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Association Analyses of the Dopamine Receptor Genes with Drinking Patterns Across Adolescence in the FinnTwin16 Sample

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Introduction

The dopamine receptor genes are good candidates for involvement in alcohol-related phenotypes based on the role of dopamine in reward behavior. There are five dopamine receptors, DRD1-5. DRD2 has been studied most extensively in relation to alcohol dependence, with mixed evidence for its involvement. Several of the other dopamine receptor genes (e.g., DRD3 and DRD4) have been associated with behavioral phenotypes related to alcohol use, such as impulsivity and novelty-seeking, although the potential role of these genes in alcohol use has not been studied extensively. As part of the longitudinal FinnTwin16 study, we genotyped SNPs in each of the dopamine receptor genes and tested for association with drinking patterns at ages 16, 17, 18.5, and in the mid 20s.

Methods

Sample

FinnTwin16 is a population-based developmental twin study. It consists of five birth cohorts of twins ascertained through Finland's population registry. Twins completed questionnaires at ages 16, 17, 18.5 and in the young 20s (mean=24.4), in which they self-reported on their frequency of alcohol use. Subjects' responses were converted to drinking days per month, and log transformed. A subset of individuals were selected for more intensive study, which included DNA collection. Table 1 shows the number of individuals in the full and genotyped samples by twin type. Table 2 shows the twin correlations for the drinking frequency item across each of the assessments. As indicated by the correlations, there is considerable evidence for genetic effects on this phenotype.

Table 1

Total Number of Individuals Within the Finntwin16 Study	
MZ Males	1032
MZ Females	746
DZ Males	886
DZ Females	924
Total	3588

Genotyped Individuals Only	
MZ	218
DZ	382
Unknown	4
Total	604

Table 2. Twin correlations and amount of variance attributed to Additive genetic effects (A), Common environmental effects (C), and Unique environmental effects (E).

	MZ	DZ	A	C	E
Age 16	0.742	0.557	0.37	0.372	0.258
Age 17	0.712	0.5	0.424	0.288	0.288
Age 18	0.641	0.437	0.408	0.233	0.359
Age 25	0.566	0.372	0.388	0.178	0.434

Genotyping

Genotyping was conducted in the laboratory of Dr. Leena Peltonen at the National Public Health Institute in Helsinki, Finland using the Sequenom MassARRAY system for high-throughput SNP genotyping. Figure 1 shows the location of SNPs in each of the 5 dopamine receptor genes.

Analyses

Linkage disequilibrium was calculated using the program GOLD (Graphical Overview of Linkage Disequilibrium; Abecasis ref). This software package provides a graphical summary of linkage disequilibrium. In addition, the SNPSpD method of Nyholt (2004) was used to ascertain tagging SNPs and provide a means to correct for multiple testing.

Variance components association analyses were conducting using the method of Fulker et al., 1999, as implemented using the program Mx by Posthuma et al., 2004. This method tests for

between- and within-family association, such that population stratification can be distinguished from true genetic effects. Tests for dominant and additive genetic effects were conducted for each SNP with drinking frequency at each time point.

Results

Association Analysis

Multiple SNPs in DRD4 yielded evidence of association with drinking frequency at age 16 (Table 3). There was no evidence of population stratification. The association was not significant at $p<.05$ at the other age assessments, but there continued to be evidence of association at trend levels. No significant association was observed with any of the other genes (Tables 3, 4, 5, and 6).

LD Analysis

Figures 2-5 show the LD between SNPs in each gene. Taking into account LD, the effective number of tag-SNPs genotyped in DRD1, DRD2, DRD3 and DRD4 were 4, 7, 4 and 3, respectively. Importantly, the SNPs in DRD4 showed low LD, indicating they yield independent evidence for association.

Conclusions

We find preliminary evidence of association with multiple SNPs in DRD4 and drinking frequency at age 16. We are currently working on more sophisticated, multivariate models that incorporate multiple assessments of drinking in tests of association.

Acknowledgements

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Figures

PRINT FROM POWERPOINT FILE

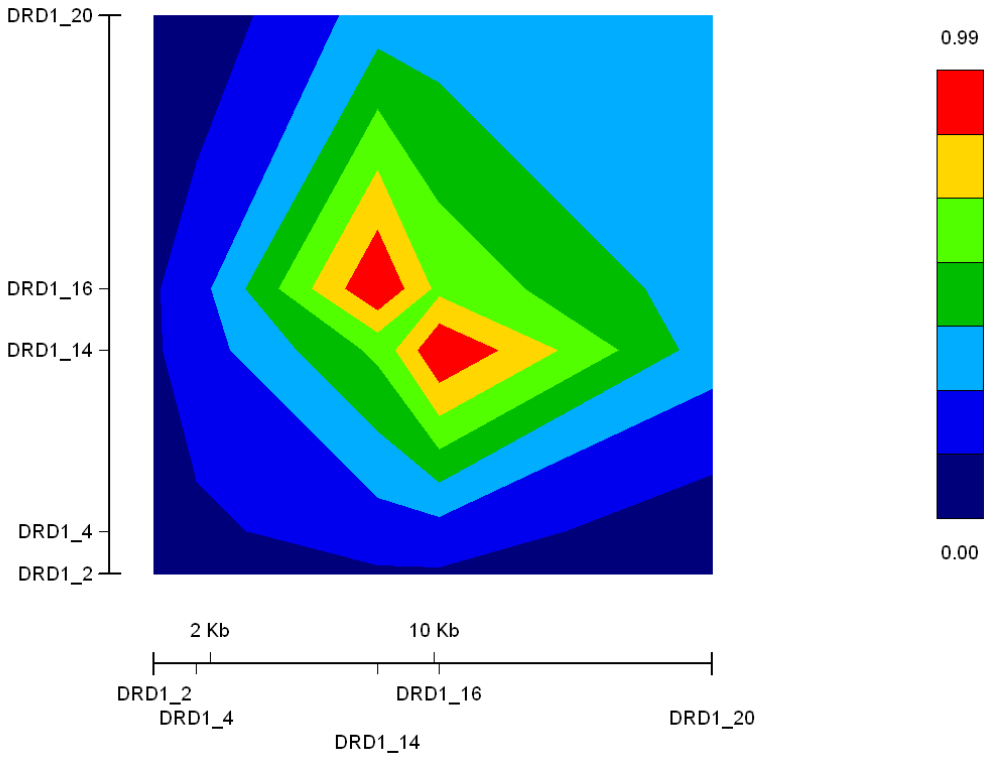

Figure 2. Distribution of pair-wise linkage disequilibrium (Δ^2) across DRD1

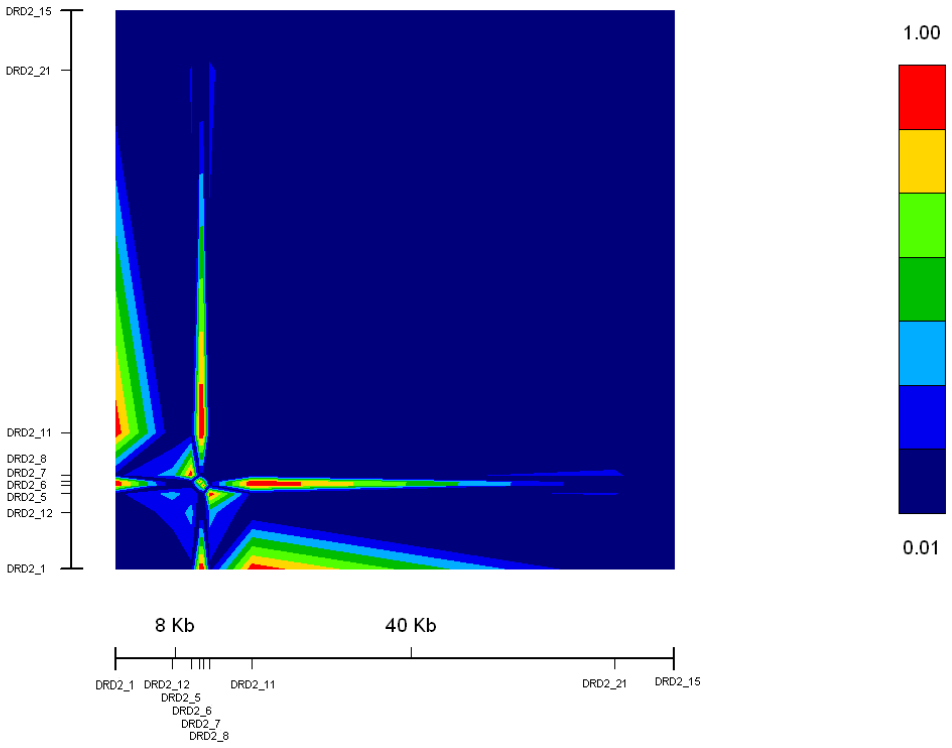

Figure 3. Distribution of pair-wise linkage disequilibrium (Δ^2) across DRD2

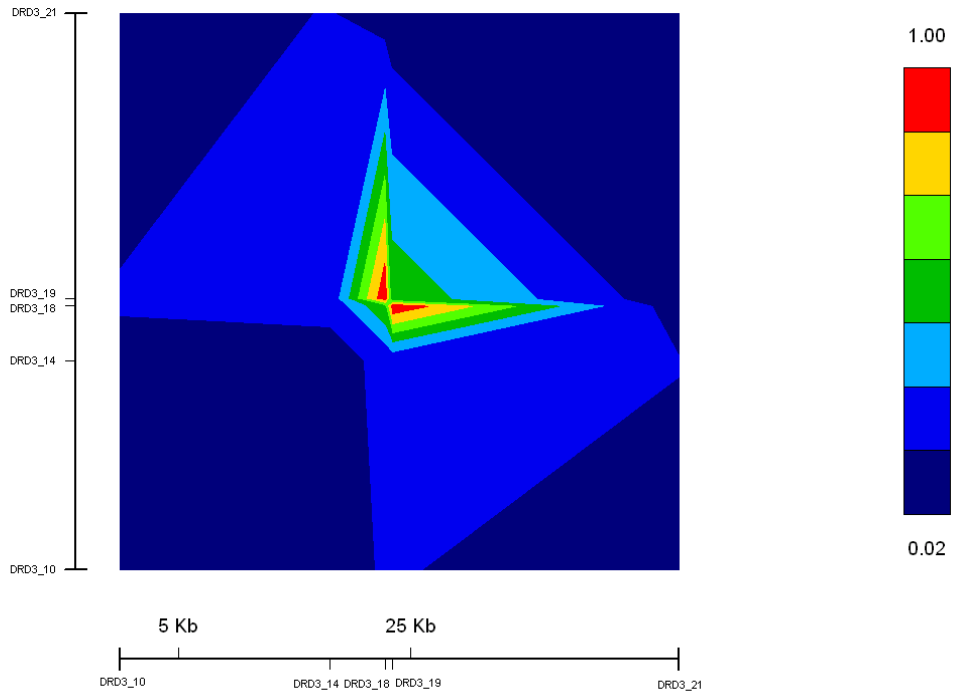

Figure 4. Distribution of pair-wise linkage disequilibrium (Δ^2) across DRD3

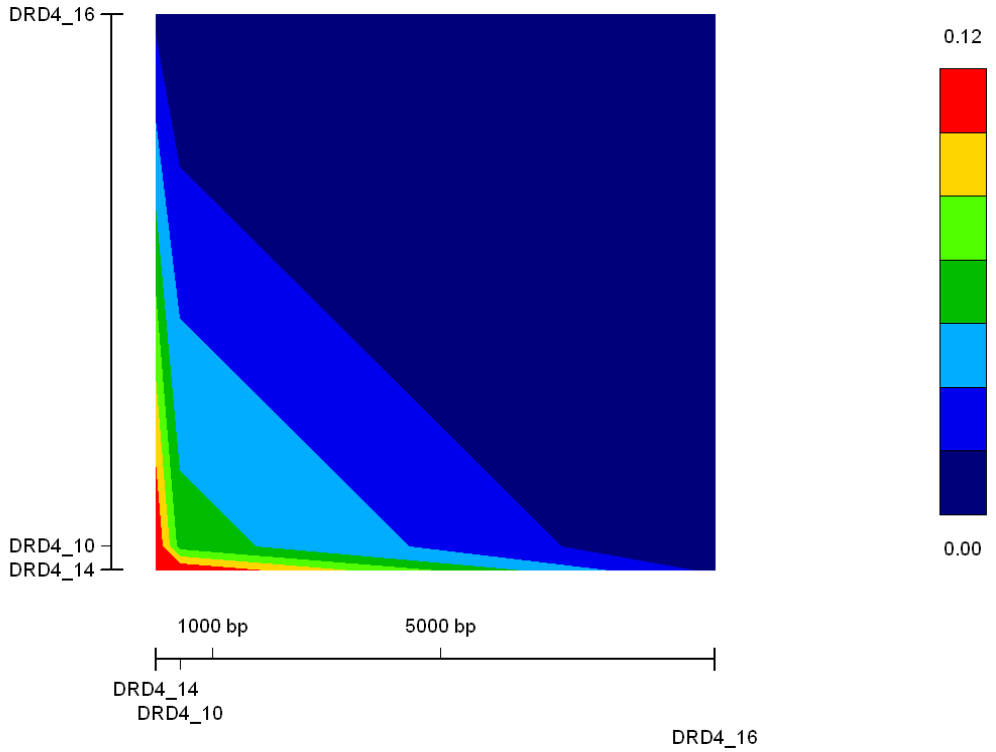

Figure 5. Distribution of pair-wise linkage disequilibrium (Δ^2) across DRD4

Table 3. Age 16

Marker	Test For Population Stratification	Test for Dominance Effects	Test for Additive Effects
DRD1_2	0.998	0.336	0.920
DRD1_4	0.448	0.205	0.987
DRD1_14	0.140	0.297	0.417
DRD1_16	0.172	0.248	0.405
DRD1_20	0.048	0.011	0.164
DRD2_1	0.606	1.000	0.981
DRD2_11	0.692	0.964	0.993
DRD2_12	0.166	0.443	0.641
DRD2_15	0.532	0.433	0.998
DRD2_21	0.867	0.174	0.727
DRD2_5	0.926	0.690	0.956
DRD2_6	0.660	1.000	0.999
DRD2_7	0.731	0.609	0.777
DRD2_8	0.996	0.547	0.998
DRD3_10	0.543	0.874	0.998
DRD3_14	0.801	0.559	0.668
DRD3_18	0.242	0.055	0.787
DRD3_19	0.142	0.144	0.567
DRD3_21	0.797	1.000	0.965
DRD4_10	0.902	**0.020**	0.908
DRD4_14	0.680	**0.023**	0.914
DRD4_16	0.999	1.000	0.392
DRD5_9	0.965	0.975	0.742

Table 4. Age 17

Marker	Test For Population Stratification	Test for Dominance Effects	Test for Additive Effects
DRD1_2	0.967	0.336	0.463
DRD1_4	0.890	0.182	0.988
DRD1_14	0.355	0.111	0.520
DRD1_16	0.321	0.082	0.554
DRD1_20	0.403	0.032	0.867
DRD2_1	0.785	0.722	0.956
DRD2_11	0.773	0.964	0.997
DRD2_12	0.306	0.929	0.661
DRD2_15	0.788	0.975	0.974
DRD2_21	0.816	0.683	0.590
DRD2_5	0.823	0.858	0.990
DRD2_6	0.828	0.879	0.998
DRD2_7	0.840	0.683	0.987
DRD2_8	0.809	0.503	0.977
DRD3_10	0.950	0.469	0.572
DRD3_14	0.491	0.456	0.817
DRD3_18	0.819	0.193	0.544
DRD3_19	0.673	0.351	0.406
DRD3_21	0.812	1.000	0.440
DRD4_10	0.627	0.114	1.000
DRD4_14	0.469	0.156	0.410
DRD4_16	0.967	1.000	0.807
DRD5_9	0.948	0.647	0.978

Table 5. Age 18.

Marker	Test For Population Stratification	Test for Dominance Effects	Test for Additive Effects
DRD1_2	0.860	0.327	0.605
DRD1_4	0.867	0.854	0.943
DRD1_14	0.610	0.143	0.969
DRD1_16	0.638	0.103	0.911
DRD1_20	0.960	0.732	0.383
DRD2_1	0.222	0.738	0.947
DRD2_11	0.210	0.628	0.842
DRD2_12	0.688	0.867	0.875
DRD2_15	0.287	0.298	0.913
DRD2_21	0.789	0.145	0.305
DRD2_5	0.987	0.296	0.616
DRD2_6	0.231	0.744	0.953
DRD2_7	0.068	0.255	0.910
DRD2_8	0.989	0.186	0.894
DRD3_10	0.323	0.412	0.803
DRD3_14	0.494	0.620	0.286
DRD3_18	0.359	0.160	0.976
DRD3_19	0.368	0.233	0.927
DRD3_21	0.996	1.000	0.976
DRD4_10	0.092	0.079	0.974
DRD4_14	0.186	0.083	0.964
DRD4_16	0.987	1.000	0.969
DRD5_9	0.999	0.818	0.538

Table 6. Age 25 (Mean = 24.3981)

Marker	Test For Population Stratification	Test for Dominance Effects	Test for Additive Effects
DRD1_2	0.635	0.975	0.759
DRD1_4	0.547	0.387	0.939
DRD1_14	0.845	0.392	0.957
DRD1_16	0.929	0.211	0.941
DRD1_20	0.865	0.874	0.509
DRD2_1	0.362	0.684	0.921
DRD2_11	0.237	0.582	0.981
DRD2_12	0.883	0.598	0.993
DRD2_15	1.000	0.153	0.995
DRD2_21	0.885	0.638	0.215
DRD2_5	0.415	0.684	0.206
DRD2_6	0.322	0.575	0.983
DRD2_7	0.485	0.537	0.976
DRD2_8	0.633	0.896	0.477
DRD3_10	0.847	0.816	0.852
DRD3_14	0.903	0.964	0.674
DRD3_18	0.997	0.811	1.000
DRD3_19	0.996	0.818	0.981
DRD3_21	0.999	1.000	0.432
DRD4_10	0.712	0.114	0.277
DRD4_14	0.914	0.291	0.628
DRD4_16	0.985	1.000	0.407
DRD5_9	0.978	0.920	0.800