Specificity of a cocaine-derived dopaminergic genetic risk score

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Background
- Cocaine dependence highly comorbid with psychiatric and other substance disorders
- 40-80% variance in cocaine dependence from additive genetic factors
- Most genetic variance in cocaine dependence shared with other substances
- Dopamine implicated as primary neurotransmitter system involved in responses to cocaine exposure
- Cocaine compulsively inhibits dopamine transportation by binding to overlapping sites on dopamine transporter
- Administration of typical drug doses majority of dopamine transporter sites
- Blocking sites results in increased synaptic dopamine, contributing to reinforcing and addictive properties of cocaine

Current Study
- Made use of
  - Large, existing, genotyped sample
  - Selected specifically for phenotype(s) of interest
  - Conducted intra-sample cross-validation
  - Focused analyses on dopamine system
  - Reduced likelihood of including “noisy” SNPs
  - Increased ability to identify optimal SNP scoring set

Participants
- 1,951 unrelated individuals from the Study of Addiction: Genetics and Environment (SAGE) who had ever used cocaine
- SAGE participants drawn from three primary studies of cocaine (FSCD), alcohol (COGA), and nicotine dependence (COGEND)

Genotyping
- DNA obtained from blood samples
- Genotyping conducted at Johns Hopkins University Center for Inherited Disease Research (CIDR) using Illumina Human IM Bead Chip
- Quality control procedures included
  - Assessment of population structure, missing call rates, Mendelian errors, duplication errors, gender and chromosomal anomalies, hidden relatedness, batch effects, and Hardy-Weinberg disequilibrium
  - Removal of duplicates, related subjects, and outliers
  - Median missing call rate < 0.05%
  - 99.5% SNPs had < 1.4% missingness
  - 948,142 SNPs passed quality control.

Gene selection
- Genes included if:
  - Autosomal
  - Deﬁned, direct effect on dopamine
  - Identiﬁed N=8 genes (see Table 1)
  - N=273 SNPs on Illumina 1M Chip
- (Genes & SNPs identical to ones in association study of sensation seeking using partially overlapping sample)

Analyses
- Sample split in half randomly creating “training” sample and “testing” sample
- Halves did not differ on covariates or phenotypes
- Dependence symptom counts residualized over covariates:
  - sex, age in quartiles; primary study source; ancestry (i.e., PC1 and PC2)
- SNPs coded for number of minor alleles
- Missing SNPs imputed as 2MAF
- Association tests run in training sample between cocaine symptoms and each SNP
- SNPs incorporated one at a time to calculate testing sample score, in order of ascending training sample p-values:
  - SNPs (weighted by training sample regression weights) added to the score until testing sample variance explained began decreasing
  - Speciﬁcity investigated by correlating score with alcohol, tobacco, and marijuana in testing sample

Results
- Top 4 training sample SNPs (Table 2) explained:
  - 0.546% variance in testing sample cocaine dependence symptoms (p = 0.037).
  - 0.004% variance in alcohol (p = 0.854).
  - 0.010% variance in nicotine (p = 0.781).
  - 0.003% variance in marijuana (p = 0.879).
- Top 4 SNPs in 4 different genes
- Linkage disequilibrium (LD) unlikely to affect results.

TABLE 1. GENES SELECTED FOR ANALYSIS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Function</th>
<th>Allele</th>
<th>MAF</th>
<th>B</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBH</td>
<td>9q34</td>
<td>Intron</td>
<td>T</td>
<td>0.23</td>
<td>-0.4</td>
<td>-2.5</td>
<td>0.012</td>
</tr>
<tr>
<td>DRD1</td>
<td>11p13.1</td>
<td>Exon</td>
<td>A</td>
<td>0.16</td>
<td>0.4</td>
<td>2.2</td>
<td>0.026</td>
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<tr>
<td>DRD2</td>
<td>11q23</td>
<td>Exon</td>
<td>A</td>
<td>0.14</td>
<td>0.5</td>
<td>2.4</td>
<td>0.015</td>
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<tr>
<td>DRD3</td>
<td>11p15.5</td>
<td>UTR-5</td>
<td>A</td>
<td>0.15</td>
<td>0.5</td>
<td>0.5</td>
<td>0.588</td>
</tr>
<tr>
<td>DRD4</td>
<td>11p15.5</td>
<td>UTR-5</td>
<td>A</td>
<td>0.15</td>
<td>0.5</td>
<td>0.5</td>
<td>0.588</td>
</tr>
</tbody>
</table>

TABLE 2. TRAINING SAMPLE TOP SNPs

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Chr Function</th>
<th>Allele</th>
<th>MAF</th>
<th>Training sample</th>
<th>Testing sample</th>
</tr>
</thead>
<tbody>
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<td>rs1611131</td>
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<td>T</td>
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<td>rs261526</td>
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<td>11p13.1</td>
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<td>0.16</td>
<td>0.4</td>
<td>2.2</td>
</tr>
<tr>
<td>rs817063</td>
<td>DRD3</td>
<td>11q23</td>
<td>A</td>
<td>0.14</td>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>rs1079597</td>
<td>DRD4</td>
<td>11p15.5</td>
<td>A</td>
<td>0.15</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Conclusions
- Association between cocaine and dopamine at system level
  - Optimal risk score incorporated 4 SNPs from 4 separate genes
  - Cocaine-derived genetic risk score predicted cocaine (R² = 0.546%, p = 0.037)
  - Did not predict alcohol, tobacco, or marijuana dependence severity (p > 0.79).
- Individual effects of SNPs did not replicate across samples
  - Training sample: p = 0.012 - 0.032
  - Testing sample: p = 0.14 - 0.59
  - Only signiﬁcant in aggregate
  - Narrow SNP selection criteria limited inclusion of spurious SNPs in risk score
  - Decreased the “noise” in true score “measurement”
  - Provides greater power
  - Detected 4 SNPs accounting for 0.55% of replication sample variance in cocaine
  - (Compare to recent genome-wide schizophrenia score21, explaining ~3% of variance with ~37,000 SNPs)

References

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