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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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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!

	<u>% Alcohol Dependent</u>
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!

	<u>% Alcohol Dependent</u>
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

	<i>Problem Drinking</i>	
	Odds	95%
	Ratio	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 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>
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

	<u>UNADJUSTED</u>		<u>ADJUSTED</u>	
	%	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

	<u>UNADJUSTED</u>		<u>ADJUSTED</u>	
	%	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)

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

	<u>WOMEN</u>	<u>MEN</u>
	%	%
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

(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

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”.

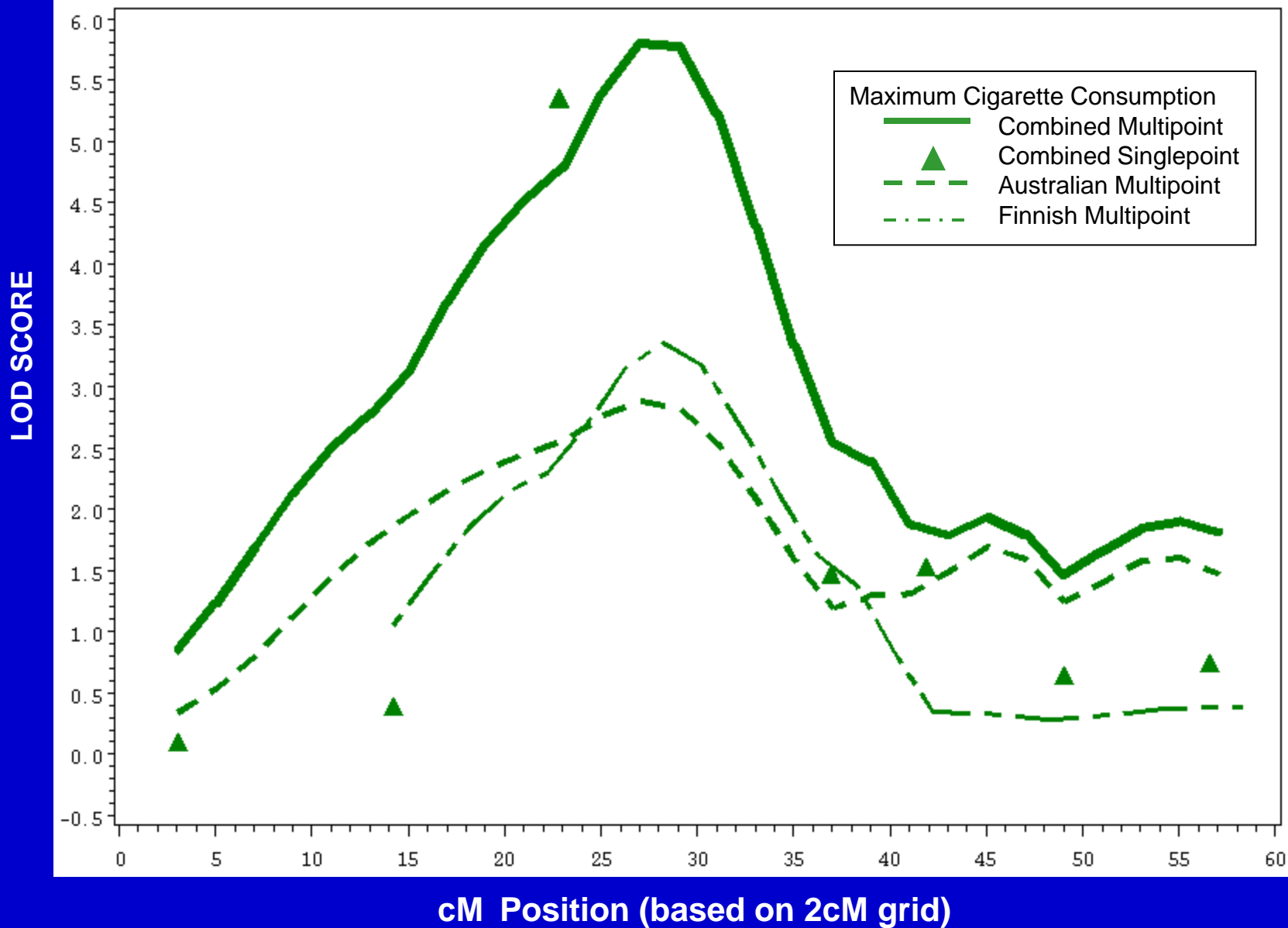
QUANTITATIVE PHENOTYPE: Maximum Cigarettes Smoked in a 24- Hour Period

Australian + Finnish families combined

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

CHROMOSOME 22

Maximum Cigarettes in a 24-hr period



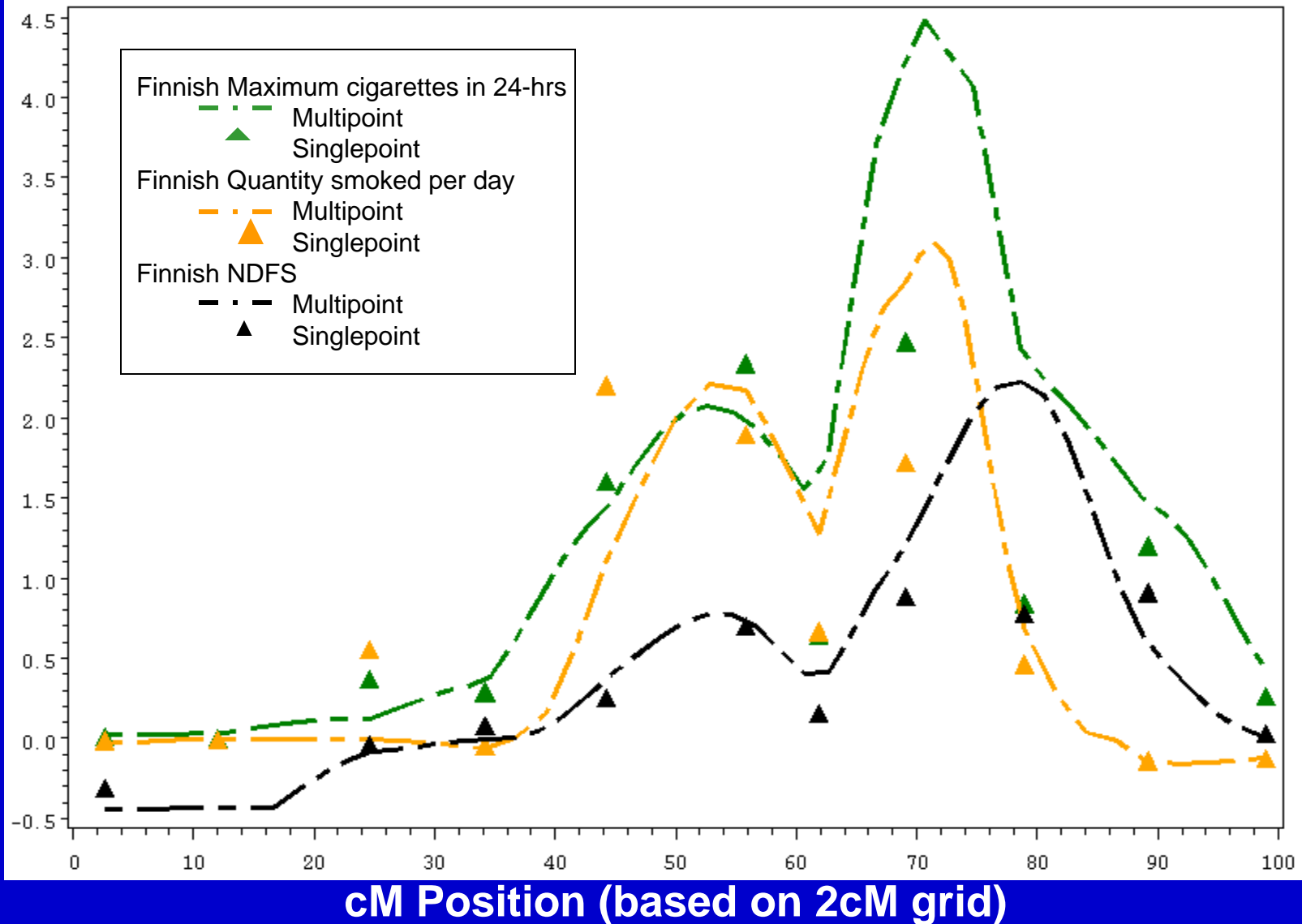
FOR THE FINNISH FAMILIES ONLY, WE ALSO FIND SUGGESTIVE EVIDENCE FOR LINKAGE ON CHROMOSOME 20, IN THE REGION OF THE ALPHA 4 NEURONAL NICOTINIC RECEPTOR (CHRNA4) GENE.

EVIDENCE IS STRONGEST FOR HEAVINESS OF SMOKING MEASURES.

CHROMOSOME 20

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

LOD SCORE

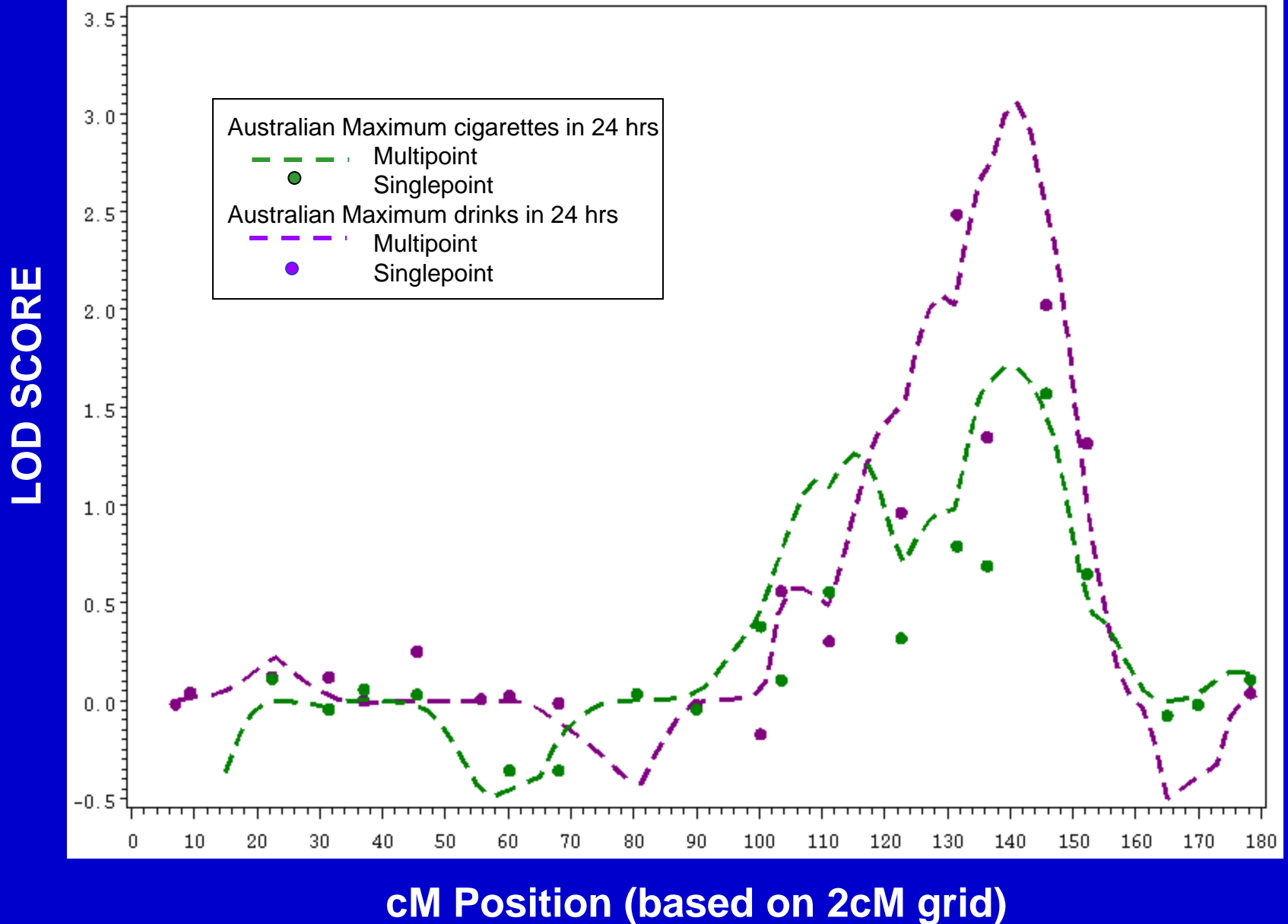


For a Heaviness-of-Drinking measure (Maximum Drinks in 24-Hours) we find a chromosome 7 linkage signal in the same region the COGA finds linkage for the same phenotype.

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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