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# Alcohol and nicotine use and dependence: Common genetic and other risk factors

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# *Alcohol and Nicotine Use and Dependence:*

# *Shared Genetic and Other Risk Factors*

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# Guze Symposium
# Presenter's Disclosure of Interest

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**Stock Equity (> 10,000)**

- None

**Speaker's Bureau (s)**

- None

**Consulting Relationships**

- None

# Why a Symposium on Smoking and Alcoholism?

**Very high rates of smoking among alcoholics (as high as 90%).**

- **Many alcoholics who quit drinking but not smoking will be killed by their smoking.**
- **Understanding the biology that underlies the association between smoking and alcoholism may give us important insights into the etiology of tobacco addiction.**
- **Improved therapies to help ALL smokers quit.**

# PERSISTENT LONG-TERM SMOKING # 1 PUBLIC HEALTH CHALLENGE

## US Deaths Attributed to Smoking

**Ages 35-69 years**

| | WOMEN | MEN |
|---|---|---|
| All Deaths | 27.1% | 29.5% |
| Cancer Related Deaths | 26.5% | 44.4% |

(Peto et al., 2003)

Cited in: Tobacco Control Country Profiles, second Edition, 2003 (Eds Shafey et al.)

# WHY IS RESEARCH ON CIGARETTE SMOKING IMPORTANT?

**Average mortality cost of long-term persistent smoking ***

| | |
|---|---|
| **Smoking throughout life:** | **10 years of life lost** |
| **Stopped by age 60:** | **7 years of life lost** |
| **Stopped by age 50:** | **4 years of life lost** |
| **Stopped by age 40:** | **1 year of life lost** |

*** Doll. R, et al. (2004) BMJ 328:1519**

**RISK OF ALCOHOLISM IS STRONGLY ASSOCIATED WITH REGULAR CIGARETTE SMOKING AND ESPECIALLY NICOTINE DEPENDENCE. WHY??**

**Those with a lifetime history of regular smoking, especially nicotine dependence, are more likely to report a history of alcohol dependence:**

***AUSTRALIAN WOMEN (N = 3424)***

***A 10-Fold Increase is Risk!***

| | % Alcohol Dependent |
|---|---|
| Never smoked | 3 |
| Experimented only | 10 |
| Non-dependent smoker | 12 |
| Nicotine dependent smoker | 31 |

**NOTE. $p < 0.001$**

## …this is also true in men.

## *AUSTRALIAN MEN (N = 2766)*

## *A 5-Fold Increase in Risk!*

| | % Alcohol Dependent |
|---|---|
| Never smoked | 10 |
| Experimented only | 22 |
| Non-dependent smoker | 30 |
| Nicotine dependent smoker | 47 |

**NOTE**. $p < 0.001$

**More Severe Alcoholics are Especially Likely to be . . .**

**1) Regular Smokers**

**2) If They're Regular Smokers –**

**Nicotine Dependent**

# Those with a larger number of symptoms of alcohol dependence are much more likely to report a history of regular smoking

**AUSTRALIAN WOMEN (N=3424)**

| Number of Alcohol Symptoms | % Regular Smokers |
|---|---|
| 0 | 31 |
| 1 | 49 |
| 2 | 59 |
| 3 | 65 |
| 4 | 75 |
| 5 | 83 |
| 6 | 85 |
| 7 | 82 |

$p < 0.001$

# … and the same is true in men

## AUSTRALIAN MEN (N=2766)

| Number of Alcohol Symptoms | % Regular Smokers |
|---|---|
| 0 | 27 |
| 1 | 45 |
| 2 | 58 |
| 3 | 62 |
| 4 | 70 |
| 5 | 76 |
| 6 | 82 |
| 7 | 82 |

$p < 0.001$

# Probability of progression to nicotine dependence by regular smokers increases as a function of number of alcohol dependence symptoms

*AUSTRALIAN WOMEN (N = 1678)*

| Number of Alcohol Symptoms | % Nicotine Dependent |
|---|---|
| 0 | 50 |
| 1 | 52 |
| 2 | 57 |
| 3 | 73 |
| 4 | 81 |
| 5 | 82 |
| 6 | 90 |
| 7 | 93 |

NOTE. $p < 0.001$

# Probability of progression to nicotine dependence by regular smokers increases as a function of number of alcohol dependence symptoms

*AUSTRALIAN MEN (N = 1478)*

| Number of Alcohol Symptoms | % Nicotine Dependent |
|---|---|
| 0 | 51 |
| 1 | 51 |
| 2 | 58 |
| 3 | 64 |
| 4 | 70 |
| 5 | 83 |
| 6 | 79 |
| 7 | 82 |

NOTE. $p < 0.001$

**Adolescents who are nicotine dependent smokers are at especially high risk of alcohol problems regardless of whether or not they have a family history of alcoholism.**

# Interaction of adolescent smoking status and family history of alcoholism (FH+ or FH-) predicts adolescent alcohol problems

| | *Problem Drinking* | |
|---|---|---|
| | Odds Ratio | 95% CI |
| Never smoked, FH- | 1.00 | -- |
| Never smoked, FH+ | 2.58 | 1.20-5.53 |
| Occasional smoker, FH- | 7.29 | 4.26-12.48 |
| Occasional smoker, FH+ | 7.58 | 4.09-14.03 |
| Regular non-dependent smoker, FH- | 10.17 | 5.58-18.53 |
| Regular non-dependent smoker, FH+ | 32.93 | 17.36-62.45 |
| Regular dependent smoker, FH- | 37.21 | 20.22-68.46 |
| Regular dependent smoker, FH+ | 35.99 | 18.81-68.89 |

NOTE. ALCOHOL PROBLEMS: DSM-IV alcohol abuse or 2 or more symptoms of alcohol dependence.

1) **Is there a causal connection? Does smoking <u>increase</u> risk of developing alcohol dependence?**

***OR***

2) **Are there shared risk-factors, and is the association between smoking and alcohol dependence indirect?**

# AUSTRALIAN TWIN PANEL: YOUNG ADULT COHORT

**(6250 young adult twins born 1964-71, aged 24-35 when interviewed)**

***Heavy drinking cohort!***

**<1% of women lifetime abstainers**
**<1% of men lifetime abstainers**

**70% of women have had 7 or more drinks in a day**
**90% of men have had 9 or more drinks in a day**

**Psychiatric & sociodemographic risk factors are similar for nicotine vs. alcohol dependence.**

# Comparison Groups

1. Nicotine Dependent AND Alcohol Dependent
2. Alcohol Dependent Only
3. Nicotine Dependent Only
4. Regular smoker,
   neither alcohol nor nicotine dependent
5. Never smoked regularly,
   not alcohol dependence

# Associations with lifetime history of Major Depression

| | OR | 95% CI |
|---|---|---|
| Alcohol & Nicotine Dependence | 2.97 | 2.44-3.61 |
| Alcohol Dependence ONLY | 2.16 | 1.83-2.55 |
| Nicotine Dependence ONLY | 1.63 | 1.32-2.00 |
| Never smoked, or regular non-Nicotine Dependent | 1.00 | -- |

# Associations with history of childhood Conduct Disorder

| | WOMEN | |
|---|---|---|
| | OR | 95% CI |
| Alcohol & Nicotine Dependence | 10.72 | 6.82-16.86 |
| Alcohol Dependence only | 2.92 | 1.57-5.44 |
| Nicotine Dependence Only | 4.46 | 2.91-6.84 |
| Non-dependent regular smoker | [4.46 | 2.91-6.84] |
| Never smoked | 1.00 | -- |

# Associations with history of childhood Conduct Disorder

| | WOMEN | | MEN | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Alcohol & Nicotine Dependence | 10.72 | 6.82-16.86 | 5.81 | 4.23-7.98 |
| Alcohol Dependence only | 2.92 | 1.57-5.44 | 3.00 | 2.14-4.21 |
| Nicotine Dependence Only | 4.46 | 2.91-6.84 | 3.07 | 2.29-4.12 |
| Non-dependent regular smoker | [4.46 | 2.91-6.84] | [3.07 | 2.29-4.12] |
| Never smoked | 1.00 | | 1.00 | |

# Associations with lifetime history of Panic disorder

| | WOMEN | |
|---|---|---|
| | OR | 95% CI |
| Alcohol & Nicotine Dependence | 1.89 | 1.12-3.21 |
| Alcohol Dependence only | [1.89 | 1.12-3.21] |
| Nicotine Dependence Only | 1.18 NS | 0.71-1.97 |
| Non-dependent regular smoker | [1.18 NS | 0.71-1.97] |
| Never smoked | 1.00 | -- |

# Associations with lifetime history of Panic disorder

| | WOMEN | | MEN | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Alcohol & Nicotine Dependence | 1.89 | 1.12-3.21 | 4.46 | 1.44-13.82 |
| Alcohol Dependence only | [1.89 | 1.12-3.21] | [4.46 | 1.44-13.82] |
| Nicotine Dependence Only | 1.18 NS | 0.71-1.97 | [4.46 | 1.44-13.82] |
| Non-dependent regular smoker | [1.18 NS | 0.71-1.97] | [4.46 | 1.44-13.82] |
| Never smoked | 1.00 | -- | 1.00 | -- |

**Thus there are certain important shared risk factors:**

**Depression**

**Anxiety**

**Anti-Social Traits**

**Are these sufficient to account for co-occurrence of smoking and alcoholism?**

# *What About Genetics?*

**It is well-known that genetic influences are important in alcoholism. How about smoking?**

# Genetic & Environmental Contributions to Nicotine Dependence Risk

| | UNADJUSTED | | ADJUSTED | |
|---|---|---|---|---|
| | % | 95% CI | % | 95% CI |
| Additive Genetic | 62 | 44-68 | 47 | 28-54 |
| Shared environmental | 0 | 0-14 | 0 | 0-15 |
| Non-shared environmental | 38 | 32-45 | 53 | 46-61 |

**NOTE. ADJUSTED:controlling for significant psychiatric & sociodemographic predictors of risk (but NOT alcoholism).**

# Genetic & Environmental Contributions to Alcohol Dependence Risk

| | UNADJUSTED | | ADJUSTED | |
|---|---|---|---|---|
| | % | 95% CI | % | 95% CI |
| Additive Genetic | 52 | 33-60 | 48 | 23-57 |
| Shared environmental | 0 | 0-15 | 0 | 0-19 |
| Non-shared environmental | 48 | 40-56 | 52 | 43-61 |

**NOTE.** ADJUSTED: **controlling for significant psychiatric & sociodemographic predictors (but NOT alcoholism).**

# What is the genetic correlation between Alcohol and Nicotine Dependence?

| | | |
|---|---|---|
| **Unadjusted** | **0.67** | (95% CI: 0.60-0.81) |
| **Adjusted** | **0.58** | (95% CI: 0.26-1.00) |

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***… Genetic effects on risk of nicotine dependence account for 45% (unadjusted) or 34% (adjusted) of the genetic variance in risk of alcohol dependence in this sample.***

# So …

**There is a substantial overlap of genetic risk for alcohol & nicotine dependence.**

**…and this is only partially explained by shared psychiatric & sociodemographic risk factors.**

**What accounts for the partial genetic correlation between alcohol & nicotine dependence?**

**At what stage(s) in the progression of smoking does the genetic correlation arise?**

# *HERITABILITY ESTIMATES FOR SMOKING INITIATION*

## (Retrospective Data: *Adult Samples*)

| | *WOMEN* | *MEN* |
|---|---|---|
| | %AG | %AG |
| **Sweden** *(Medlund et al., 1977)* | 44 | 51 |
| **Denmark** *(Raachou-Nieken, 1960)* | 79 | 84 |
| **Finland** *(Kaprio et al 1988)* | 37 | 50 |
| **Australia** *(1981 Survey: Heath et al., 1993)* | 77 | 28 |
| **Australia** *(1989 Survey: Madden et al., 1993)* | 60 | 80 |
| **U.S.A. WWII Veterans** (Carmelli, et al 1992) | -- | 59 |
| **U.S.A. Virginia** (Heath, et al, 1993) | 84 | 84 |
| **U.S.A. Vietnam-era Veterans** *(True et al., 1997)* | -- | 39 |

***NOTE:*** **%AG represents percent of phenotypic variance due to additive genetic effects; %SE due to shared environmental effects; and %NSE due to non-shared environmental effects.**

**We can use family history data to discern differences in degree of genetic risk in those who have <u>NOT</u> become alcoholic.**

**Especially powerful with twin data!**

# ALCOHOL COMPARISON GROUPS

1. Alcohol Dependent

2. Non-Alcohol Dependent, High Genetic Risk
   MZ cotwin is alcohol dependent

3. Non-Alcohol Dependent, Intermediate Genetic Risk
   DZ twin sister or brother is alcohol dependent

4. Non-Alcohol Dependent, Low Genetic Risk
   Cotwin also has NO history of alcohol dependence

# AMONG ALL PARTICIPANTS

## RISK OF BECOMING A REGULAR SMOKER AS A FUNCTION OF GENETIC RISK OF ALCOHOLISM

| | WOMEN | MEN |
|---|---|---|
| | % | % |
| Alcohol dependent | 73 | 70 |
| Non-alcohol dependent | | |
| - High genetic risk | 68 | 58 |
| - Intermediate genetic risk | 57 | 52 |
| - Low genetic risk | 41 | 42 |

# AMONG REGULAR SMOKERS

## RISK OF PROGRESSION TO NICOTINE DEPENDENCE AS A FUNCTION OF GENETIC RISK OF ALCOHOLISM

| | WOMEN | MEN |
|---|---|---|
| | % | % |
| Alcohol dependent | 80 | 72 |
| Non-alcohol dependent | | |
| - High genetic risk | 55 | 59 |
| - Intermediate genetic risk | 54 | 56 |
| - Low genetic risk | 52 | 55 |

# Interpretation?

1) Genetic correlation between nicotine dependence and alcohol dependence seems to be largely driven by genetic correlation between regular smoking and alcohol dependence.

2) Among regular smokers, the correlation between alcohol dependence and nicotine dependence is largely determined by non-shared environmental factors.

**The critical comparison for testing the assumption of a direct causal influence is of MZ pairs discordant for both alcohol dependence and smoking status.**

**If there is a causal link, the twin who has smoked regularly should also be more likely to have a history of alcohol dependence (But there may be non-causal explanations!).**

**In MZ twins discordant for nicotine dependence, where only ONE twin had become alcohol dependent:**

**58 Cases:** **Nicotine Dependent Twin was Alcohol Dependent**

**21 Cases:** **Non-nicotine Dependent Twin was Alcohol Dependent**

**HIGHLY SIGNIFICANT: Odds Ratio 2.70**

**$p < .001$**

**In contrast, in MZ pairs discordant for regular cigarette smoking, where only ONE twin had become alcohol dependent:**

**27 Cases:** **Regularly Smoking Twin was Alcohol Dependent**

**19 Cases:** **Non-Regularly Smoking Twin was Alcohol Dependent**

**Odds Ratio 1.42, $p < .001$**

# Which comes first: Alcohol or Nicotine Dependence?

**(based on retrospective reports)**

| | WOMEN (%) | MEN (%) |
|---|---|---|
| Nicotine Dependence | 39 | 43 |
| Both same year | 22 | 16 |
| Alcohol Dependence | 39 | 41 |

# Which comes first: Regular smoking versus Nicotine Dependence?

| | WOMEN (%) | MEN (%) |
|---|---|---|
| **Regular smoking** | **91** | **90** |
| **Both same year** | **6** | **4** |
| **Alcohol Dependence** | **3** | **6** |

# Update

**Individuals at high genetic risk of alcohol dependence are on average also at increased genetic risk of becoming regular smokers, an outcome that usually precedes the onset of alcohol dependence.**

**Among regular smokers, there may be a unidirectional or reciprocal causal relationship between nicotine and alcohol dependence**

- **in discordant MZ pairs, who are genetically identical, the nicotine dependent twin is significantly more likely to also be alcohol dependent.**

**Gene-mapping studies aim to identify genes that contribute to risk of alcoholism on nicotine dependence.**

**We are using a genetic linkage approach – studying the co-inheritance of dependence phenotypes and genetic markers to try to identify chromosomal regions containing risk-increasing genes.**

***Are the same regions identified for smoking and for alcoholism?***

# NICOTINE ADDICTION GENETICS PROJECT (NAG)

**Large-scale linkage study to identify specific chromosomal locations that may contain genes that influence heavy smoking and/or nicotine dependence.**

**Heavy smoking index cases and their siblings were ascertained through two twin panels:**

**(i) Finnish Twin Panel**
**(Senior Co-Investigators Kaprio & Peltonen)**

**(ii) Australian Twin Panel**
**(Senior Co-Investigator Martin)**

# AUSTRALIAN TARGET SAMPLE:

**Information about smoking history and heaviness of smoking on individuals from >11,000 families was used to identify most informative sibships.**

# FINNISH TARGET SAMPLE:

**SOURCE: Older Finnish Twin Cohort**
**(65% born 1931-1950),**
**with few surviving parents.**

# NICOTINE ADDICTION GENETICS PROJECT (NAG)

| | Dx Telephone Interview | Blood/Buccal Samples |
|---|---|---|
| AUSTRALIA | 3453 (52% Women) | 3056 (54% Women) |
| FINLAND | 2043 (46% Women) | 2022 (46% Women) |

# NICOTINE ADDICTION GENETICS PROJECT (NAG)

**Genome Scans Completed:**

**289 Australian families**

**(another 100 families still to be scanned)**

**159 Finnish families**

**Note: ABI Prism Linkage Mapping Set**
**(400 markers, average distance of 10 cM)**

# PHENOTYPE DEFINITION FOR NICOTINE DEPENDENCE

**GUIDED BY QUANTITATIVE GENETIC ANALYSES OF DATA FROM A SAMPLE OF TWIN PAIRS FROM THE AUSTRALIAN TWIN PANEL.**

**(N=977 MZ, 1316 DZ pairs)**

# Genetic Factor Loadings of DSM-IV and the Heaviness of Smoking Dependence Symptoms

| | AUSTRALIAN WOMEN | |
|---|---|---|
| | Additive Genetic Factor #1 | Additive Genetic Factor #2 |
| Time to first cigarette | .78 | .03 |
| Cigarettes smoked per day | .86 | -.08 |
| | | |
| Tolerance | .88 | -.09 |
| Withdrawal | .67 | -.15 |
| More than intended | .83 | -.08 |
| Difficulty quitting | .76 | -.31 |
| Ever chain smoked | .70 | .05 |
| Gave up activities | .57 | -.49 |
| Smoke despite problems | .71 | .00 |

*(Lessov, et al. Psychological Medicine, 34:865-879, 2004)*

# PHENOTYPE DEFINITION for HEAVINESS OF SMOKING

**"Maximum cigarettes smoked in a 24-hour period"**

- **Tolerance measure that has a high factor loading in our phenotypic factor analysis, and a high genetic factor loading.**

- **Avoids problem with typical quantity measure. Prohibitions against smoking (e.g., in workplace) have reduced the utility of average quantity measures.**

# Genetic Correlation
# MaxCigs and ND Factor Score

| | $r_g$ | 95% CI |
|---|---|---|
| WOMEN | 0.84 | 0.78-0.89 |
| MEN | 0.88 | 0.84-0.92 |

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**MaxCigs:** Maximum cigarettes smoked in a 24-hour period

**ND Factor Score:** Nicotine dependence factor score derived from DSM-IV and HSI items

# QUANTITATIVE PHENOTYPE: DEPENDENCE FACTOR SCORE:

**Australian + Finnish Families Combined**
**Multipoint Results**

| Chromosome | Position (cM) | Nearest Marker | Lod Score |
|---|---|---|---|
| 2 | 78.7 | D2S337 | 2.26 |
| 13 | 81.0 | D13S265 | 1.84 |
| 22 | 57.1 | D22S274 | 3.23 |

**NOTE: Quantitative trait analyses using MERLIN-REGRESS**

# QUANTITATIVE PHENOTYPE: Fagerstrom Nicotine Dependence (FTND)

**Australian + Finnish Families Combined**
**Multipoint Results**

| Chromosome | Position (cM) | Nearest Marker | Lod Score |
|---|---|---|---|
| 2 | 78.7 | D2S337 | 2.30 |
| 22 | 57.1 | D22S274 | 3.69 |

# QUANTITATIVE PHENOTYPE:

## DSM-IV Nicotine Dependence Symptom Count

**Australian + Finnish Families Combined**
**Multipoint Results**

| Chromosome | Position (cM) | Nearest Marker | Lod Score |
|---|---|---|---|
| 2 | 86.8 | D2S337 | 2.16 |

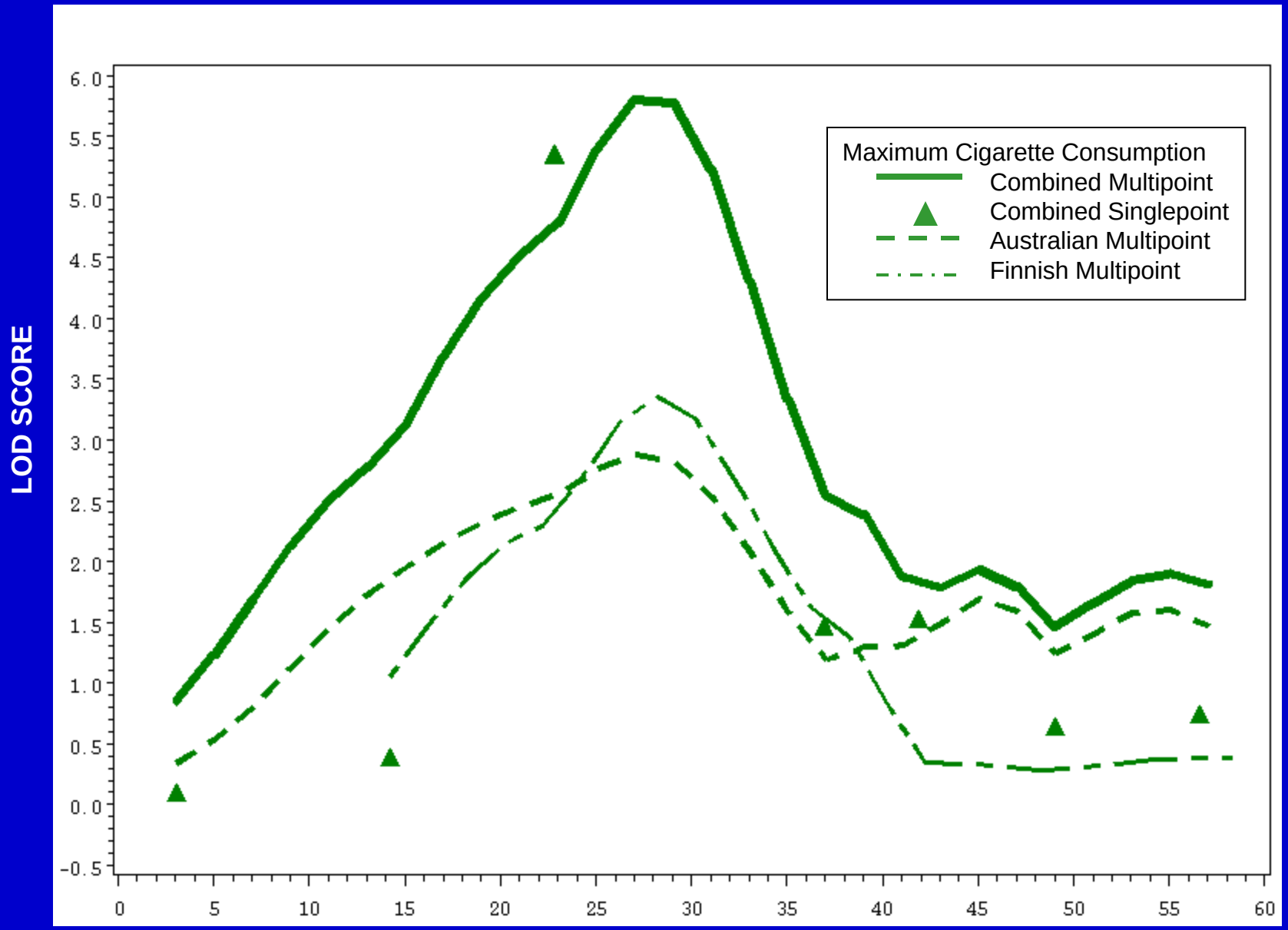
**CHROMOSOME 2 SUGGESTIVE LINKAGE FOR FACTOR SCORE, FTND ARE IN THE SAME APPROXIMATE LOCATION WHERE A MAJOR US ALCOHOLISM GENE-MAPPING STUDY ("COGA") HAS POSITIVE FINDINGS FOR "HABITUAL SMOKING AND ALCOHOLISM" PHENOTYPE, OTHER MEASURES THAT MAY BE CHARACTERIZED AS "IMPULSIVE /BEHAVIORAL UNDERCONTROL".**

# QUANTITATIVE PHENOTYPE: Maximum Cigarettes Smoked in a 24-Hour Period

**Australian + Finnish families combined**

| Chromosome | Position (cM) | Lod Score |
|---|---|---|
| 20 | 72.6 | 3.04 |
| 22 | 27.1 | 5.64 |

# CHROMOSOME 22
# Maximum Cigarettes in a 24-hr period

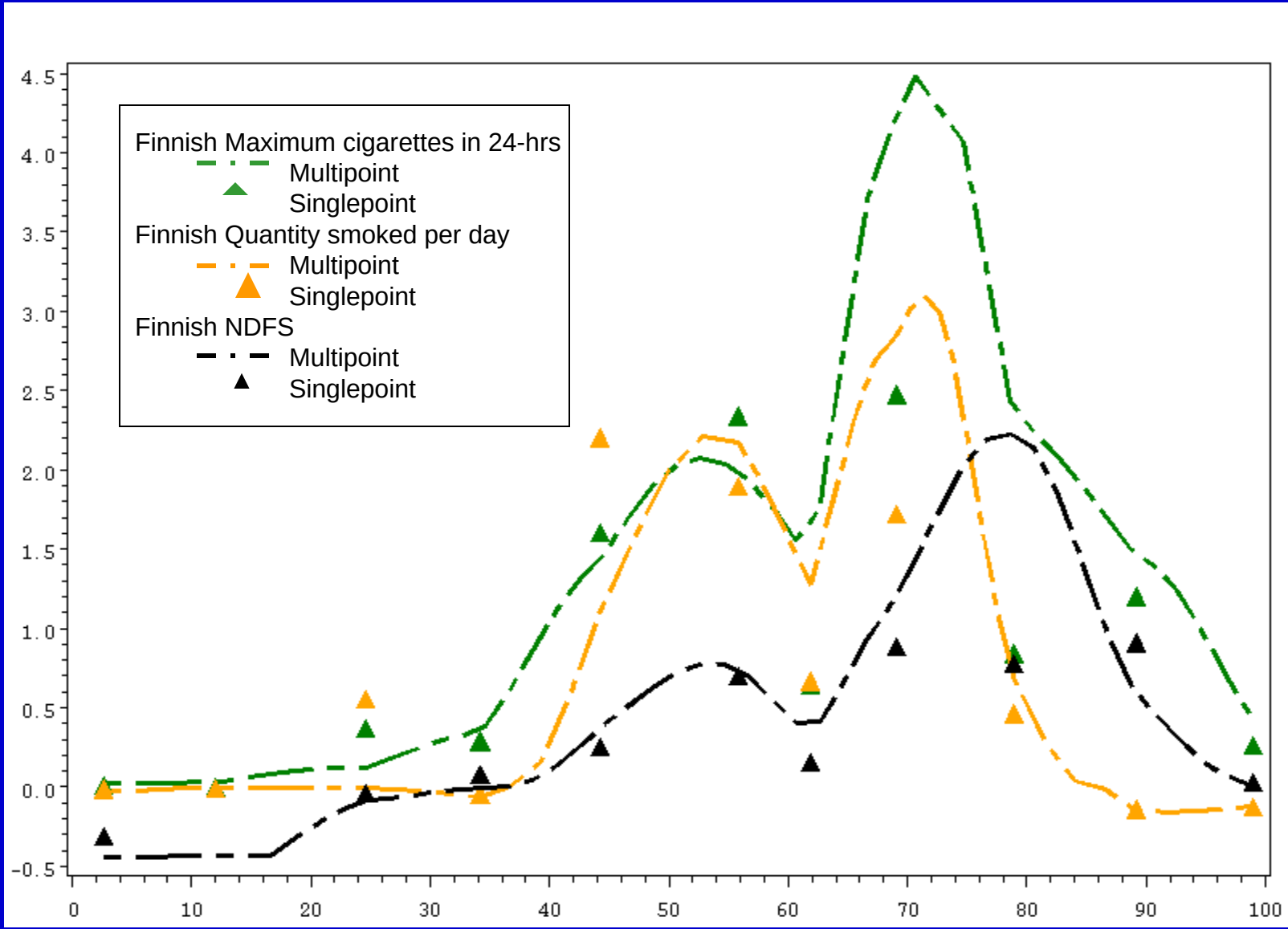



cM Position (based on 2cM grid)

**FOR THE FINNISH FAMILIES ONLY, WE ALSO FIND SUGGESTIVE EVIDENCE FOR LINKAGE ON CHROMOSOME 20, IN THE REGION OF THE ALPHA 4 NEURONAL NICOTINIC RECEPTOR (CHRNA4) GENE.**

**EVIDENCE IS STRONGEST FOR HEAVINESS OF SMOKING MEASURES.**

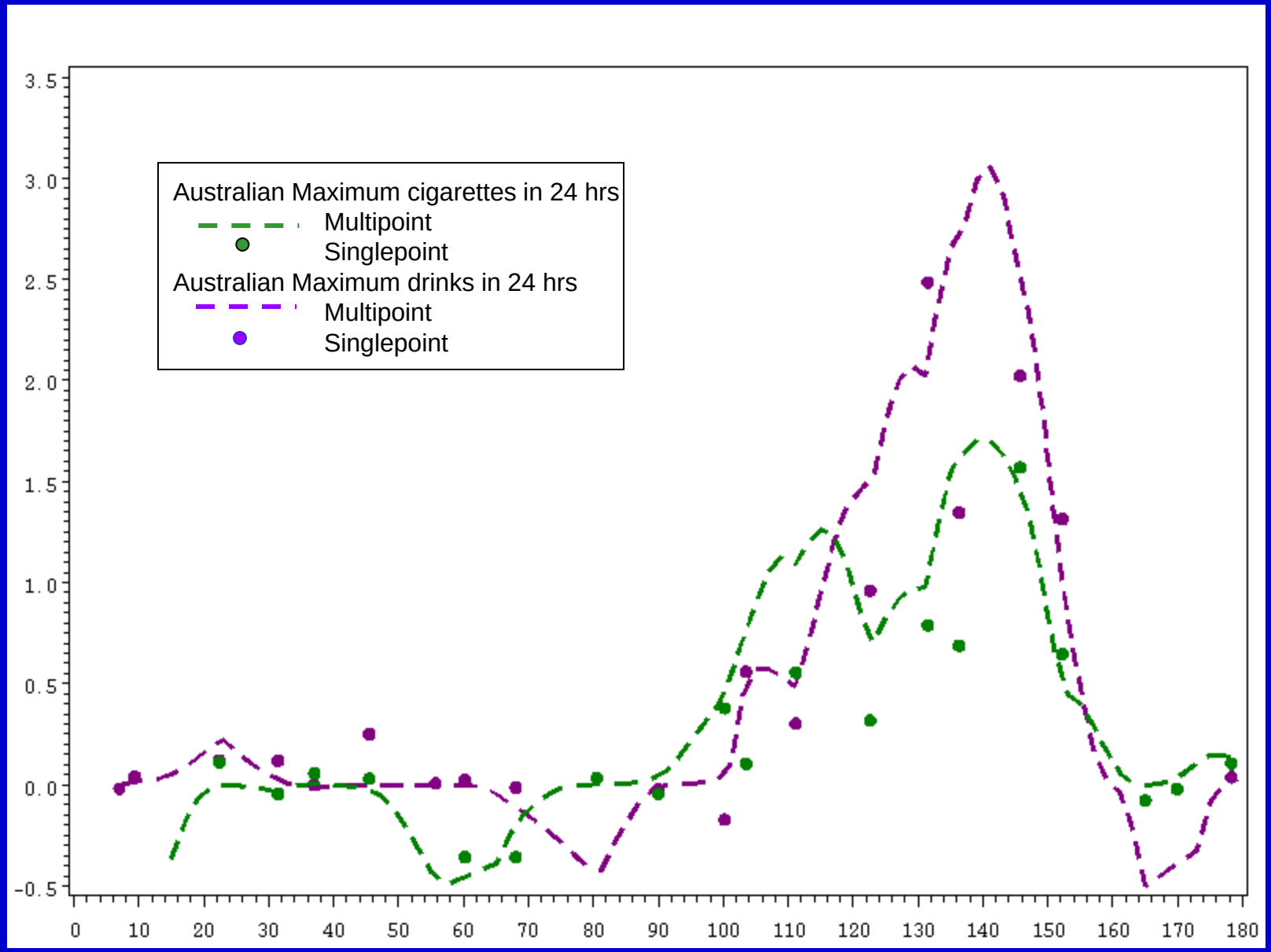
# CHROMOSOME 20
# Nicotine Dependence Factor Score (NDFS), Quantity smoked per day & Maximum Cigarettes in 24-hours



**For a Heaviness-of-Drinking measure (Maximum Drinks in 24-Hours) we find a chromosome 7 linkage signal in the same region the COGA finds linkage for the same phenotype.**

**But, also a “BLIP” for a Heaviness-of-Smoking phenotype.**

# CHROMOSOME 7
## Maximum Cigarettes & Maximum Drinks in a 24 hour period



# SUMMARY

1) One of our probable linkage peaks on chromosome 2 coincides with a linkage peak for co-morbid alcoholism and habitual smoking (Bierut et al., 2004).

2) Our highest linkage peak is on chromosome 22 (LOD=5.64) for the MaxCigs. We know of no alcoholism linkage in this region.

3) We also obtain a multipoint LOD of 3.69 for a second smoking phenotype (FTND), at a different location. A region where an alcoholism signal has been reported.

# SUMMARY cont'd

4) In our Finnish subsample only, we observe a linkage peak for measures of quantity smoked, and for our nicotine dependence factor score, near the location of the alpha-4 neuronal nicotinic receptor gene, on chromosome 20.

5) One of our probable linkage peaks on chromosome 7 for maximum number of drinks in a 24-hour period is in the same location as a smaller peak for maxcigs.

# CONCLUSION

**We are far from having a complete answer about why alcoholics are especially likely to be nicotine dependent smokers.**

**But, overlap of genetic risk-factors does appear to be a contributing factor.**

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