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DSM-IV Nicotine Withdrawal and Alcohol Dependence: Association Findings with the Nicotinic Acetylcholine Alpha-3, Alpha-5, Beta-4 Receptor Gene Cluster in Australian Families

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Introduction: Smoking/ Nicotine Withdrawal

- **25% of the US adult population continues to smoke (CDC, 2002).**
- **Over 50% of smokers report symptoms of nicotine withdrawal after they quit or cut-down (Breslau et al., 1992; Pergadia et al., 2006).**
- **Up to 47% of the variance in nicotine withdrawal can be accounted for by genetic factors (Pergadia et al., 2006).**

Introduction: Alcohol Use Problems

- **19% of the US adult population has experienced an alcohol use disorder at some point in their life (Kessler et al., 2005).**
- **Up to 47% of the variance in alcohol dependence may be accounted for by genetic influences, even after controlling for demographics and co-morbid psychopathology (Knopik et al., 2004).**

Introduction: Nicotine and Alcohol Use Problems

- **Increasing levels of nicotine withdrawal severity are associated with increased risk of alcohol dependence (Breslau et al., 1992; Madden et al., 1997; Xian et al., 2004).**
- **There is evidence for genetic overlap between nicotine dependence and alcohol dependence in men (Madden et al., Guze 2006; True et al., 1999), and for genetic overlap between history of smoking and alcohol intoxication, especially in women (Madden et al., 1997).**
- **Even after accounting for regular smoking, significant phenotypic ($r = .15$) and genetic overlap ($r_g = .26$) is found between nicotine withdrawal and alcohol dependence, suggesting that some additional genetic factors might be accounting for the covariation at this later stage of smoking behavior (nicotine withdrawal; Pergadia et al., Guze 2006).**

Candidate Genes for Nicotine Withdrawal

- **Pharmacologic (Damaj et al., 2003) and genetic knock-out work in mice (Salas et al., 2004) implicate the importance of nicotinic acetylcholine alpha-3, alpha-5, beta-4 receptor gene cluster in nicotine withdrawal behavior.**
- **A recent genome-wide association study in humans (Saccone et al., 2007) found this cluster of genes to be highly associated with nicotine dependence.**
- **However, the extent to which the nicotinic acetylcholine alpha-3, alpha-5, beta-4 receptor genes are associated with nicotine withdrawal (or co-morbid nicotine withdrawal and alcohol dependence) remains to be studied in humans.**

Aims

- **To examine the genetic association between DSM-IV nicotine withdrawal and alcohol dependence and the nicotinic acetylcholine alpha-3, alpha-5, beta-4 receptor genes using family data.**

DSM-IV Nicotine Withdrawal (APA, 1994)

- Withdrawal, as manifested by either of the following:
 - 1) 4 or more of the following:
 - Depressed mood
 - Insomnia
 - Irritability
 - Nervousness
 - Difficulty concentrating
 - Restlessness
 - Decreased heart rate
 - Increased appetite
 - 2) Smoked cigarettes to relieve or avoid withdrawal symptoms.

DSM-IV Alcohol Dependence

(APA, 1994)

Three or more of the following symptoms clustering in any 12 month period:

- 1) Tolerance
 - Need more alcohol for intoxication effects, or
 - Same amount of alcohol has less of an effect
- 2) Withdrawal
 - Alcohol withdrawal syndrome, or
 - Withdrawal relief: use alcohol to avoid or relieve symptoms
- 3) Use alcohol more than intended
- 4) Persistent desire or unsuccessful efforts to cut down on alcohol
- 5) Great deal of time spent obtaining, using or recovering from alcohol
- 6) Important social, occupational, or recreational activities given up or reduced because of alcohol use
- 7) Continued use despite knowledge or persistent or recurrent physical or psychological problems caused or made worse by alcohol

Sample: Australian site of the Nicotine Addiction Genetics (NAG) project (PI: Madden)

- Nicotine gene-mapping project ascertained using an affected sib-pair design
- Over 400 families associated with the Australian twin registry, including spouse families, where proband is a heavy smoker: 20+ cigarettes per day, where samples of DNA and phenotypic information is available (over 600 ASP and over 450 parent-offspring trios)
- For this PDT association analyses (which included sibs concordant and discordant for hypothesized phenotypes): N=507 families, 1845 individuals, average sib-age: 42

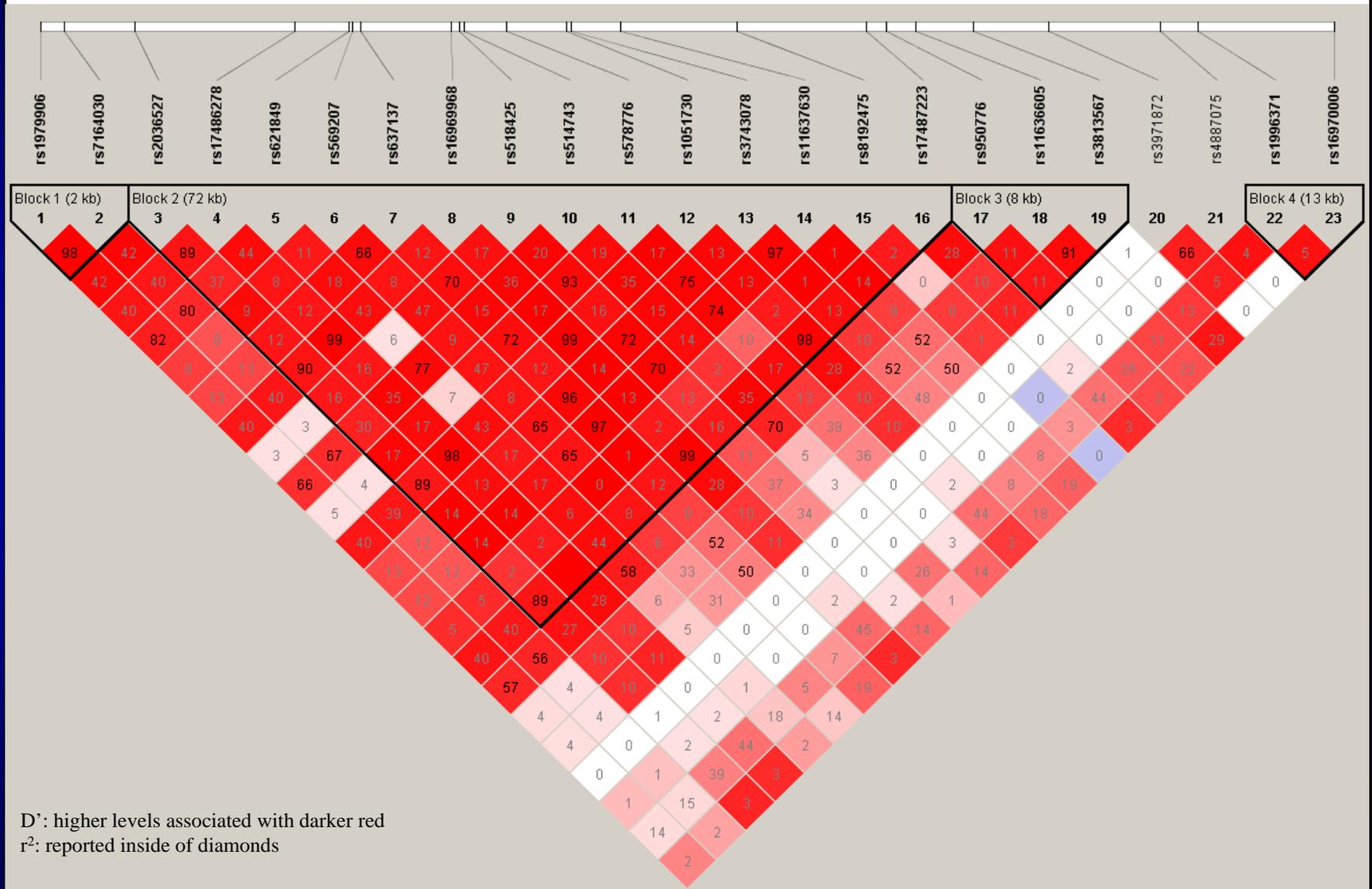
DSM-IV Nicotine Withdrawal and Alcohol Dependence Prevalence Rates

Lifetime Measure	Prevalence
DSM-IV Nicotine Withdrawal	41.7%
DSM-IV Alcohol Dependence	30.5%

PDT results for CHRNA3, CHRNA5, CHRNB4 for DSM-IV nicotine withdrawal and alcohol dependence in Australian NAG families

	Nicotine Withdrawal (NW)		Alcohol Dependence (AD)		NW or AD		NW & AD	
	Z	P value	Z	P value	Z	P value	Z	P value
<u>CHRNA3</u>								
rs8192475	0.03	0.97	0.29	0.77	0.04	0.97	0.64	0.52
rs1051730	1.51	0.13	0.62	0.53	0.69	0.49	0.29	0.77
rs11637630	2.00	0.045	1.03	0.30	1.74	0.08	1.50	0.13
rs3743078	2.30	0.02	1.23	0.22	1.97	0.049	1.84	0.07
rs578776	2.11	0.03	1.14	0.25	2.16	0.03	1.19	0.23
<u>CHRNA5</u>								
rs2036527	1.77	0.08	0.40	0.69	0.88	0.38	0.71	0.48
rs514743	0.15	0.88	1.06	0.29	0.58	0.56	0.79	0.43
rs7164030	0.17	0.86	0.30	0.76	0.08	0.94	0.17	0.86
rs16969968	1.41	0.16	0.45	0.66	0.54	0.54	0.50	0.61
rs17486278	1.48	0.14	1.20	0.23	0.46	0.65	0.19	0.85
rs1979906	0.39	0.70	1.02	0.30	0.30	0.77	0.20	0.84
rs518425	<i>1.96</i>	<i>0.05</i>	0.26	0.79	<i>1.94</i>	<i>0.05</i>	0.53	0.60
rs569207	2.65	0.008	2.66	0.008	2.99	0.003	1.59	0.11
rs621849	0.18	0.86	1.05	0.29	0.63	0.53	0.72	0.47
rs637137	1.84	0.07	0.75	0.46	1.66	0.09	1.08	0.28
<u>CHRNB4</u>								
rs3971872	0.57	0.57	0.85	0.400	0.56	0.58	0.14	0.89
rs11636605	0.70	0.48	0.34	0.74	0.46	0.64	0.67	0.51
rs16970006	0.36	0.72	1.24	0.22	0.61	0.55	0.82	0.41
rs950776	1.02	0.31	0.03	0.98	0.61	0.54	0.20	0.84
rs17487223	1.90	0.06	0.64	0.52	0.98	0.33	0.45	0.65
rs1996371	1.83	0.07	0.170	0.87	1.15	0.25	0.49	0.62
rs3813567	0.80	0.42	0.19	0.85	0.18	0.86	1.00	0.32
rs4887075	0.56	0.58	1.58	0.11	0.36	0.72	0.77	0.44

Linkage Disequilibrium Plot: Nicotinic Acetylcholine Alpha-3, Alpha-5, Beta-4 Receptor Genes



Preliminary Findings

- Preliminary results suggest an association between DSM-IV nicotine withdrawal and alcohol dependence and polymorphisms within two hypothesized candidate genes: CHRNA5 and CHRNA3.
- For CHRNA3 the findings appear to be driven by nicotine withdrawal
 - Within CHRNA3: rs11637630 and rs3743078 are in very high LD ($r^2=0.97$), whereas they are in relatively lower LD with rs578776 ($r^2=0.74$ and $r^2=0.75$, respectively), suggesting that rs578776 is exerting some unique genetic influence nicotine withdrawal, whereas the genetic effects of rs11637630 and rs3743078 overlap.
 - Interesting, in Saccone et al. (2007) rs578776 ranked number three in terms of predicting nicotine dependence in a study over 348 candidate genes.
- One SNP within the CHRNA5, rs569207 was associated with both nicotine withdrawal and alcohol dependence, suggesting that it might be associated with a general genetic vulnerability to substance use behavior.

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