Linkage signals for illicit drug phenotypes

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Linkage Signals for Illicit Drug Phenotypes

The Nicotine Addiction Genetics (NAG) Project

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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 = **541**
  Male = **495**
- Mean age = **48 years**
Prevalence (%) of illicit drug abuse (DSM-IV) in NAG

Prevalence (%) of illicit drug dependence (DSM-IV) in NAG
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).
Nicotine Addiction Genetics (NAG): Chromosome 1
Nicotine Addiction Genetics (NAG): Chromosome 6

The graph represents the distribution of mjsx_lod and pos_cm along the chromosome. The peaks and valleys indicate areas of interest for further genetic analysis.
Nicotine Addiction Genetics (NAG): Chromosome 8

Graph showing polydep4_lod and info against pos_cm.
NICOTINE ADDICTION GENETICS (NAG): CHROMOSOME 10

polydep4_lod

info

pos_cm

info

polydep4_lod
Nicotine Addiction Genetics (NAG): Chromosome 13
Log (maximum alcohol drinks)

Is there an overlap with regions for illicit drugs?

Ref: Saccone, Heath, Madden (unpublished)
**Linkage signals for Nicotine-related measures**

*Are there differences from the illicit drug linkage regions?*

*Ref: Madden & Heath (unpublished)*

<table>
<thead>
<tr>
<th>Position</th>
<th>Phenotype</th>
<th>LOD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr 2: 84cM</td>
<td>FTND</td>
<td>1.81</td>
<td>.002</td>
</tr>
<tr>
<td>Chr 7: 117cM</td>
<td>Max. Cigs</td>
<td>1.86</td>
<td>.002</td>
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<tr>
<td>Chr 13: 105cM</td>
<td>FTND</td>
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<tr>
<td>Chr 20: 74cM</td>
<td>Max. Cigs</td>
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<tr>
<td>Chr 22: 57cM</td>
<td>FTND</td>
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</tbody>
</table>
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