Association Between Novelty Seeking and the Type 4 Dopamine Receptor Gene in a Large Finnish Cohort Sample

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Objective: An association between the type 4 dopamine receptor (DRD4) gene and the behavioral trait of novelty seeking has been reported, but several studies have failed to replicate this finding. In the present study, the authors tested for this association in a representative sample from the Finnish population. **Method:** The authors administered the Temperament and Character Inventory to 4,773 individuals from the 1966 birth cohort of northern Finland. They then genotyped 190 subjects with extreme scores for a 48 base-pair repeat polymorphism in the DRD4 gene. **Results:** There was a significant difference in allele frequencies between the two groups. The 2- and 5-repeat alleles were significantly more common in the group of high scorers than in the group of low scorers. **Conclusions:** These results confirm the original findings of an association between the DRD4 gene and novelty seeking, while showing that novelty seeking is probably not influenced by the polymorphism itself but, rather, a different DNA variant in the DRD4 gene or another gene in linkage disequilibrium with it.

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An association between a polymorphism in the type 4 dopamine receptor gene (DRD4) and the behavioral trait of novelty seeking (1) has been reported (2, 3). In the original articles, high novelty seeking scores were associated with the 7-repeat allele of this functional 48bp repeat polymorphism. Multiple replication studies have failed to confirm the finding (4–8) or yielded only weak support for it (9–11). Some studies (4, 5) found associations between the 7-repeat allele and low novelty seeking scores in analyses of certain subgroups of the population studied. The objective of our study was to confirm or refute the findings through use of a large, general population-based birth cohort sample.

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METHOD

Within the framework of the 1966 Northern Finland birth cohort study (12), 4,773 individuals completed the Temperament and Character Inventory (13) and gave a blood sample in accordance with the Helsinki declaration. We selected 50 men and 50 women with extremely high scores on the novelty seeking subscale of the Temperament and Character Inventory and the same number of subjects with extremely low scores. Written informed consent was obtained after written and verbal description of the study to the subjects.

Polymerase chain reaction was performed as described by Lichter et al. (14), with slight modifications. One primer was fluorescently labeled with Cy5 for size separation on an automated DNA sequencer (ALF express, Pharmacia Biotech AB). Genotyping was done through use of the Allelinks (Pharmacia Biotech AB) software.

Association between high or low scorer group status and the DRD4 allele frequencies was tested by using the Pearson chi-square statistic. For each allele we also calculated the chi-square statistic for presence versus absence of the allele in the individuals belonging to the low and high scoring groups.

RESULTS

The mean novelty seeking score was 20.3 (SD=5.9; 95% confidence interval=20.2–20.5). All the subjects included in the analysis had novelty seeking scores more than one standard deviation from the mean of the cohort (low scorers ≤12, high scorers ≥31), and the means for the groups with extreme scores (7.48 and

TABLE 1. Number of Observed Genotypes for Each Allele of the Type 4 Dopamine Receptor Gene (DRD4) for Subjects From the 1966 Finnish General Population Birth Cohort With Extreme Scores on Novelty Seeking (N=190)

	Number of Observed Genotypes		
DRD4 Allele	Extremely Low Score Group (194 alleles)	Extremely High Score Group (186 alleles)	Total (380 alleles)
2	8	20	28
3	11	12	23
4	140	123	263
5	2	10	12
6	0	0	0
7	32	21	53
8	1	0	1

33.48, respectively) lay outside 1.96 standard deviations from the mean for the whole cohort.

The allele frequencies in the groups of extreme high and extreme low scorers are shown in table 1. The single 8-repeat allele was pooled with the 7-repeat allele in all analyses. For 10 individuals the DNA did not amplify, and they were excluded in all analyses.

There was a significant difference in allele frequencies between the groups (χ^2=14.1, df=4, p=0.007), and the largest proportional differences in allele frequencies between the groups were observed for the 2- and 5-repeat alleles that were more common in the high scoring group (table 1). When comparing subjects grouped on the basis of presence or absence of each allele, i.e., treating genotypes rather than alleles as observations, we observed significant associations between high novelty seeking scores and the presence of the 2-repeat (χ^2=6.1, df=1, p=0.01) and 5-repeat (χ^2=5.0, df=1, p=0.03) alleles. The results for the other alleles were nonsignificant.

DISCUSSION

This is in several respects a more robust study than those published earlier. First, the subjects represent a large birth cohort rather than subjects selected for a known psychiatric diagnosis (4, 5, 8), level of education (2, 10), or sexual orientation (3) studied in some earlier reports. Second, the study subjects were stratified according to the novelty seeking scores, and the groups were compared with respect to genotype. In most earlier studies (2, 3, 4–6, 8–11), the strategy has been the reverse. Third, the study cohort was collected from a genetically isolated population, ideal for association studies.

The chi-square method that we used to test for any difference in allele frequencies between the groups has the obvious advantage that only one testing is performed, and the p value obtained needs not be corrected. However, it has been proposed that the method might overestimate the significance level if the locus studied is not truly codominant (15). Therefore, we also compared individuals with and without each allele. In contrast to the original reports, this analysis showed that the presence of the 2- and 5-repeat alleles is significantly associated with high novelty seeking scores in the Finnish population. There are a few possible explanations for this difference. First, it is possible that the studied polymorphism does not influence novelty seeking scores. The primary incentive to study this polymorphism was that it is a biologically reasonable candidate locus with functional differences between the different alleles (2, 3). However, our results show that novelty seeking score is, rather, influenced by a different variant in the DRD4 gene or by another gene in linkage disequilibrium. If this is the case, the gene influencing novelty seeking score could be in linkage disequilibrium with a different allele of the studied polymorphism in the Finnish population than in the other populations studied.

Second, it is possible that by selecting from the population those individuals with extreme scores, we have included a greater proportion of subjects with diagnosable personality disorders in the analysis. It is therefore possible, although unlikely, that the polymorphism studied is primarily associated with any such disorder and only secondarily associated with novelty seeking scores. Our study design cannot rule out that possibility, but since it is widely accepted that personality disorders can be conceptualized as extreme variants of normally distributed personality traits (16), we feel that our result is still valid.

Finally, even though our subjects are all the same age and represent a highly genetically and culturally homogeneous population, there is still a small chance of selection bias. This possibility will be excluded only by additional, preferably family-based, studies.

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