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Genome-wide Linkage Analysis for Quantitative Indices of Alcohol Consumption in Australian Adults

Results from the Nicotine Addiction Genetics Project

Arpana Agrawal; A. C. Heath; S.F. Saccone; M.L. Pergadia; J.C. Wang; G. W. Montgomery; A. Goate; J. P. Rice; J. Kaprio; R.D. Todd; N.G. Martin; P.A. F. Madden.

FIGURE 2: Prevalence of a lifetime history of DSM-IV alcohol abuse/dependence as a function of quantity of alcoholic drinks consumed per day during the heaviest drinking period in 43,093 participants from the NESARC

NICOTINE GENETICS CONSORTIUM SENIOR INVESTIGATORS

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ALCOHOL DEPENDENCE

- Heritability in adult samples is 40-60%;

- Linkage analyses in dense multiplex families show linkage on chromosomes 1, 2, 4, 6, 7, 9, 11;

- Strength: Diagnostic, Clinical Relevance, Comparability across studies;

- Limitations: Psychometric weakness, underpowered in samples ascertained for other traits;

Quantitative Indices of Alcohol Consumption

- Maximum alcohol consumption in 24-hours (MaxDrinks)
- Frequency of alcohol consumption during heaviest 12-month period
- Weekly consumption during heaviest 12-month period
- Frequency of drinking to intoxication during heaviest 12-month period
- Maximum drinks consumed till tolerance

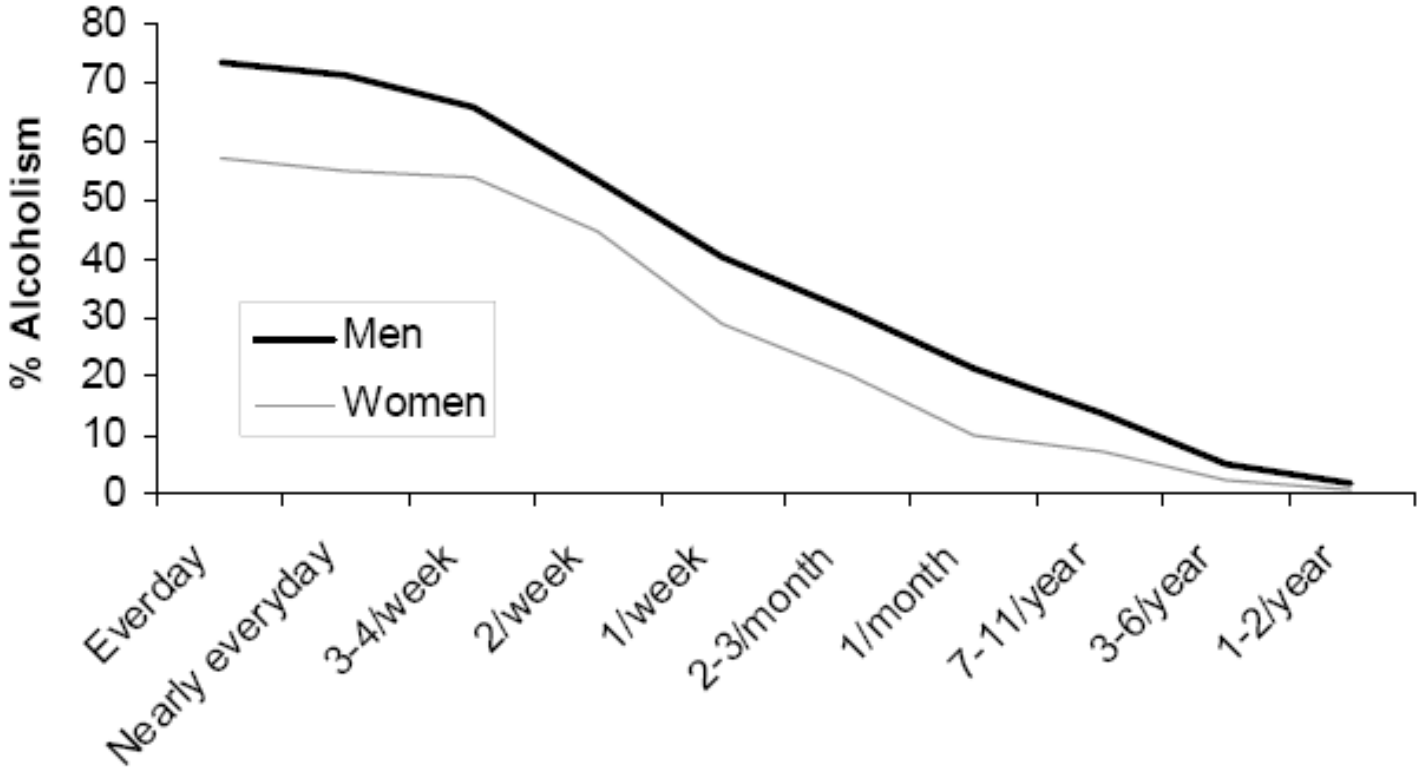


FIGURE 1: Prevalence of a lifetime history of DSM-IV alcohol abuse/dependence as a function of frequency of consumption of alcoholic drinks during the heaviest drinking period in 43,093 participants from the NESARC

Alcoholism and Alcohol Consumption: Genetic overlap

Table 1. Twin-cotwin correlations between quantitative indices of alcohol consumption and DSM-IV alcohol dependence in 6,257 adult Australian twins. MZ pairs shown in lower diagonal, DZ pairs in upper diagonal

	Alcoholism	Maxdrink	Freq	Quant/day	Drinks to Intoxication	Max Tolerance
Alcoholism	**0.39** | 0.15	0.12	0.14	0.16	0.13	0.15
Maxdrinks	**0.35**	**0.63** | 0.24	0.2	0.22	0.21	0.17
Frequency	**0.28**	**0.44**	**0.50** | 0.23	0.14	0.19	0.14
Quantity/day	**0.29**	**0.48**	**0.27**	**0.42** | 0.24	0.18	0.17
Drinks to Intoxication	**0.35**	**0.41**	**0.39**	**0.32**	**0.45** | 0.19	0.11
Max Tolerance	**0.22**	**0.48**	**0.34**	**0.37**	**0.39**	**0.39** | 0.15

MZ BELOW DIAGONAL; DZ ABOVE DIAGONAL;

AIM

To conduct linkage analyses for 6 quantitative indices of alcohol consumption in the Australian component of the NICOTINE ADDICTION GENETICS PROJECT (PI Madden).

METHODS

- **Variables were normalized by adjusting for skewness and kurtosis;**
- **PROC FACTOR was used to create a factor score on the normalized variables;**
- **All variables, except the factor score were log-transformed, to approximate a normal distribution;**
- **PROC REG was used to eliminate confounding effects of gender and age;**
- **Residuals from the BIGSIB community sample were used to score residuals from NAG**
- **MERLIN-REGRESS was used for singlepoint and multipoint linkage analyses, with means and variances from BIGSIB, and h^2=0.50;**

Australian NAG Sample

Australian families with at least one current or former heavy smoker (defined as smoking at least a pack a day or 40 or more cigarettes in their lifetime) (65) were identified from Twin89, Twin81 and Spouse81. The heavy smoking member of a discordant twin pair or a randomly selected member from a concordant heavy smoking twin pair or a spouse, either a heavy smoker themselves or married to a heavy smoking twin, were invited to participate.

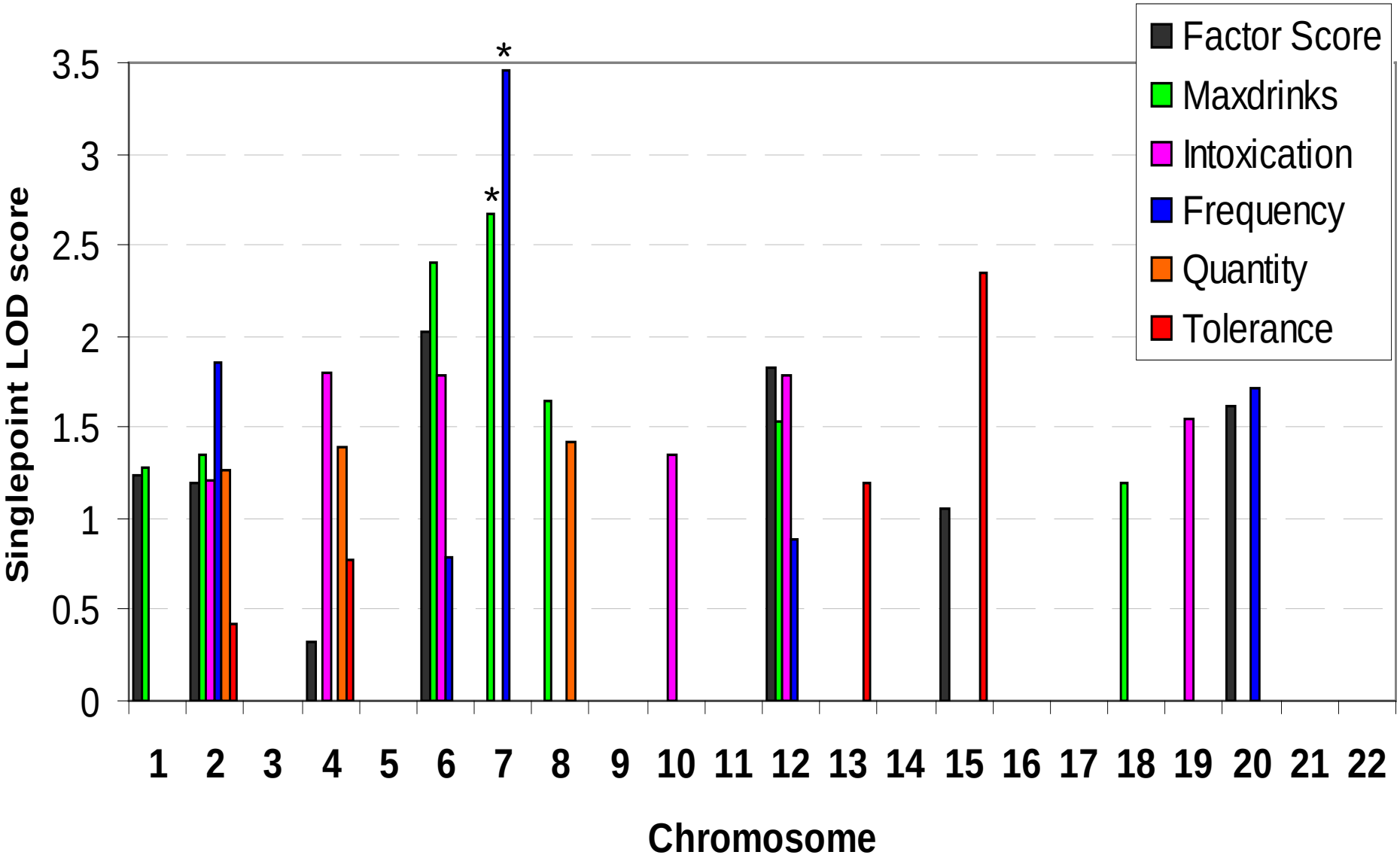
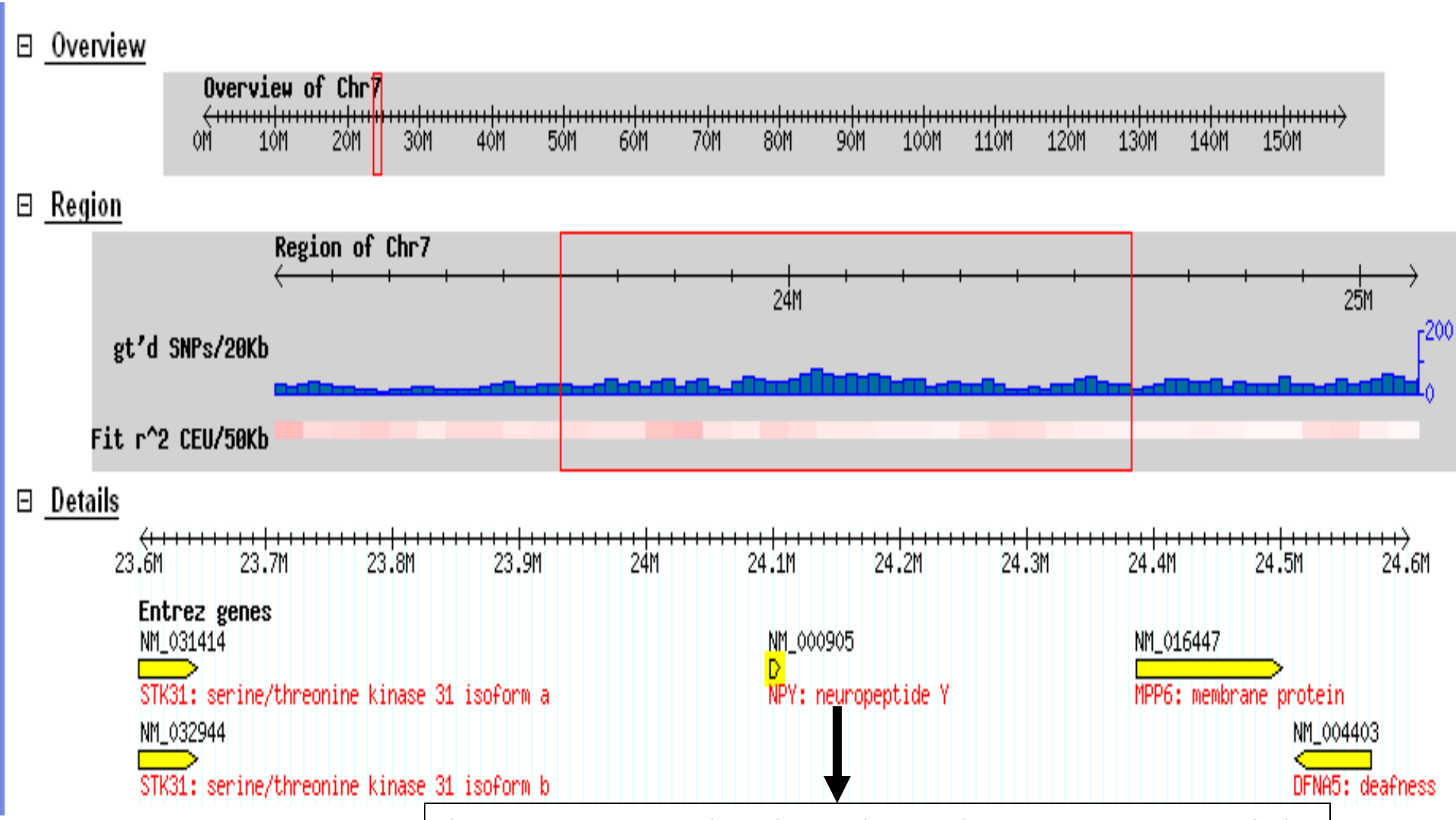


Figure 3. Singlepoint LOD scores for quantitative indices of alcohol consumption in Australian adults

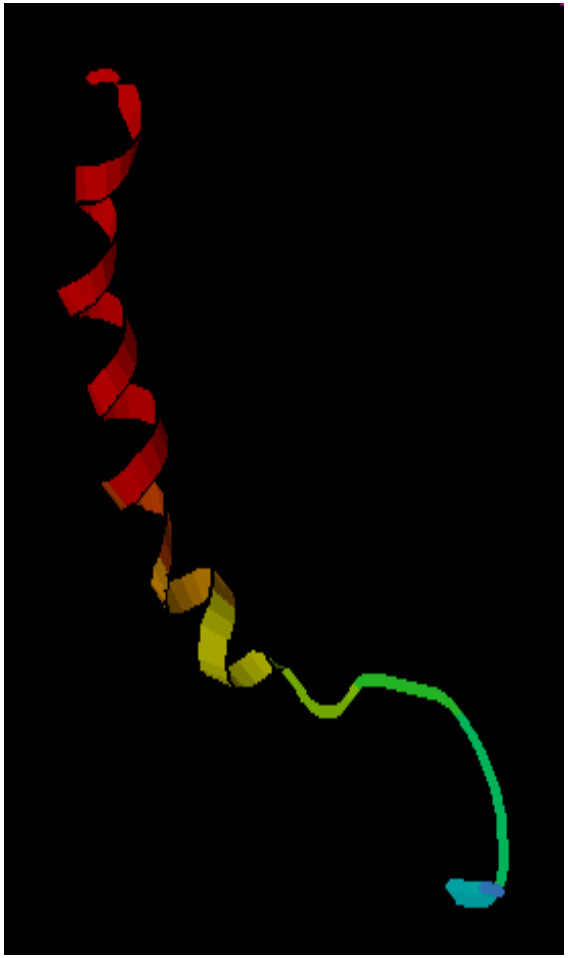
*** Regions with putative candidate genes for alcohol-related traits**

CANDIDATE GENES ON CHROMOSOME 7p
Neuropeptide Y



Association with ethanol uptake in murine models

Neuropeptide Y



- A 36-amino acid neurotransmitter found in the brain and autonomic nervous system;

- The receptor protein that NPY operates on is a G-protein coupled receptor in the rhodopsin like GPCR family;

- Demonstrated role in animal models for feeding behavior and ethanol consumption;

- The Leu7Pro polymorphism in NPY is associated with increased alcohol consumption in humans (Lappalainen et al., 2006)

Cholinergic Muscarinic Receptor 2

- Muscarinic receptors membrane-bound acetylcholine receptors that are more sensitive to muscarine than to nicotine;

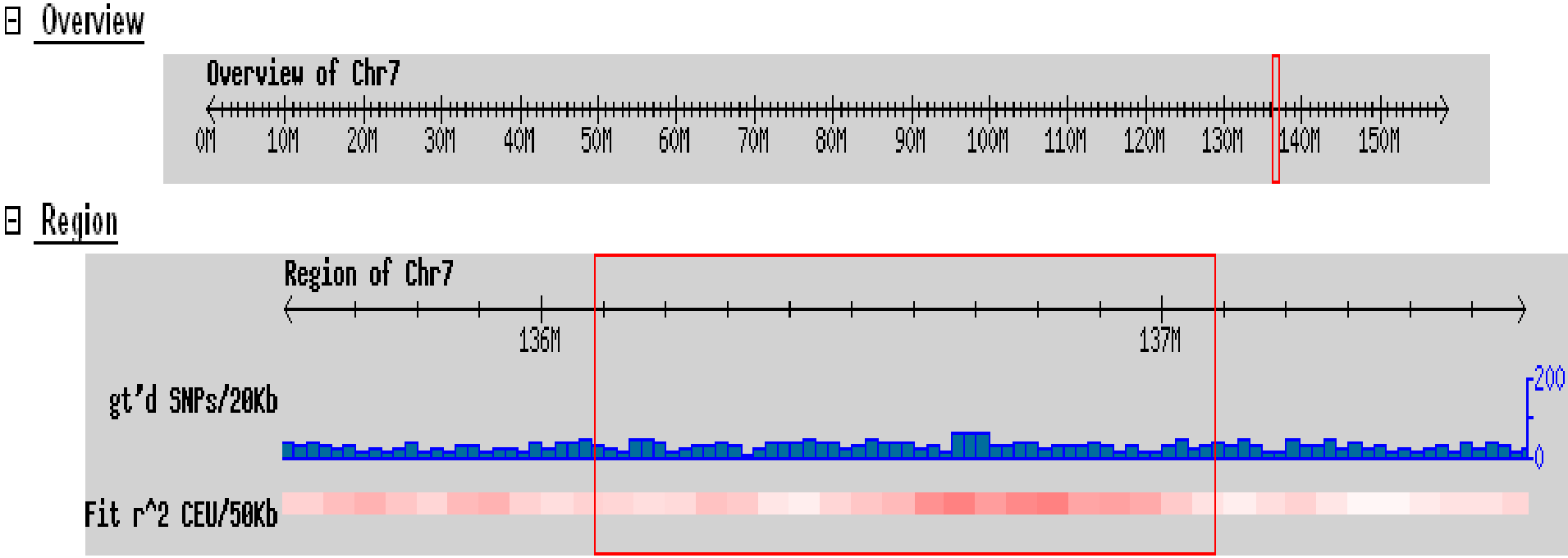
- G-protein coupled, causing decrease in cAMP in the cell, leading to inhibitory-type effects.

- CHRM2 receptors are found in cardiac tissue and cause a slowing of sinoatrial depolarization and a decrease in conduction velocity;

- CHRM2 is associated with alcohol and drug dependence, with depressive disorders and IQ;

CANDIDATE GENES ON CHROMOSOME 7q

Cholinergic receptor, muscarinic 2



Association with alcohol and illicit drug dependence

SAMPLE

DNA and diagnostic interview data were available on 2,185 individuals from 508 nuclear families, which includes 658 founders (parents, with 250 families with both parents genotyped) and 1527 offspring (mean age 40 years), including sibling pairs.