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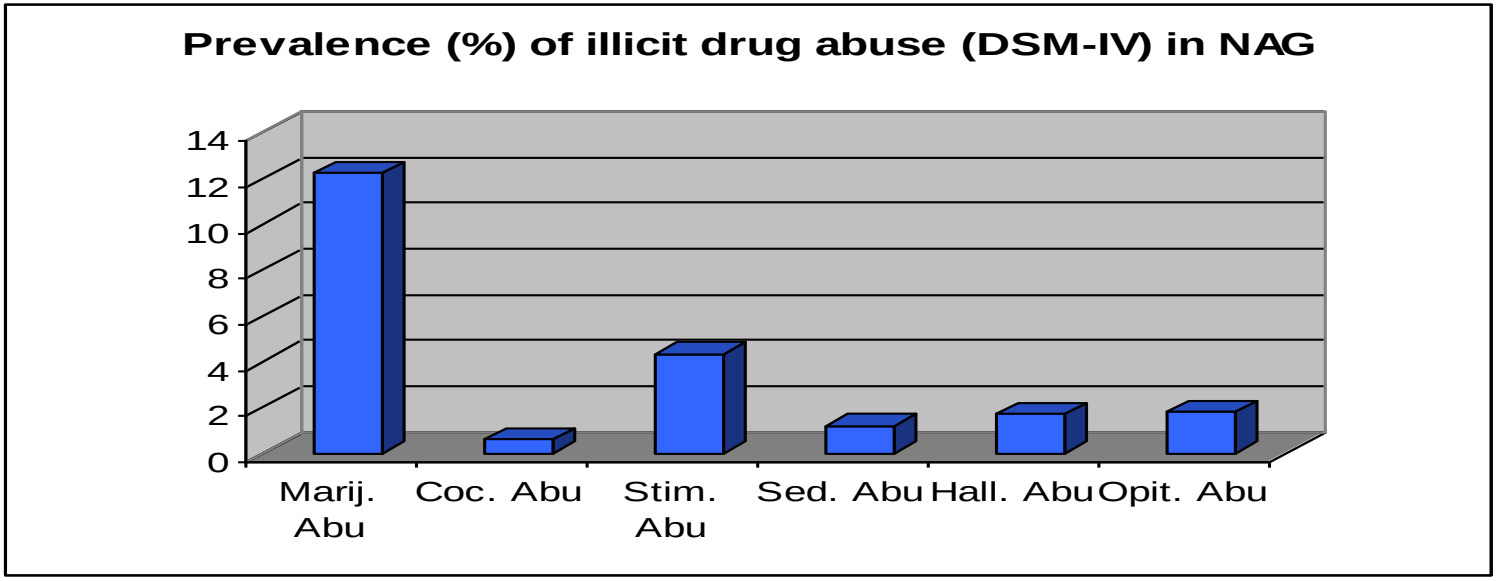
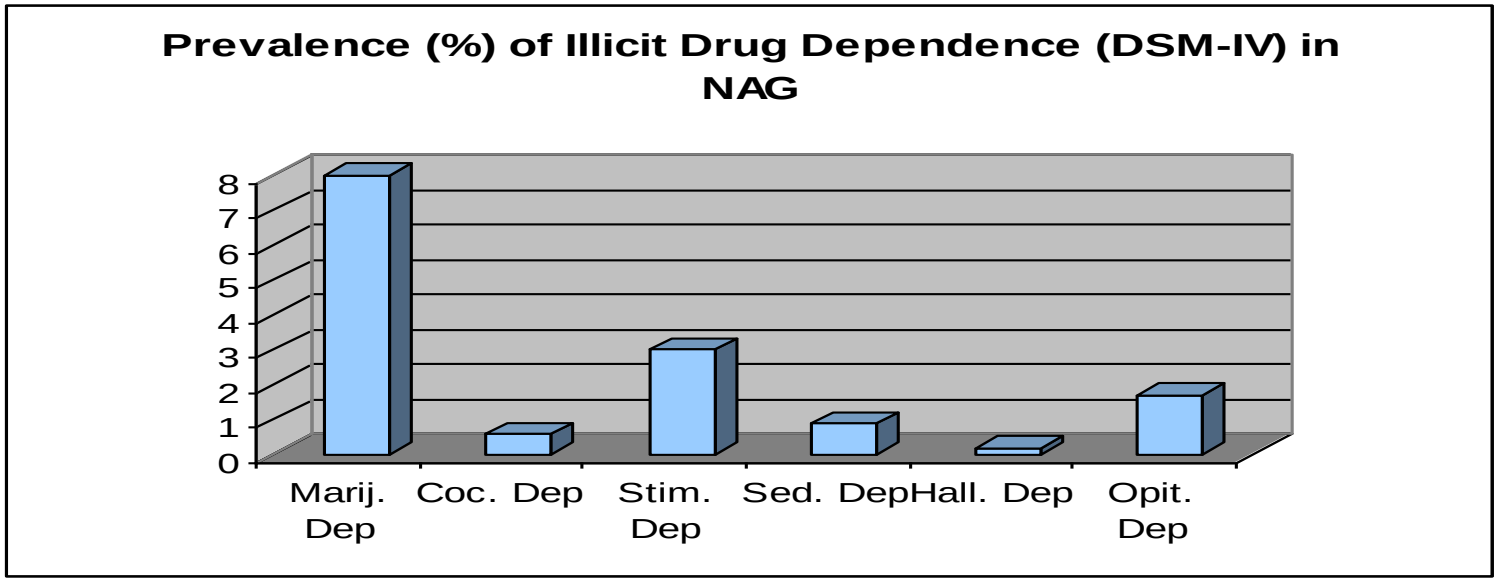
The Nicotine Addiction Genetics Project
(P.I: Dr. Pamela A.F. Madden)

- 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
14
12
10
8
6
4
2
0
Marij. Abu
Coc. Abu
Stim. Abu
Sed. Abu
Hall. Abu
Opit. Abu

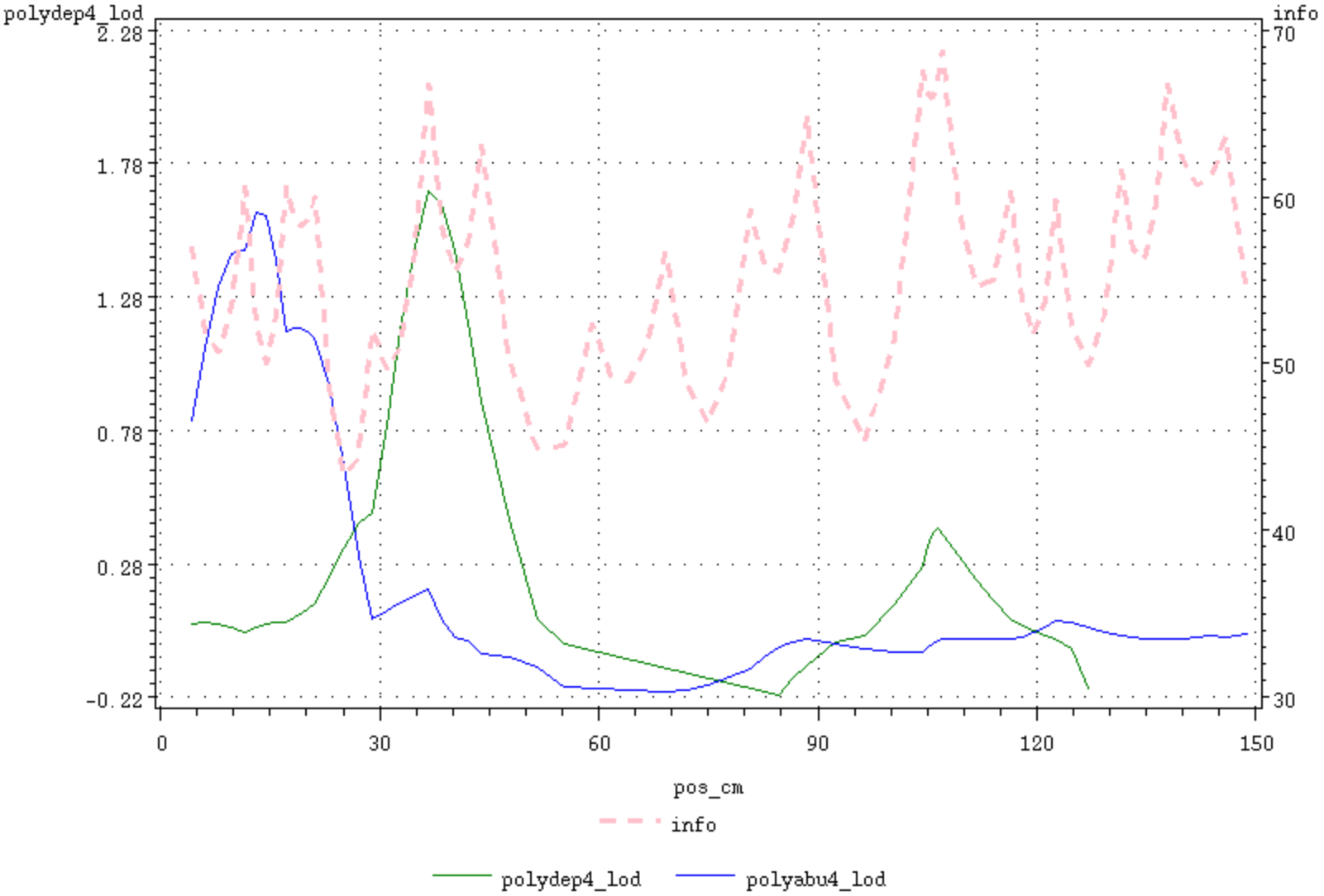

Prevalence (%) of Illicit Drug Dependence (DSM-IV) in NAG
8
7
6
5
4
3
2
1
0
Marij. Dep
Coc. Dep
Stim. Dep
Sed. Dep
Hall. Dep
Opit. Dep

Phenotypic Definitions for Illicit Drugs

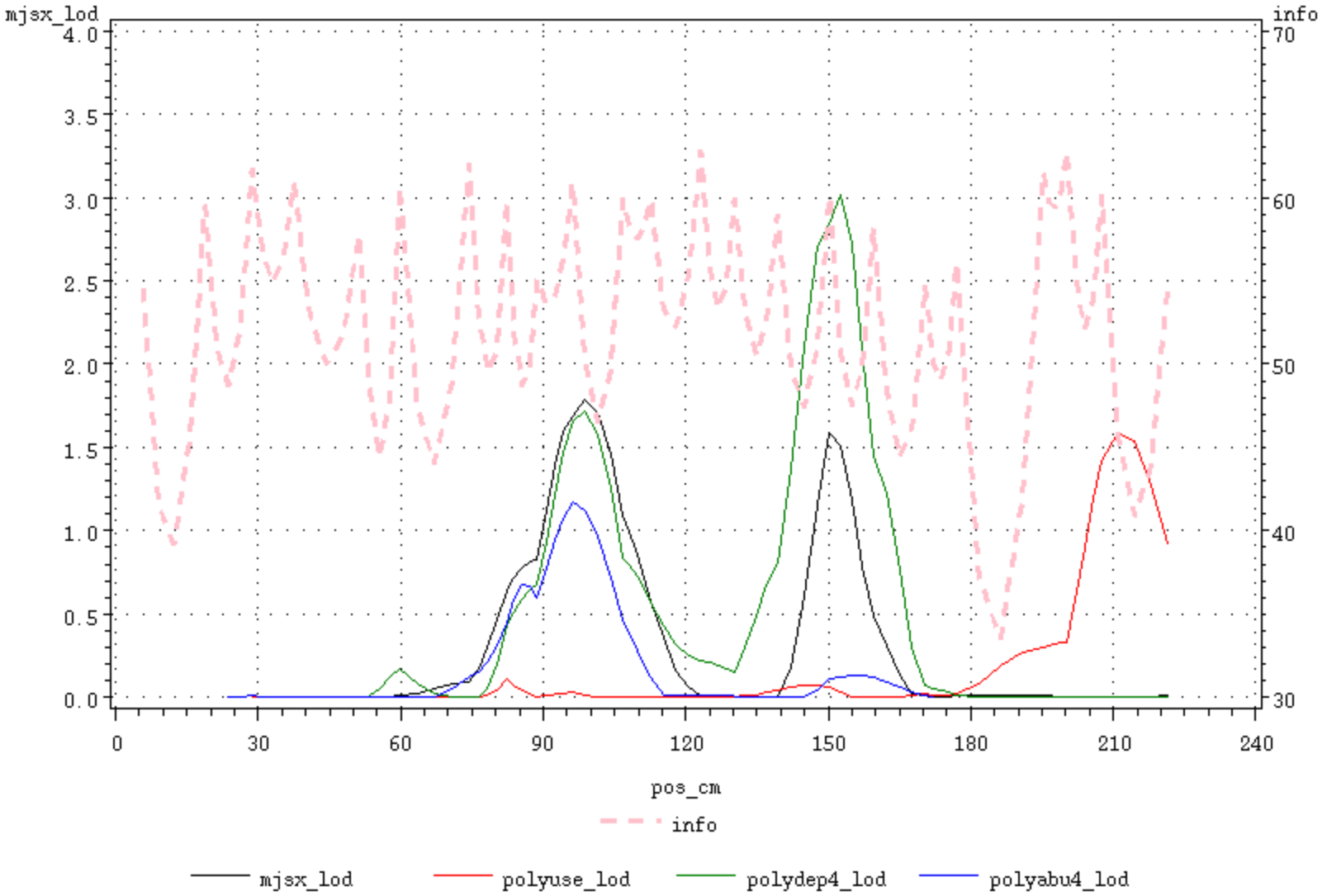
- **Mjsx** : Sum of marijuana dependence symptoms
- **Polyuse** : Sum of binary use variables (response to "have you ever used…") for marijuana, cocaine, sedatives, stimulants, hallucinogens and opiates
- **Polydep4** : Sum of binary DSM-IV dependence for marijuana, cocaine, sedatives, stimulants, hallucinogens 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).

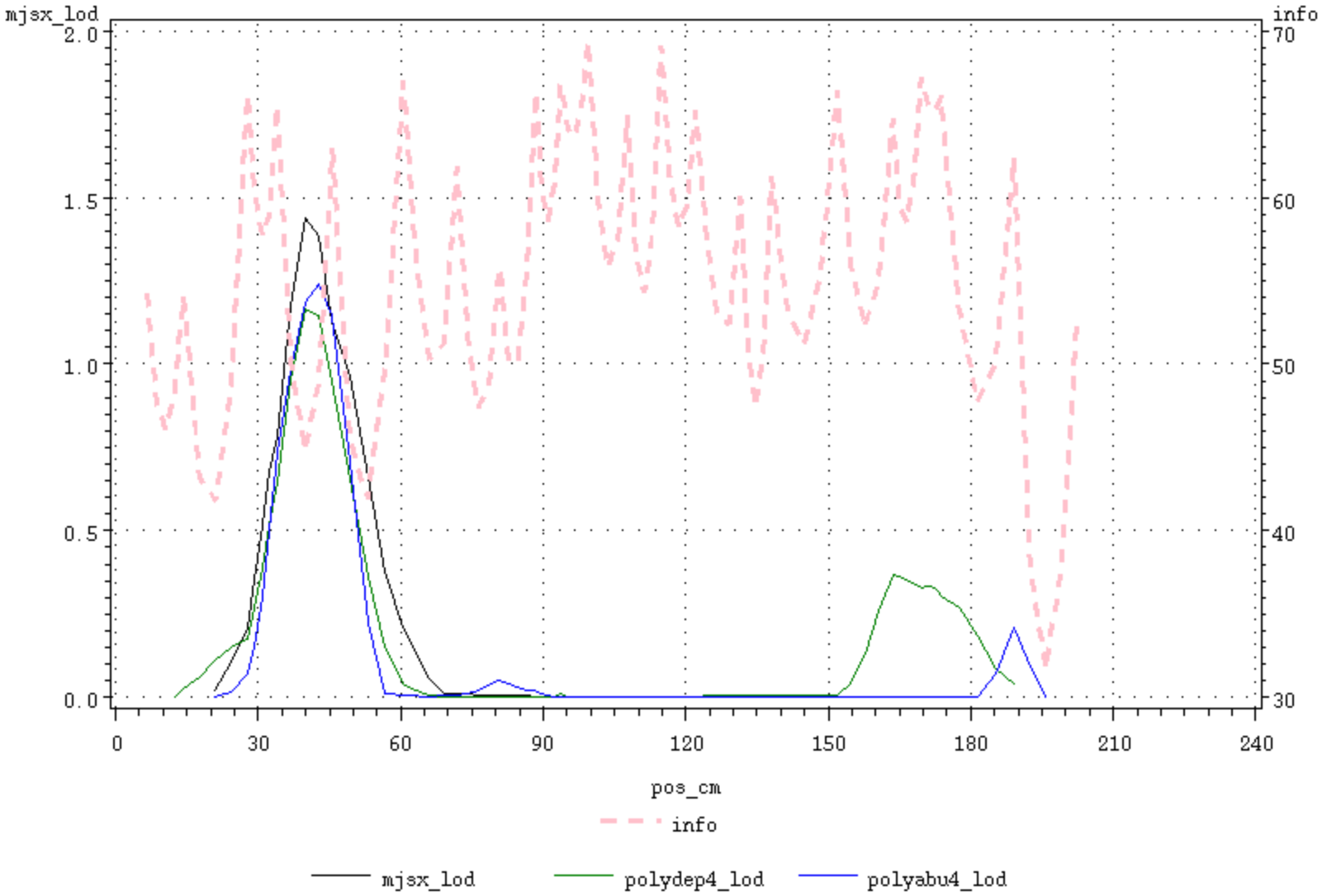
Nicotine Addiction Genetics (NAG): Chromosome 1



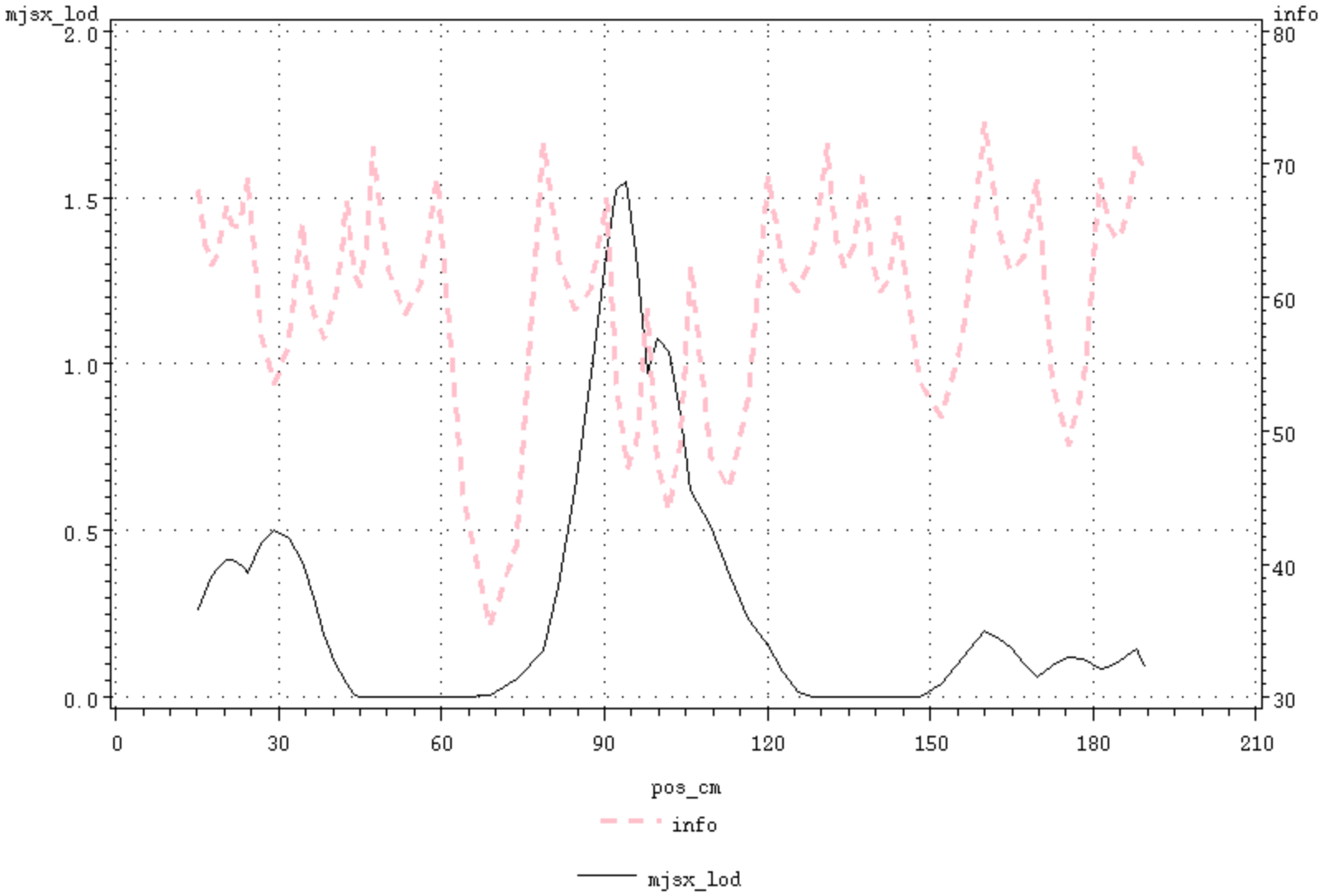
Nicotine Addiction Genetics (NAG): Chromosome 3



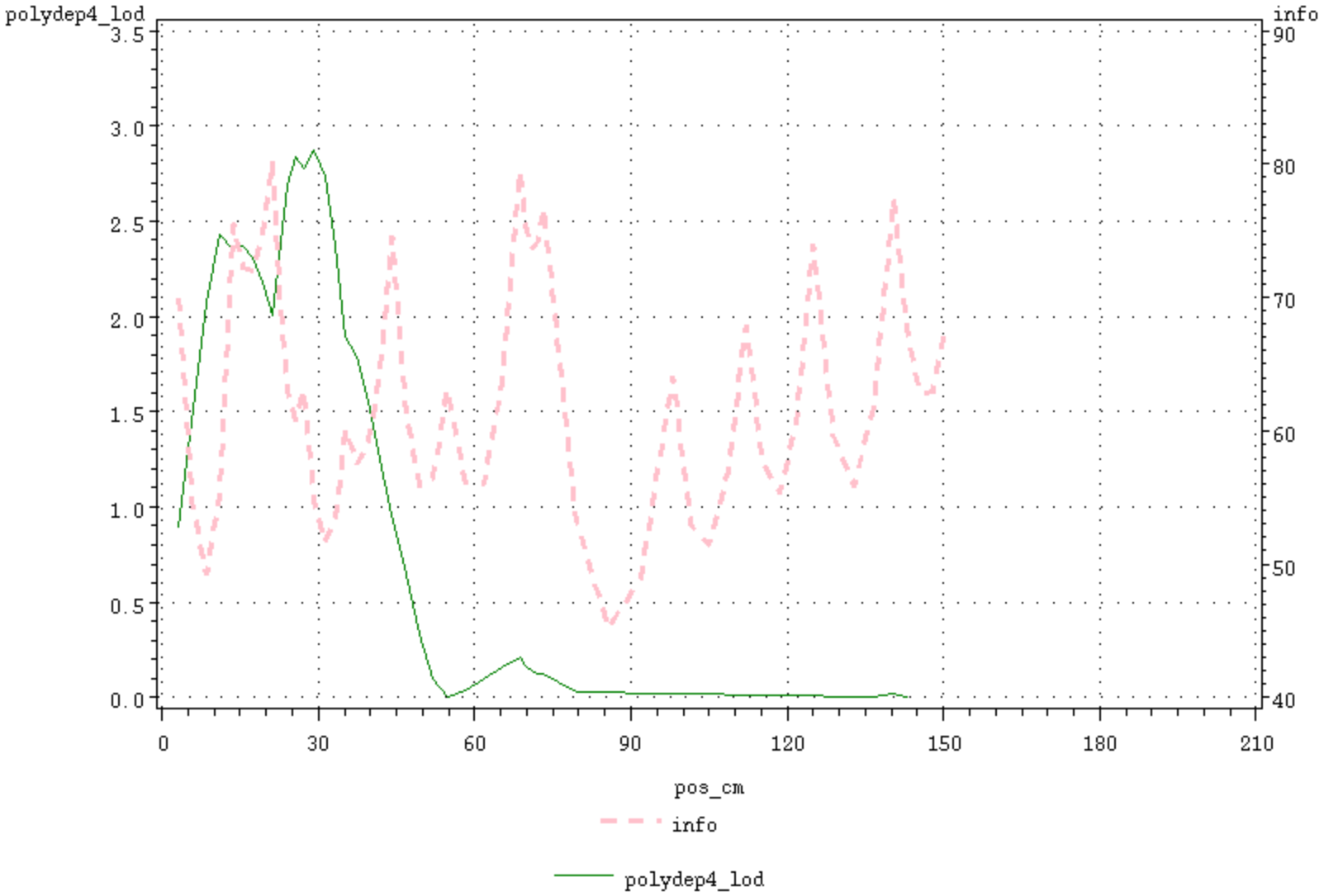
Nicotine Addiction Genetics (NAG): Chromosome 4



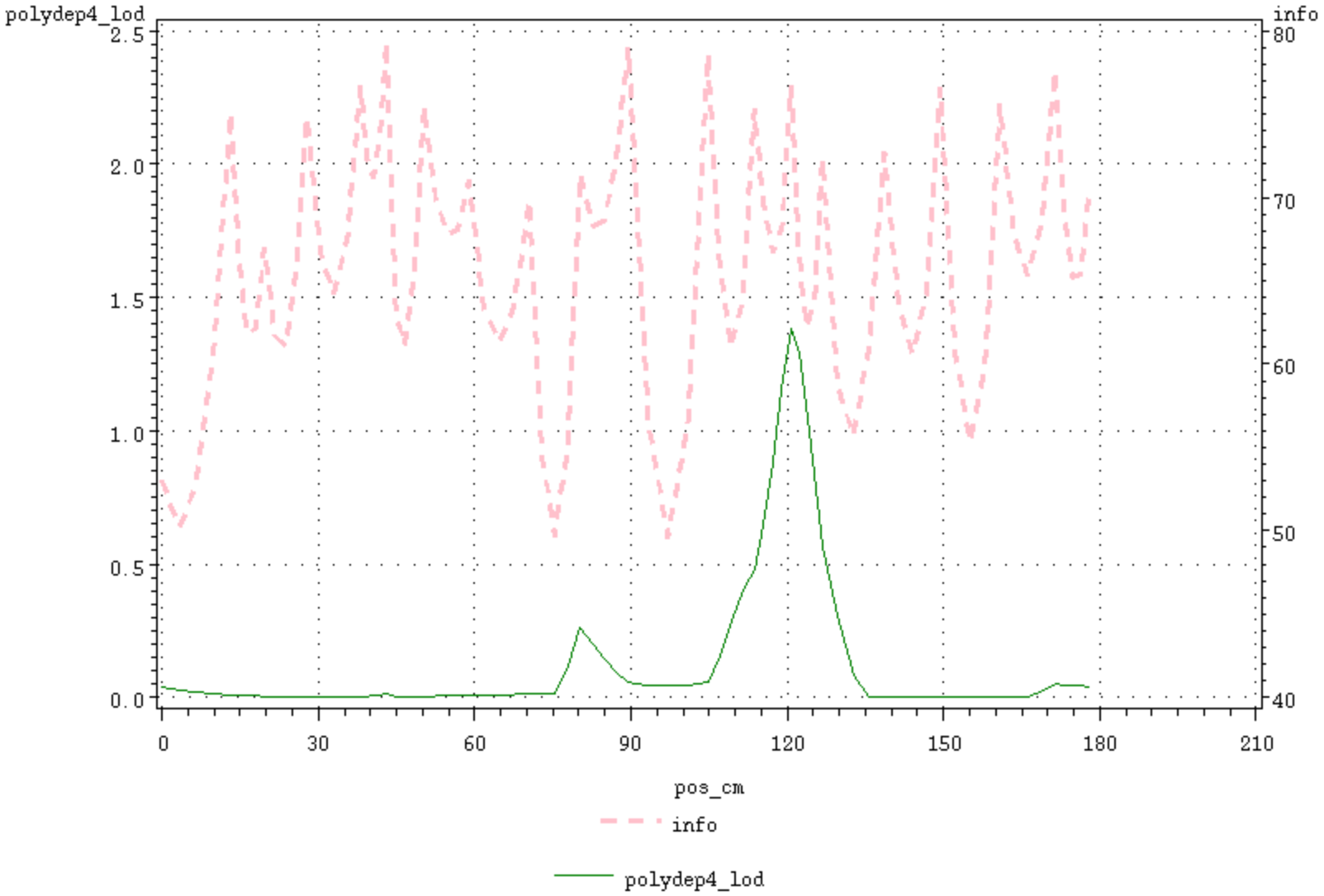
Nicotine Addiction Genetics (NAG): Chromosome 6



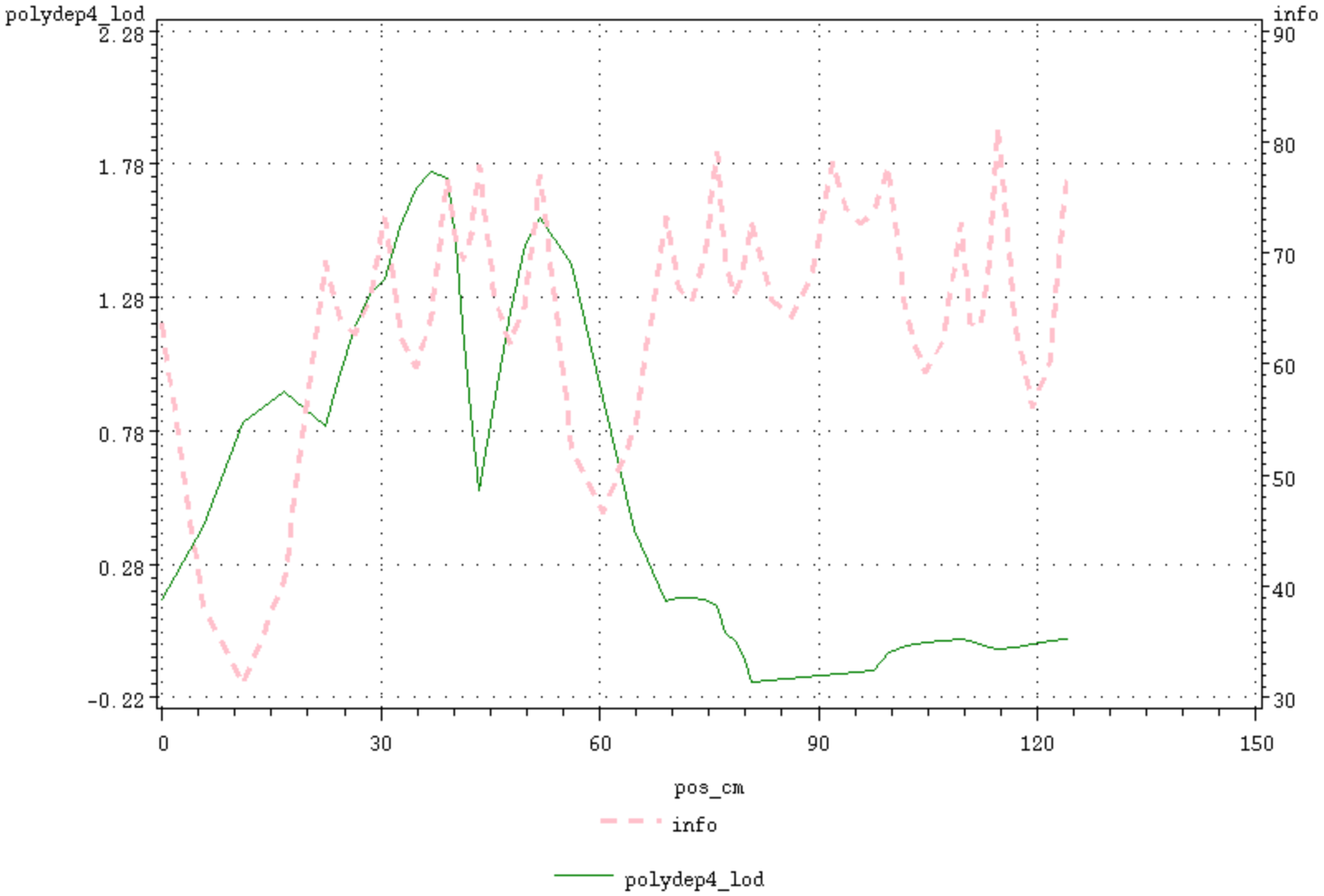
Nicotine Addiction Genetics (NAG): Chromosome 8



Nicotine Addiction Genetics (NAG): Chromosome 10



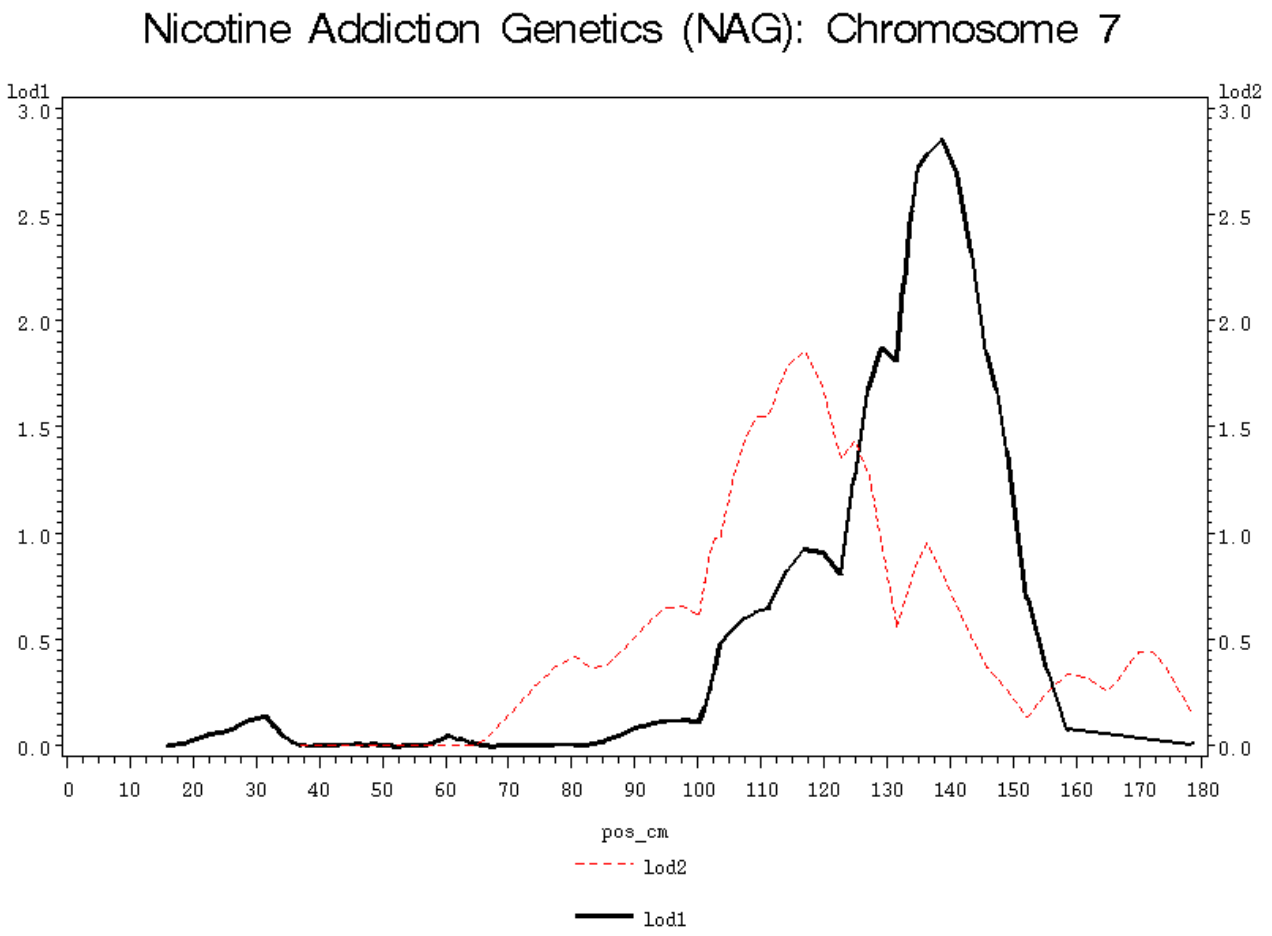
Nicotine Addiction Genetics (NAG): Chromosome 13



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)

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