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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

polydep4 lod

polyabu4 lod
Nicotine Addiction Genetics (NAG): Chromosome 3

The graph shows the LOD scores for different markers on Chromosome 3. The x-axis represents the position in centimorgans (pos_cm), while the y-axis represents the LOD score. The markers are differentiated by color:
- mjsx_lod (black solid line)
- polyuse_lod (red solid line)
- polydep4_lod (green solid line)
- polyabu4_lod (blue solid line)

The LOD scores vary across the chromosome, with peaks indicating regions of interest for further genetic analysis.
Nicotine Addiction Genetics (NAG): Chromosome 4

pos_cm

mjsx_lod
polydep4_lod
polyabu4_lod

info

mjsx_lod
polydep4_lod
polyabu4_lod

0
30
60
90
120
150
180
210
240

0
0.5
1.0
1.5
2.0

0
10
20
30
40
50
60
70
Nicotine Addiction Genetics (NAG): Chromosome 6
Nicotine Addiction Genetics (NAG): Chromosome 8

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>
</tr>
<tr>
<td>Chr 13: 105cM</td>
<td>FTND</td>
<td>1.71</td>
<td>.002</td>
</tr>
<tr>
<td>Chr 20: 74cM</td>
<td>Max. Cigs</td>
<td>1.96</td>
<td>.001</td>
</tr>
<tr>
<td>Chr 22: 57cM</td>
<td>FTND</td>
<td>2.01</td>
<td>.001</td>
</tr>
</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