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SPECIFICITY OF A COCAINE-DERIVED DOPAMINERGIC GENETIC RISK SCORE

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Background

- Cocaine dependence highly comorbid with psychiatric and other substance disorders[1]
- 40-80% variance in cocaine dependence from additive genetic factors[2-4]
- Most genetic variance in cocaine dependence shared with other substances[5]
- Dopamine implicated as primary neurotransmitter system involved in responses to cocaine exposure[6-8]
- Cocaine competitively inhibits dopamine transportation by binding to overlapping sites on dopamine transporter[9]
- Administration of typical dose blocks majority of dopamine transporter sites[10]
- 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 "noise" SNPs
  - Increased ability to identify optimal SNP scoring set

Participants

- 1591 unrelated individuals from the Study of Addiction: Genetics and Environment (SAGE) who reported having ever used cocaine.
- SAGE participants drawn from three primary studies of cocaine (FSCD), alcohol (COGA), and nicotine dependence (COGEND)

Measures

- Cocaine, alcohol, nicotine, and marijuana dependence symptom counts
- Assessed via the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II), which has demonstrated validity and reliability.
- Marijuana symptom counts log-transformed [i.e., ln(symptoms+1)] to obtain normally distributed residuals
- Other substance symptom counts (i.e., cocaine, alcohol, nicotine) untransformed

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%;
  - 95% SNPs had <1.4% missingness
- 948,142 SNPs passed quality control.

Gene selection

- Genes included if:
  - Autosomal;
  - Definite, 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[11])

TABLE 1. GENES SELECTED FOR ANALYSIS

Gene	Location	SNPs	Role in Dopamine (DA)
DRD3	3q13.3	32	codes D3 subtype of DA receptors
SLC6A3	5p15.3	35	transporter, mediates DA reuptake
DRD1	5q35.1	9	codes D1 subtype of DA receptors
DDC	7p12.2	81	protein coded converts L-DOPA to DA
DBH	9q34	37	converts DA to norepinephrine
DRD4	11p15.5	4	codes D4 subtype of DA receptors
DRD2	11q23	40	codes D2 subtype of DA receptors
COMT	22q11.21	35	affects catecholamine degradation

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 2*MAF
- 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:

$$(1) \quad \text{Score} = \Sigma\ (N_{\text{Minor Alleles for SNP } i} * B_{\text{SNP } i})$$

- 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

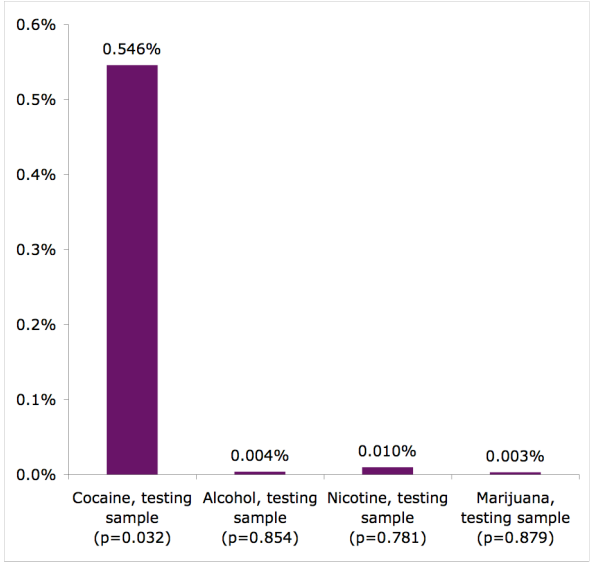
TABLE 2. TRAINING SAMPLE TOP SNPs USED TO ESTIMATE TESTING SAMPLE GENETIC RISK SCORES

						Training sample			Testing sample		
SNP	Gene	Chr	Function	Allele	MAF	B	Z	p	B	Z	p
rs1611131	DBH	9	Intron	G	0.23	-0.4	-2.5	0.012	-0.1	-0.9	0.348
rs5326	DRD1	5	UTR-5	A	0.14	0.5	2.4	0.015	0.1	0.5	0.588
rs9817063	DRD3	3	NearGene-3	C	0.45	0.3	2.2	0.026	0.2	1.5	0.142
rs1079597	DRD2	11	Intron	A	0.16	0.4	2.2	0.032	0.2	1.4	0.159

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

FIGURE 1. VARIANCE EXPLAINED BY TOP 4 TRAINING SAMPLE SNPs



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 ($R^2 = 0.546\%$, $p = 0.037$)
  - Did not predict alcohol, tobacco, or marijuana dependence severity ($p > 0.78$).
- 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 score[12], explaining ~3% of variance with >37,000 SNPs)

References

1. Ford JD, Gelernter J, DeVoe JS, et al. (2009) Association of psychiatric and substance use disorder comorbidity with cocaine dependence severity and treatment utilization in cocaine-dependent individuals. *Drug and Alcohol Dependence* 99:193-203.
2. Kendler KS, Karkowski LM, Neale MC, Prescott CA (2000) Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Arch Gen Psychiatry* 57:261-9.
3. Kendler KS, Prescott CA (1998) Cocaine use, abuse and dependence in a population-based sample of female twins. *Br J Psychiatry* 173:345-50.
4. van den Bree MB, Johnson EO, Neale MC, Pickens RW (1998) Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug and Alcohol Dependence* 52:231-41.
5. Kendler K, Myers J, Prescott C (2007) Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Arch Gen Psychiatry* 64:1313-20.
6. Dackis CA, Gold MS (1985) New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci Biobehav Rev,* 9:469-77.
7. Haile CN, Kosten TR, Kosten TA (2007) Genetics of dopamine and its contribution to cocaine addiction. *Behav Genet* 37:119-45.
8. Kuhar MJ, Ritz MC, Boja JW (1991) The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* 14:299-302.
9. Beuming T, Kniazeff J, Bergmann M, et al. (2008) The binding sites for cocaine and dopamine in the dopamine transporter overlap. *Nat Neurosci* 11:780-9.
10. Volkow ND, Wang GJ, Fischman MW, et al. (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386:827-30.
11. Derringer J, Krueger RF, Dick DM, et al. (accepted) Predicting sensation seeking from dopamine genes: A candidate system approach. *Psychol Sci*.
12. The International Schizophrenia Consortium (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460:748-52.

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