiveness) encompass traits similar to novelty seeking (6).

After isolation of DNA from the subjects' venous blood, three different dopamine D₄ receptor polymorphisms were analyzed: the exon III 48 bp polymorphism (7), an exon I 12 bp repeat sequence (8), and an exon I 13 bp deletion (9), which are predicted to result in a truncated, nonfunctional protein. To affirm that determination of the exon III 48 bp polymorphism was adequate, 107 DNA samples were analyzed independently at two different laboratories, with identical results. The exon III 48 bp genotypes were clustered in three ways (3, 4): genotypes containing alleles with two to five repeats (short) versus six repeats or more (long), genotypes with the 7 allele versus all other genotypes, and genotype 4,4 versus 4,7. Associations between Karolinska Scales of Personality test scores and dopamine D₄ receptor genotypes were compared by two-tailed t tests.

RESULTS

No significant relation to personality traits was found for either the dopamine D₄ receptor exon III 48 bp polymorphism or the exon I 12 bp polymorphism. However, if one does not correct for multiple tests, the subjects heterozygous for the exon I 13 bp deletion scored significantly lower than the subjects without the deletion on the Karolinska Scales of Personality socialization subscale (high scores on positive childhood experiences, good school and family adjustment) and significantly higher on the guilt subscale (high scores on remorseful, ashamed of bad thoughts) (table 1).

TABLE 1. Associations Between Dopamine D₄ Receptor Genotypes and Scores on the Karolinska Scales of Personality of 126 Healthy Swedish Subjects

Genotype	Impulsiveness			Monotony Avoidance			Solidity ^c			Socialization			Guilt		
	Score			Score			Score			Score			Score		
	Mean ^a	SD	t ^b	Mean ^a	SD	t ^b	Mean ^a	SD	t ^b	Mean ^a	SD	t ^b	Mean ^a	SD	t ^b
Exon III 48 bp repeat															
Length			-1.47			-1.01			-1.12			-0.81			0.47
Short (N=85)	50.5	9.0		54.0	10.9		47.1	7.1		47.1	10.0		47.0	9.0	
Long (N=41)	53.0	8.7		56.0	9.4		48.6	6.6		48.6	9.7		46.2	8.3	
7 allele			-0.90			-0.70			-0.49			-0.43			0.75
Absent (N=87)	50.9	9.2		54.2	11.0		47.4	7.2		47.3	10.1		47.1	9.1	
Present (N=39)	52.4	8.5		55.6	9.3		48.1	6.3		48.1	9.7		45.9	7.8	
Genotype			-0.53			-1.46			-0.87			-0.39			0.87
4,4 (N=55)	51.3	9.1		52.6	11.6		47.0	7.3		46.9	10.9		47.9	9.4	
4,7 (N=34)	52.3	8.4		56.1	9.7		48.4	6.6		47.7	9.1		46.2	8.0	
Exon I 12 bp repeat			-0.29			-0.75			-0.72			-0.11			-0.34
1,1+1,2 (N=14)	50.4	13.2		52.7	10.7		46.4	9.4		47.3	12.0		46.0	9.9	
Others (N=112)	51.5	8.3		54.9	10.4		47.8	6.6		47.6	9.7		46.8	8.6	
Exon I 13 bp deletion			0.12			-0.23			-0.07			2.73**			-2.62*
Absent (N=117)	51.4	9.0		54.6	10.6		47.6	7.0		48.2	9.6		46.2	8.5	
Present (N=9)	51.0	8.6		55.4	8.8		47.8	6.5		39.1	10.4		55.0	9.0	

^aPersonality test scores are given as T scores, which are standardized to have a mean of 50 (SD=10) in the Karolinska Scales of Personality normative sample.

^bBy unpaired two-tailed t test; df=87 for calculations with the 4,4 versus the 4,7 genotype; for all other calculations, df=124. Adjustment for multiple tests was not performed.

^cSolidity is a combination of the impulsiveness and monotony avoidance subscales, where low solidity scores correspond to high impulsiveness and high monotony avoidance scores.

*p=0.01. **p=0.007.

DISCUSSION

The previous finding of an association between dopamine D₄ receptor genotypes and personality traits encompassed in novelty seeking was not replicated. There are several possible explanations for this discrepancy. It is possible that the Karolinska Scales of Personality does not adequately measure traits of novelty seeking. However, the concepts of novelty seeking (from the Tridimensional Personality Questionnaire) and monotony avoidance and impulsiveness (from the Karolinska Scales of Personality) all derive from the concept of solidity as described in Sjöbring's system of personality dimensions (10). Thus, it has been shown empirically that Karolinska Scales of Personality monotony avoidance and impulsiveness are correlated with novelty seeking (6, 11). It could be argued that the match between these Tridimensional Personality Questionnaire and Karolinska Scales of Personality scales is not perfect, but they refer to a similar personality dimension, even though it is operationalized by different methods and researchers.

A second possibility is that the relation between dopamine D₄ receptor genotypes and novelty seeking is real in the populations investigated in Israel and the United States but not in the Swedish population. This would mean that the genetic basis for the same personality trait differs among different populations. A third explanation for the lack of replication is that the previous studies are examples of false positive findings. The functional relevance of the dopamine D₄ receptor

is still unclear, which may call for careful interpretation of results involving the D₄ receptor gene. The present results may also represent false negative findings. The power to detect an association (effect size) (SD=0.50, one-tailed p<0.05) was 0.83 in the comparison of short versus long genotypes and of genotypes with the 7 allele versus all other genotypes, and it was 0.74 in the comparison of 4,4 versus 4,7 genotypes. Considering the finding of a nonsignificant tendency in the proposed direction (i.e., association of the long exon III 48 bp alleles and high ratings on the Karolinska Scales of Personality impulsiveness and monotony avoidance subscales), we cannot exclude the possibility that a larger study group size might have yielded a significant association.

Without adjustment for multiple tests, the subjects heterozygous for the exon I 13 bp deletion polymorphism scored significantly lower on the Karolinska Scales of Personality socialization subscale and higher on the guilt subscale. This tentative association needs replication because of the many tests performed and the small group of subjects heterozygous for this polymorphism.

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