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2006

## 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*

*Pamela Madden, Ph.D.*

*Washington University School of Medicine*

# Guze Symposium

## Presenter's Disclosure of Interest

**Name & Presentation Date:** *Overview: Alcohol and Nicotine Use and Dependence: Common Genetic and Other Risk Factors*; March 2, 2006

### Sources of Research Support

DA12854 (to PAFM)

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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**

	<b>WOMEN</b>	<b>MEN</b>
<b>All Deaths</b>	<b>27.1%</b>	<b>29.5%</b>
<b>Cancer Related Deaths</b>	<b>26.5%</b>	<b>44.4%</b>

(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!***

	<b><u>% Alcohol Dependent</u></b>
<b>Never smoked</b>	<b>3</b>
<b>Experimented only</b>	<b>10</b>
<b>Non-dependent smoker</b>	<b>12</b>
<b>Nicotine dependent smoker</b>	<b>31</b>

**NOTE. p < 0.001**



**...this is also true in men.**

***AUSTRALIAN MEN (N = 2766)***

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

	<b><u>% Alcohol Dependent</u></b>
<b>Never smoked</b>	<b>10</b>
<b>Experimented only</b>	<b>22</b>
<b>Non-dependent smoker</b>	<b>30</b>
<b>Nicotine dependent smoker</b>	<b>47</b>

**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)**

<b>Number of Alcohol Symptoms</b>	<b>% Regular Smokers</b>
<b>0</b>	<b>31</b>
<b>1</b>	<b>49</b>
<b>2</b>	<b>59</b>
<b>3</b>	<b>65</b>
<b>4</b>	<b>75</b>
<b>5</b>	<b>83</b>
<b>6</b>	<b>85</b>
<b>7</b>	<b>82</b>

---

**p < 0.001**

**... and the same is true in men**

**AUSTRALIAN MEN (N=2766)**

<b>Number of Alcohol Symptoms</b>	<b>% Regular Smokers</b>
<b>0</b>	<b>27</b>
<b>1</b>	<b>45</b>
<b>2</b>	<b>58</b>
<b>3</b>	<b>62</b>
<b>4</b>	<b>70</b>
<b>5</b>	<b>76</b>
<b>6</b>	<b>82</b>
<b>7</b>	<b>82</b>

---

**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)*

<b>Number of Alcohol Symptoms</b>	<b>% Nicotine Dependent</b>
<b>0</b>	<b>50</b>
<b>1</b>	<b>52</b>
<b>2</b>	<b>57</b>
<b>3</b>	<b>73</b>
<b>4</b>	<b>81</b>
<b>5</b>	<b>82</b>
<b>6</b>	<b>90</b>
<b>7</b>	<b>93</b>

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**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)*

<b>Number of Alcohol Symptoms</b>	<b>% Nicotine Dependent</b>
0	51
1	51
2	58
3	64
4	70
5	83
6	79
7	82

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**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**

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

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



**1) Is there a causal connection? Does smoking increase 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

	<u>OR</u>	<u>95% CI</u>
<b>Alcohol &amp; Nicotine Dependence</b>	<b>2.97</b>	<b>2.44-3.61</b>
<b>Alcohol Dependence ONLY</b>	<b>2.16</b>	<b>1.83-2.55</b>
<b>Nicotine Dependence ONLY</b>	<b>1.63</b>	<b>1.32-2.00</b>
<b>Never smoked, or regular non-Nicotine Dependent</b>	<b>1.00</b>	<b>--</b>

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# Associations with history of childhood Conduct Disorder

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

---

# Associations with history of childhood Conduct Disorder

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

# Associations with lifetime history of Panic disorder

## WOMEN

	OR	95% CI
<b>Alcohol &amp; Nicotine Dependence</b>	<b>1.89</b>	<b>1.12-3.21</b>
<b>Alcohol Dependence only</b>	<b>[1.89</b>	<b>1.12-3.21]</b>
<b>Nicotine Dependence Only</b>	<b>1.18<sup>NS</sup></b>	<b>0.71-1.97</b>
<b>Non-dependent regular smoker</b>	<b>[1.18<sup>NS</sup></b>	<b>0.71-1.97]</b>
<b>Never smoked</b>	<b>1.00</b>	<b>--</b>

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# Associations with lifetime history of Panic disorder

	WOMEN		MEN	
	OR	95% CI	OR	95% CI
<b>Alcohol &amp; Nicotine Dependence</b>	1.89	1.12-3.21	4.46	1.44-13.82
<b>Alcohol Dependence only</b>	[1.89	1.12-3.21]	[4.46	1.44-13.82]
<b>Nicotine Dependence Only</b>	1.18 <sup>NS</sup>	0.71-1.97	[4.46	1.44-13.82]
<b>Non-dependent regular smoker</b>	[1.18 <sup>NS</sup>	0.71-1.97]	[4.46	1.44-13.82]
<b>Never smoked</b>	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

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

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

# Genetic & Environmental Contributions to Alcohol Dependence Risk

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

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

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

<b>Unadjusted</b>	<b>0.67</b>	(95% CI: 0.60-0.81)
<b>Adjusted</b>	<b>0.58</b>	(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*)

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

**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 NOT 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

	<u>WOMEN</u>	<u>MEN</u>
	%	%
<b>Alcohol dependent</b>	<b>73</b>	<b>70</b>
<b>Non-alcohol dependent</b>		
- High genetic risk	68	58
- Intermediate genetic risk	57	52
- Low genetic risk	41	42

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# AMONG REGULAR SMOKERS

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

	<u>WOMEN</u>	<u>MEN</u>
	%	%
<b>Alcohol dependent</b>	<b>80</b>	<b>72</b>
<b>Non-alcohol dependent</b>		
- High genetic risk	55	59
- Intermediate genetic risk	54	56
- Low genetic risk	52	55

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# 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)

	<b>WOMEN</b>	<b>MEN</b>
	(%)	(%)
<b>Nicotine Dependence</b>	<b>39</b>	<b>43</b>
<b>Both same year</b>	<b>22</b>	<b>16</b>
<b>Alcohol Dependence</b>	<b>39</b>	<b>41</b>

---

# Which comes first: Regular smoking versus Nicotine Dependence?

	<b>WOMEN</b>	<b>MEN</b>
	(%)	(%)
<b>Regular smoking</b>	<b>91</b>	<b>90</b>
<b>Both same year</b>	<b>6</b>	<b>4</b>
<b>Alcohol Dependence</b>	<b>3</b>	<b>6</b>

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# 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

*(Lesso, 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”.**

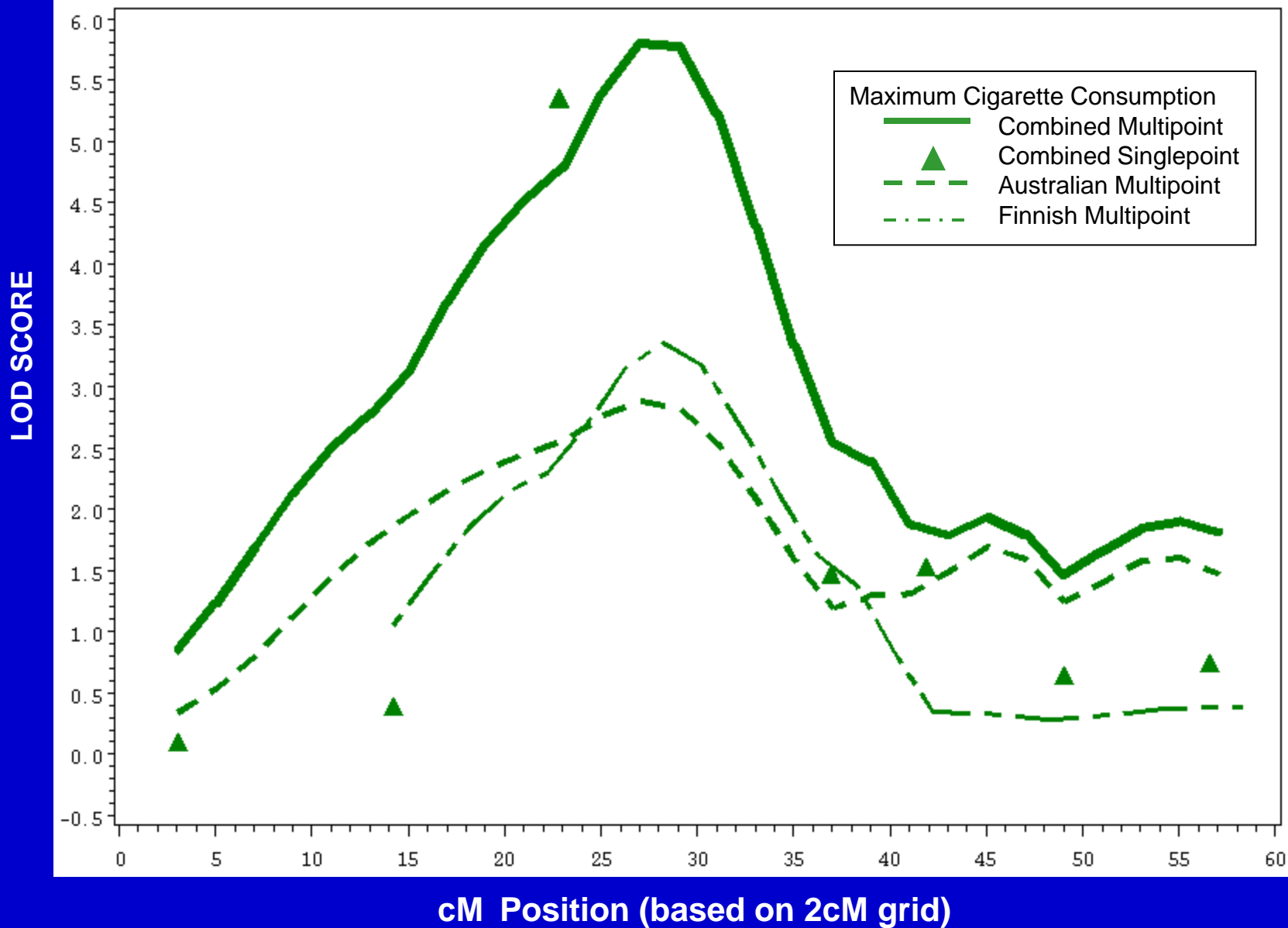
# **QUANTITATIVE PHENOTYPE: Maximum Cigarettes Smoked in a 24- Hour Period**

**Australian + Finnish families combined**

<b><u>Chromosome</u></b>	<b><u>Position (cM)</u></b>	<b><u>Lod Score</u></b>
<b>20</b>	<b>72.6</b>	<b>3.04</b>
<b>22</b>	<b>27.1</b>	<b>5.64</b>

# CHROMOSOME 22

## Maximum Cigarettes in a 24-hr period

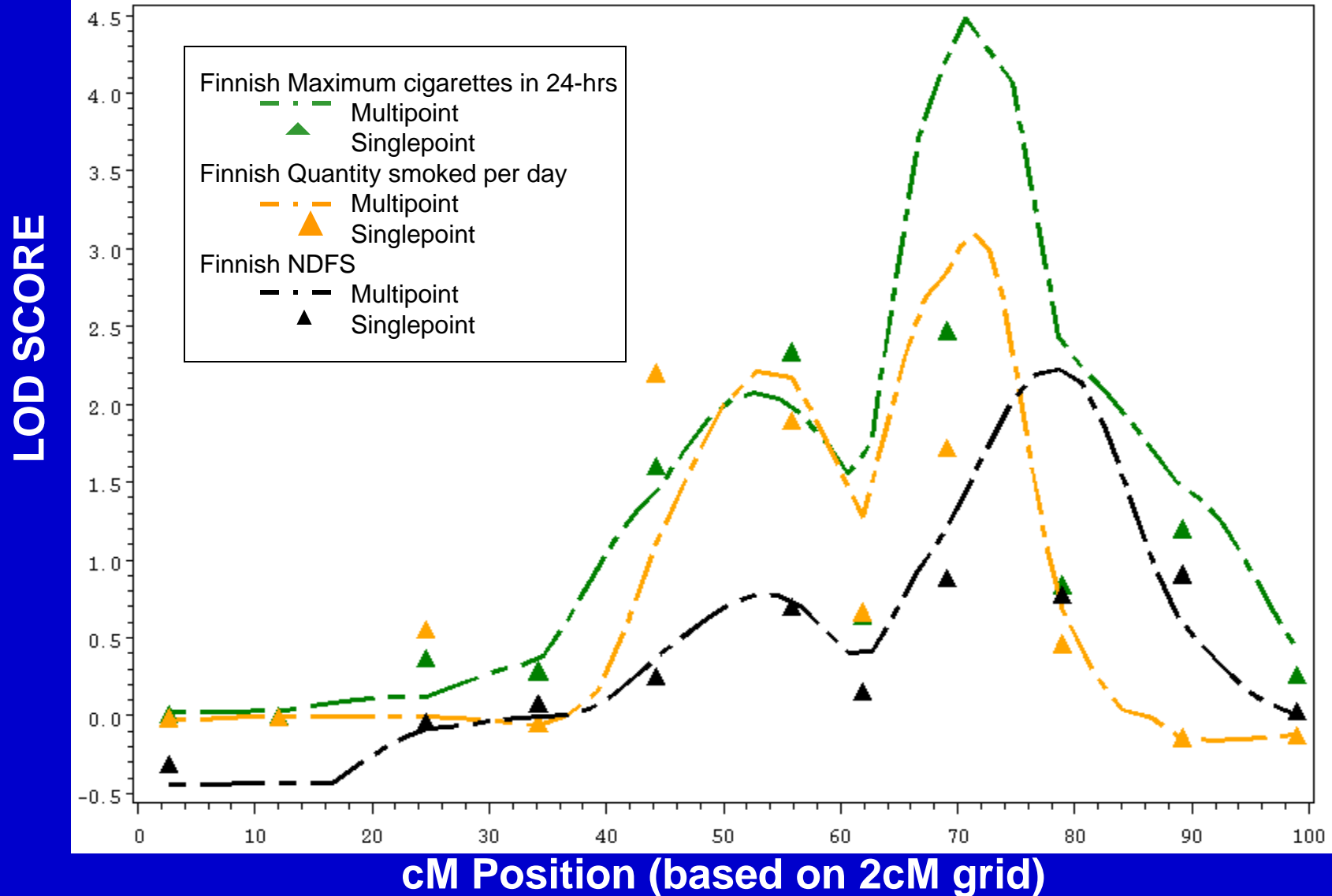


**FOR THE FINNISH FAMILIES ONLY, WE ALSO FIND SUGGESTIVE EVIDENCE FOR LINKAGE ON CHROMOSOME 20, IN THE REGION OF THE ALPHA 4 NEURONAL NICOTINIC RECEPTOR (CHRNA4) GENE.**

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

# CHROMOSOME 20

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

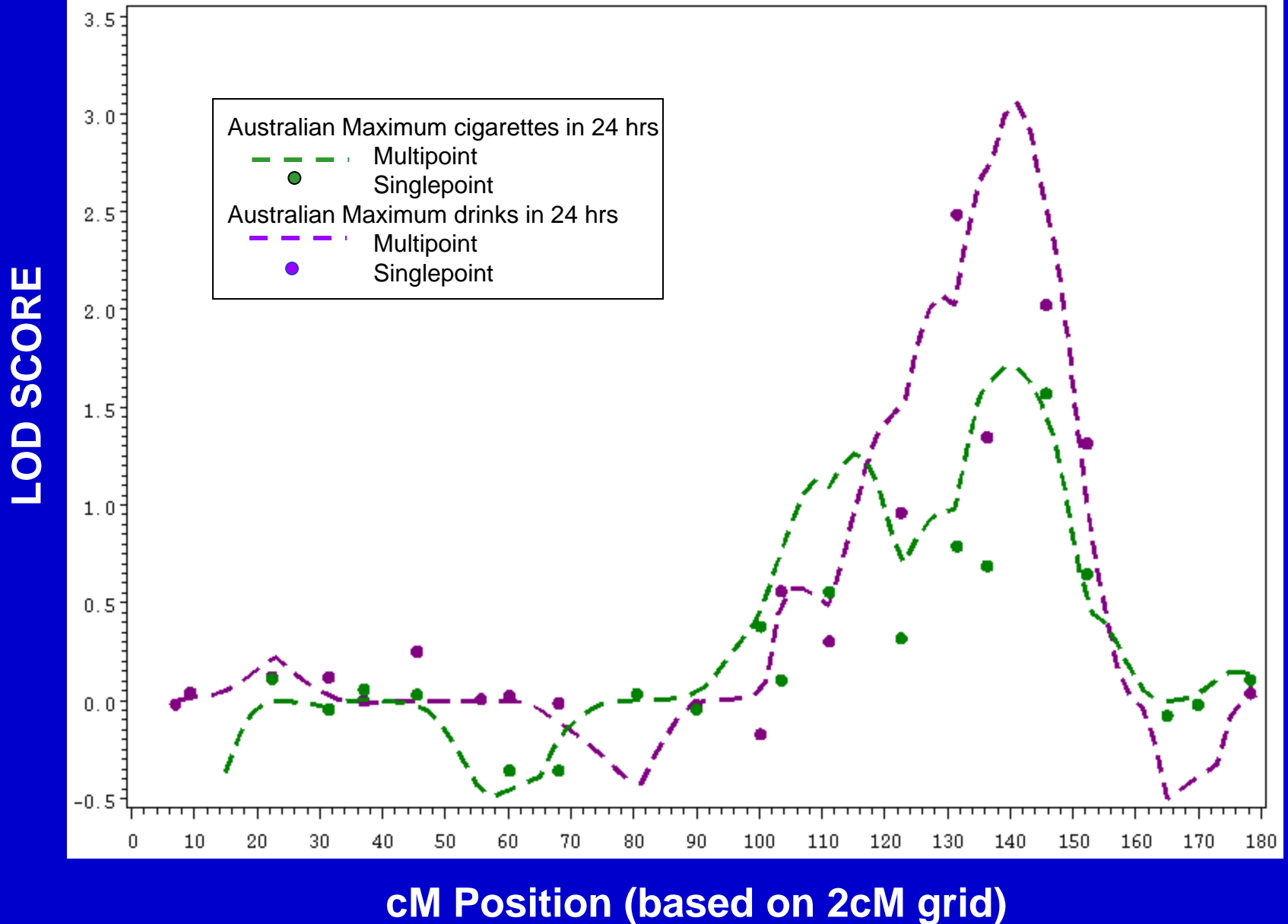


**For a Heaviness-of-Drinking measure (Maximum Drinks in 24-Hours) we find a chromosome 7 linkage signal in the same region the COGA finds linkage for the same phenotype.**

**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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