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Linkage Signals for Illicit Drug Phenotypes



The Nicotine Addiction Genetics (NAG) Project

<u>Arpana Agrawal</u>, Andrew C. Heath, Scott Saccone, Michele Pergadia, Danielle Dick, Julia Grant, Su Ge, Michael Lynskey, John Rice, Alexandre Todorov, Richard Todd, Alison Goate, Jen Wang, Shantia Shears, Grant Montgomerey, Nicholas Martin, and Pamela A. F. Madden

NICOTINE GENETICS CONSORTIUM SENIOR INVESTIGATORS

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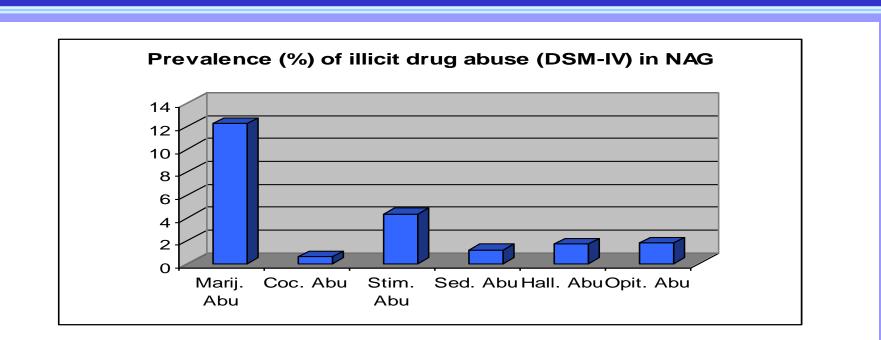
Jaakko Kaprio, M.D., Ph.D. Leena Peltonen, M.D., Ph.D. Markku Koskenvuo, M.D., Ph.D. *University of Helsinki, Finland*

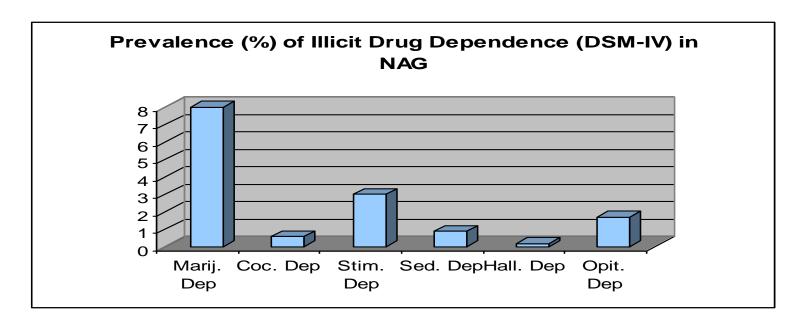
The Nicotine Addiction Genetics Project (P.I: Dr. Pamela A.F. Madden)

- Families from the Australian twin registry
- **Proband is a heavy smoker** (20+ cigarettes/day and also includes 40+ cigarettes lifetime)
- Interviewee is affected twin or spouse from discordant pairs of ATR or spouse or random twin from concordant pairs
- Affected sibpair + additional affected sibs + both biological parents + unaffected sibs with nicotine exposure (fewer than 100 cigs lifetime)
- Estimated **400 families** with current tally of 200 families

Current data (Nfams=196)

- N = 196 families with **1036** individuals
- Average family size = 5
- Founders = **395**
- Female = 541Male = 495
- Mean age = **48 years**





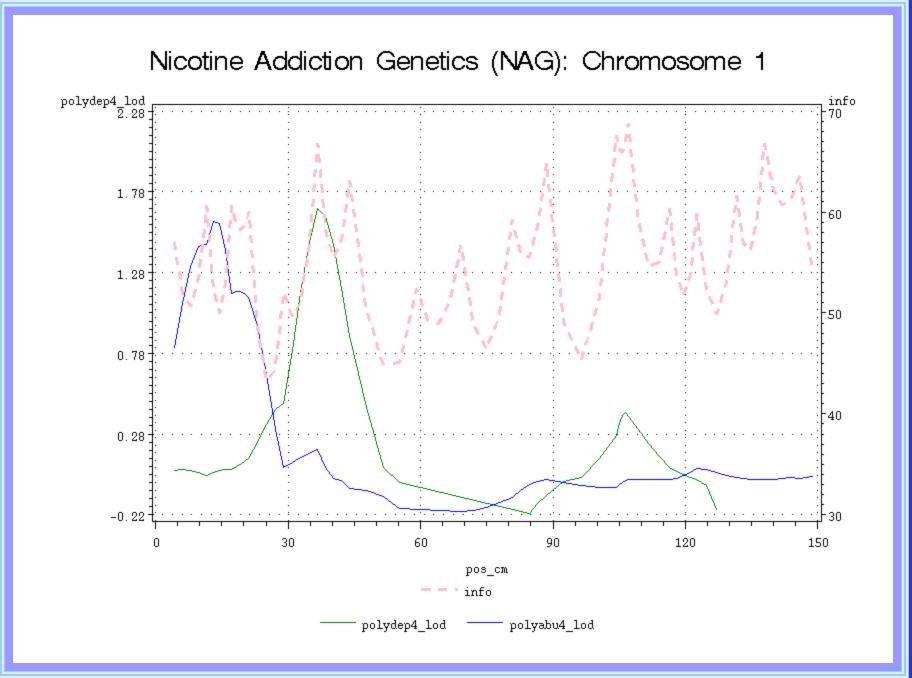
Phenotypic Definitions for Illicit Drugs

Mjsx : Sum of marijuana dependence symptoms
Polyuse : Sum of binary use variables (response to "have you

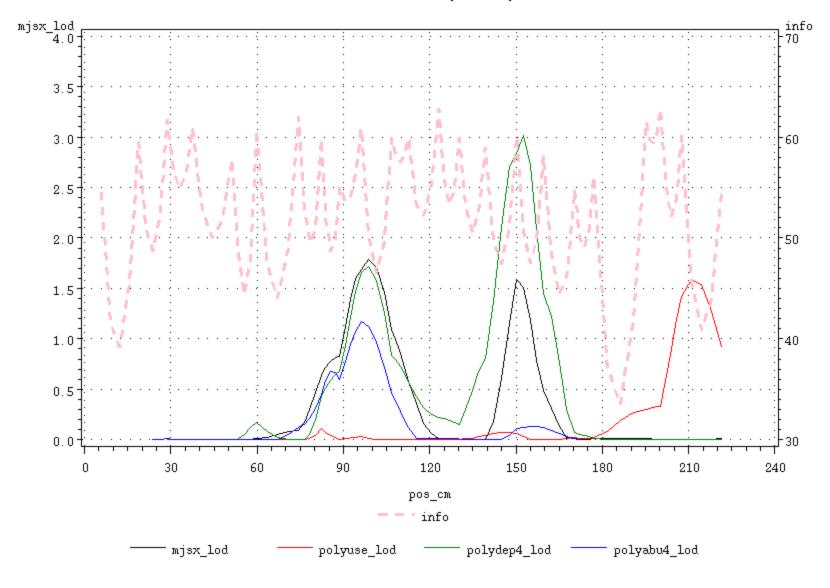
ever used...") for marijuana, cocaine, sedatives, stimulants, hallucinogens and opiates

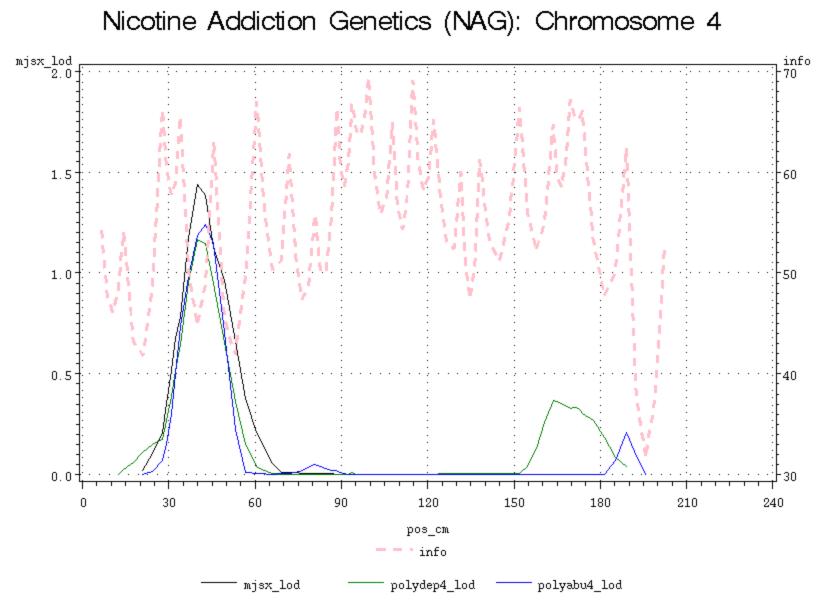
- **Polydep4** : Sum of binary DSM-IV dependence for marijuana, cocaine, sedatives, stimulants, hallucinogens and opiates
- **Polyabu4** : Sum of binary DSM-IV abuse for marijuana, cocaine, sedatives, stimulants, hallucinogens and opiates
- log(maxdrink) : maximum drinks in a 24-hr period

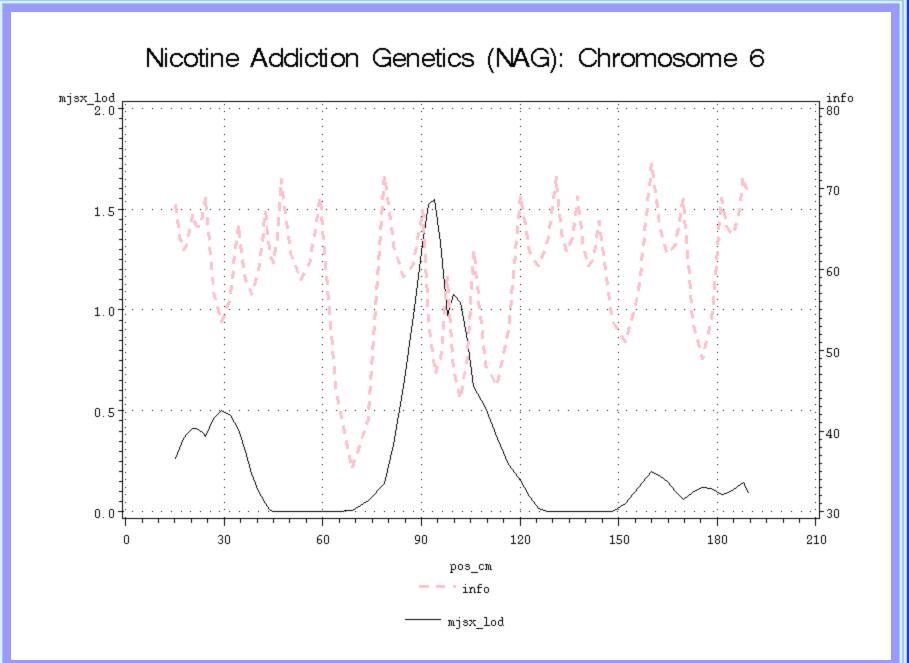
All semi-continuous variables were **log-transformed**, gender, age and age^2 was regressed out and **residuals** were used for linkage analyses in **MERLIN-REGRESS** (without ascertainment correction).

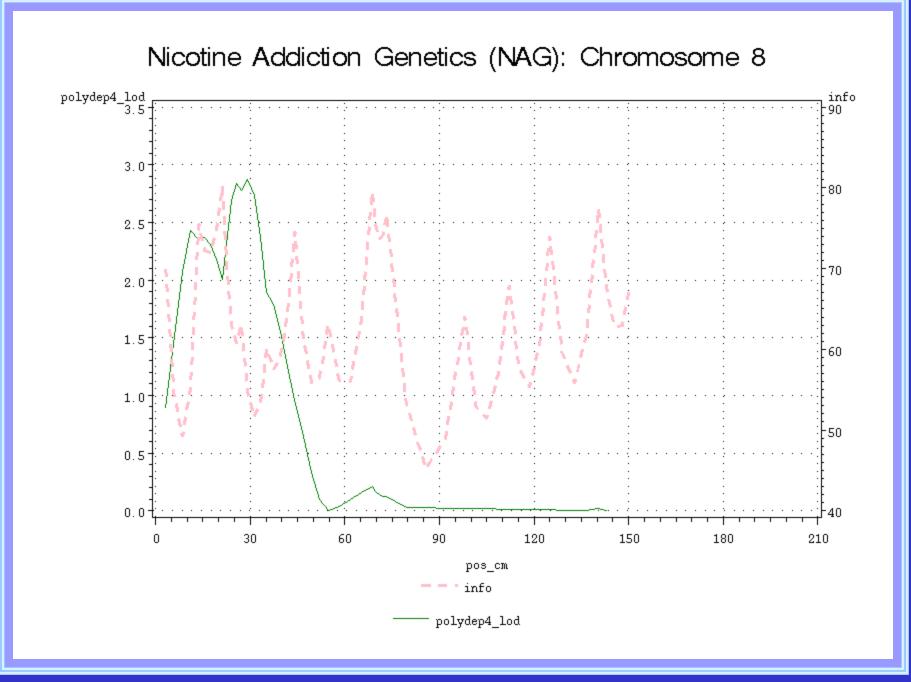


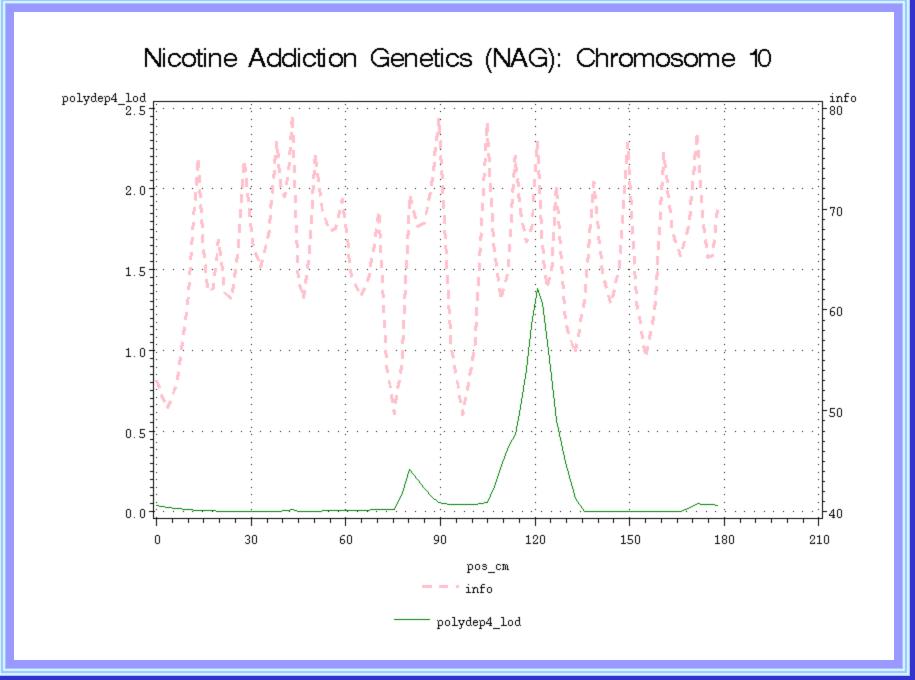


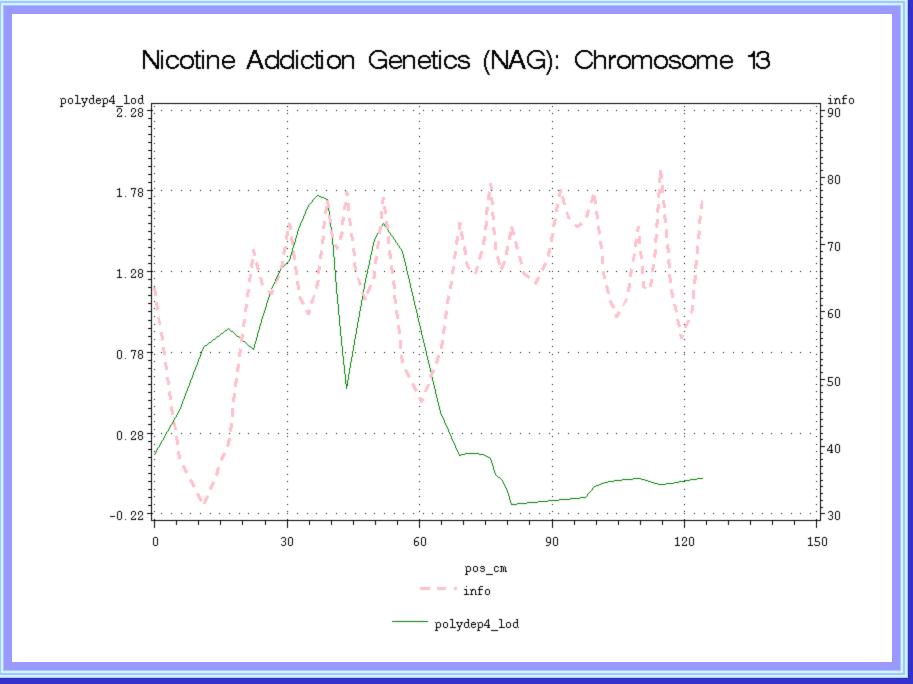








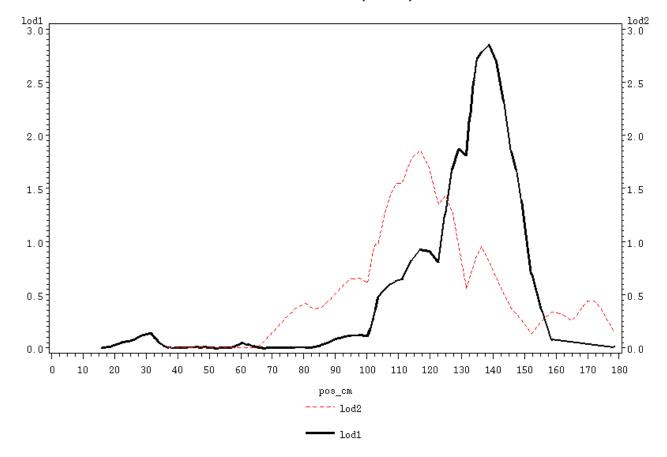




Log (maximum alcohol drinks)

Is there an overlap with regions for illicit drugs? Ref: Saccone, Heath, Madden (unpublished)

Nicotine Addiction Genetics (NAG): Chromosome 7



Linkage signals for Nicotine-related measures

Are there differences from the illicit drug linkage regions? Ref: Madden & Heath (unpublished)

Position	Phenotype	LOD	P-value
Chr 2: 84cM	FTND	1.81	.002
Chr 7 : 117cM	Max. Cigs	1.86	.002
Chr 13: 105cM	FTND	1.71	.002
Chr 20: 74cM	Max. Cigs	1.96	.001
Chr 22: 57cM	FTND	2.01	.001

Conclusions

- The signals on chr 3, 4, 6, 8 and 10 seem to be **unique to illicit drug dependence**
- The signals from log(maxdrinks) overlaps with the finding from log (maxcigs)
- This signal on **chr 7** is well supported by other studies (e.g. COGA)
- The signal on **chr 6** maps fairly close to the **cannabinoid receptor** gene

Cannabinoid Receptor 1: Chromosome 6 *Possible Candidate Gene ?*

- CNR1 located chromosome 6@ 90cM
- G-protein coupled receptor
- CB1 K/O mice exhibit reduced mortality, hypoalgesia but show some analgesic effects of THC (Zimmer et al, 1999, PNAS)
- Association study with 154 mood disordered patients and 165 control failed to show association between CB1 and psychotic symptoms
- Association study with 127 schizophrenic patients and 146 control failed to show association between CB1 and schizophrenia
- No association with alcohol-related phenotypes
- One study suggests that restricting AN and binging/purging AN may be associated with different alleles (14 vs 13 rep) of CNR1
- Long repeats correlated with ADHD in alcoholics in a Spanish sample

Work in Progress

• Aim 1: Refine illicit drug use, abuse & dependence **phenotypes** & combine with alcohol/nicotine

- Aim 2: Perform analyses on **full sample** of 400 families
- Aim 3: Calculation on **empirical p-values** from a 1,000 replicates of the data
- Aim 4: To include other **comorbid psychopathology**, such as conduct disorder, personality traits, depression