

## The Genetic Bases for Vulnerability to Substance Abuse



George R Uhl MD PhD



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### Motivations for interest in genetics of addictions *(and whole genome association approaches)*

Importance for understanding addictions, which have such large roles in US deaths, costs and increasingly involve misuse of prescribed medications

Apparent successes of whole genome association approaches in elucidating polygenic variants for addictions

Potential usefulness *(and cautions)* re incorporating molecular genetics "pharmacogenetics" in research and in practice

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### Classical genetic approaches

Family studies  
Compare risks in eg sibs and other first- and second-degree relatives to risk in the general population

Adoption studies  
Compare risks in adoptees with risks in biological and adoptive parents

Twin studies  
Compare disease concordance in MZ vs DZ twin pairs



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Classical genetic studies support large genetic determinants for vulnerability to dependence on addictive substances

Family studies: Abuser's sibs have 5-8 fold greater risk than members of the general population  
 Adoption studies: Adoptees with abuser biological parents are more likely to become abusers  
 Twin studies: Greater MZ than DZ concordance supports genetic contributions:  
 alcoholism: 0.5-0.6  
 polysubstance abuse: 0.4-0.8  
 Stronger genetic contributions to dependence than to abuse

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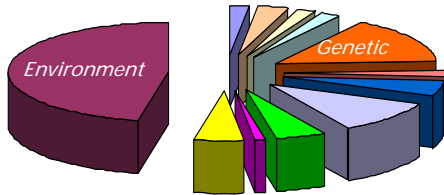
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Current data: nearly equal genetic and environmental contributions to vulnerability to dependence on addictive substances




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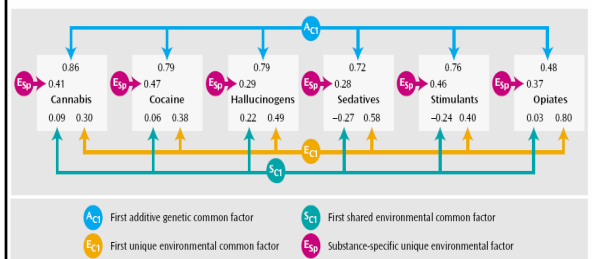
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Most genetic influence on vulnerability to drug abuse/dependence is common to most drug classes (eg Kendler et al, 2003)

FIGURE 2. Best-Fit Model for the Lifetime Abuse/Dependence of Six Illicit Substance Classes by Monozygotic and Dizygotic Twins (N=2,392 Individuals) From a Population-Based Registry\*



\*Latent variables—all of which have a variance of 1.0—are depicted in circles, and observed variables (types of substance abuse/dependence) are depicted in rectangles. The path coefficients represent standardized partial regression coefficients, so they must be squared to equal the amount of variance in the dependent (downstream) variable that is accounted for by the independent (upstream) variable.

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**Caveat I** Despite the substantial evidence for strong heritability for substance dependence, many features of the “genetic architecture” of addictions remain unknown: *esp* genetic heterogeneity, size of effects of individual genes

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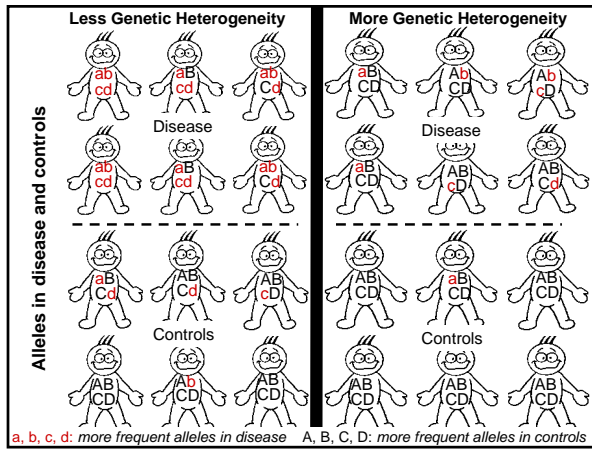
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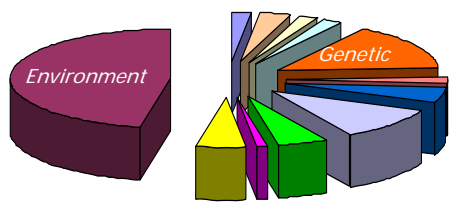
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**Caveat II:** pie graph depictions do not show gene gene ( $G \times G$ ) and gene environment ( $G \times E$ ) interaction terms




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**Close up: focus on nicotine**

Individual differences in vulnerability to DSM nicotine dependence are *ca.* 0.5 heritable (rest from nonshared environmental influences)



Individual differences in vulnerability to dependence using DSM and Fagerstrom criteria are both *ca.* 0.5 heritable (the genetics of these two approaches to defining nicotine dependence overlaps but is not identical)

Genetic bases for individual differences in smoking initiation are *ca.* 0.5 heritable (this genetics overlaps but is not identical to nicotine dependence genetics. The rest comes from both shared and nonshared environmental influences)

Individual differences in success at smoking cessation are *ca.* 0.5 heritable (no strong data for heritability of success at stopping other substances)

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**Large heritability for nicotine dependence: recent twin study data**

Dutch twin study (Vink et al, 2005)

Nicotine dependence : A 0.75 E 0.25

Virginia twin study (Maes et al, 2004)

Nicotine dependence: A 0.60 E 0.4

Minnesota twin study (adolescents: McGue et al, 2000)

Nicotine dependence A 0.44 C 0.37 E 0.19

Vietnam era twin study (NB: ~~not~~ nicotine dependence)

Scandinavian female twins supports roles for permissive vs non permissive




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Twin data indicates *ca.* 0.5 heritability for smoking cessation success (Broms et al, 2006, see also Vietnam Era and Australian twin study data)

|   | Additive genetic variance<br>95% CI | Shared environmental variance<br>95% CI | Unique environmental variance<br>95% CI |
|---|-------------------------------------|---|---|
| <b>Men</b>  |                                     |   |   |
| ACE model for both age at initiation and smoking cessation                      |                                     |   |   |
| Age at initiation   | .59 .43, .88                        | .19 .11, .25                            | .22 .19, .26                            |
| Smoking cessation   | .45 .21, .64                        | .10 .00, .26                            | .45 .36, .54                            |
| Genetic-environmental correlation   | .23 .16, .29                        | —                                       | -.09 -.13, -.04                         |
| ACE model for age at initiation and AE model for smoking cessation (best model) |                                     |   |   |
| Age at initiation   | .59 .43, .88                        | .19 .11, .28                            | .22 .19, .25                            |
| Smoking cessation   | .59 .50, .65                        | —                                       | .43 .35, .50                            |
| Genetic-environmental correlation   | .22 .16, .29                        | —                                       | -.08 -.12, -.04                         |
| <b>Women</b>  |                                     |   |   |
| ACE model for both age at initiation and smoking cessation                      |                                     |   |   |
| Age at initiation   | .34 .27, .42                        | .51 .45, .58                            | .15 .12, .17                            |
| Smoking cessation   | .50 .19, .80                        | .00 .00, .23                            | .50 .40, .60                            |
| Genetic-environmental correlation   | —                                   | -.00 -.10, .06                          | -.13 -.17, -.08                         |
| ACE model for age at initiation and AE model for smoking cessation (best model) |                                     |   |   |
| Age at initiation   | .34 .28, .42                        | .51 .45, .58                            | .15 .12, .17                            |
| Smoking cessation   | .50 .30, .80                        | —                                       | .50 .40, .61                            |
| Genetic-environmental correlation   | —                                   | —                                       | -.13 -.15, -.08                         |

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### Bases for whole genome association in addictions

*Classical genetics and working hypotheses re genetic architecture for addictions*

**Theoretical: association vs linkage**

Genomic: variants

Technical: genotyping (*individual DNAs; DNA pools*)

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*How are we finding the DNA (gene) variants that contribute to vulnerability addictions*



1) **Top down:** Genome scanning/positional cloning:

**Linkage:** Study how DNA markers and disease move together through families. Study related individuals in large or small pedigrees. Works well for Mendelian disorders, more poorly for polygenic diseases

**Association:** Study how DNA markers and disease move together through a population Study unrelated individuals with disease vs matched controls with no disease. Works better for polygenic diseases

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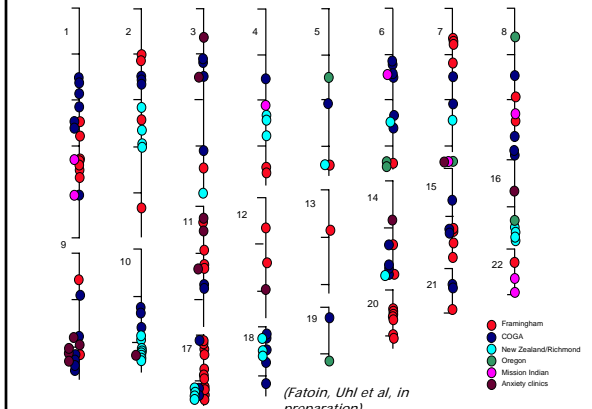
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Only random distribution of nominally-significant linkage signals for nicotine in recent metaanalysis



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*How do we find the DNA (gene) variants that contribute to addictions*



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**Whole genome association: hope for broad medical application**

Clinical applications of whole-genome association studies: future applications at the bedside

WGA Whole Genome Association

| Conditions of interest      | Data for defining/subtyping conditions or for intermediate clinical phenotyping | Data for adjustment/stratification or for risk factor phenotyping |
|-----------------------------|---|---|
| Arterio-vascular            | Aortic/aortic index   | Gender  |
| Coronary artery disease     | Blood levels  | Age   |
| Congestive heart failure    | Glucose levels  | Education   |
| Atrial fibrillation         | HbA1c levels  | Occupation  |
| Hypertension                | Cholesterol/lipid levels  | Geographic locale   |
| Cardiovascular disease      | Apoptin levels  | Height  |
| Peripheral vascular disease | Plasma homocysteine factors   | Weight  |
| Metabolic syndrome          | Inflammatory markers  | Body mass index   |
| Diabetes Type 1             | Creatine kinase MB fraction   | Counference measurements  |
| Diabetes Type 2             | Hepatic transaminase (alanine and aspartate aminotransferase)                   | Physical activity   |
| Sudden cardiac death        | Blood cholesterol   | Caloric intake  |
| Myocardial infarction       | Carotid ultrasonography and stenosis  | Smoking   |
| Hypertension                | Left ventricular ejection fraction, echo and MRI                                | Alcohol use   |
|                             | Electrocardiogram   | Family  |

Genetic Association Information Network Launched

NIH, NHLBI, WGA

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**Bases for whole genome association in addictions**

*Classical genetics and working hypotheses re genetic architecture for addictions*

Theoretical: association vs linkage

Genomic: variants

Technical: genotyping (individual DNAs; DNA pools)

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**Primer: genomics for "whole genome association"**

\*Genomic sequence (36.1) 2,858,160,000 bp  
 \*mRNA transcripts: 33,083 (219,066 exons)  
 \*SNPs (dbSNP 126)  
     submitted: 27,846,394 rs numbers:  
 11,961,761  
     validated: 5,646,244 rs numbers in genes:  
 4,116,991  
     frequency info: 682,608 genotype info:  
 5,546,513  
 \* Insertion/Deletions (Marshfield)  
 200,000 in database [~20% of human polymorphisms]  
**VNTRs**  
 Short tandem repeat polymorphisms/simple sequence length polymorphism/microsatellites  
 Diallelic insertion/deletions

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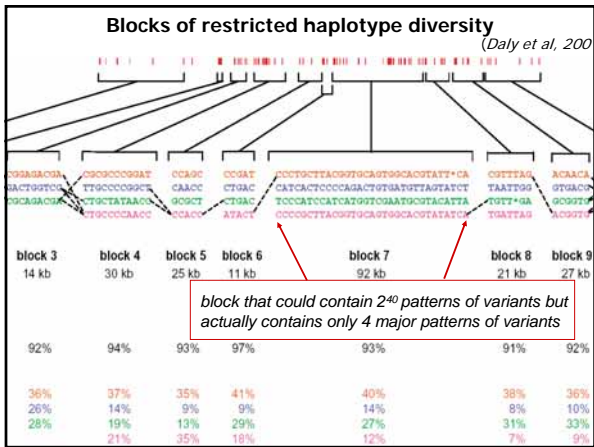
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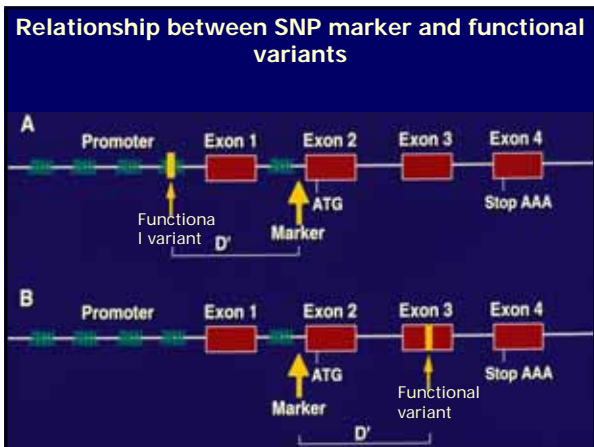
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**Bases for whole genome association:**

with more and more SNP markers, we can gain information about more and more of the variants in more and more of the haplotype blocks in the genome

with enough SNP markers, we can identify most of the variants that distinguish disease from control individuals

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**Bases for whole genome association and its use in addictions**

*Classical genetics and working hypotheses re genetic architecture for addictions*

Theoretical: association vs linkage

Genomic: variants

Technical: genotyping (*individual DNAs; DNA pools*)

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**How do we genotype enough SNPs to sample more and more of the haplotype blocks in the genome: multi-pool microarray based association genome scanning**

Validate microsatellite pooling 1995 (*Walther, Uhl et al, unpublished observations*)

Validate 1.5k microarr:

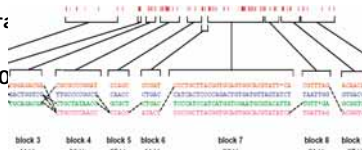
Model whole genome scan power 2000

(*Naiman, Uhl et al, unpublished*)

Validate 10k microarra pooling 2002

Validate 100k microarray pooling 2003-4 (*Johnson et al, 2006*)

Validate 500k microarray pooling 2005 (*Liu et al, in press*)



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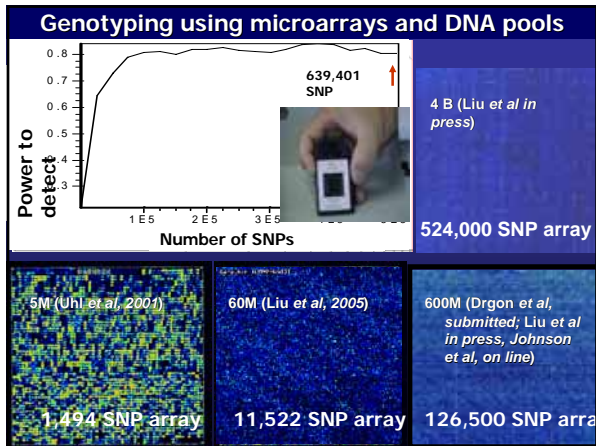
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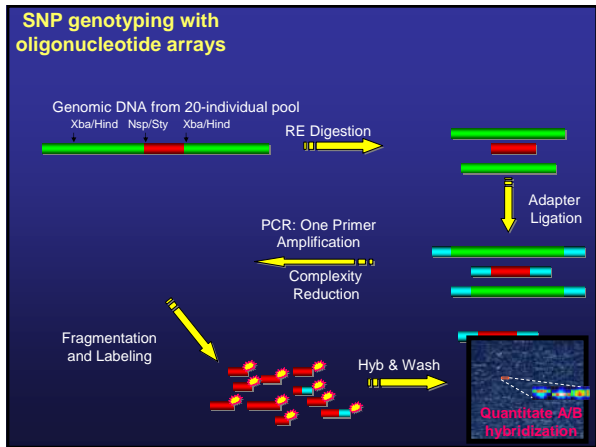
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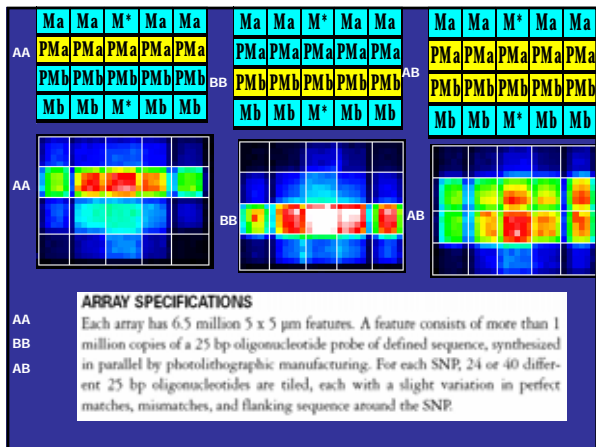
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**Whole genome association analyses** compare allele frequencies in disease vs control samples

Can thus genotype:

- a) individual samples
- b) DNA pools (*groups of individuals of the same phenotype and the same ethnic/racial backgrounds*)
  - use enough chips/pool to accurately estimate the "real" mean value in each pool*
  - use enough pools/phenotype to accurately estimate the "real" variance within a phenotype/ethnicity group]*

**Need to validate pooled genotyping**

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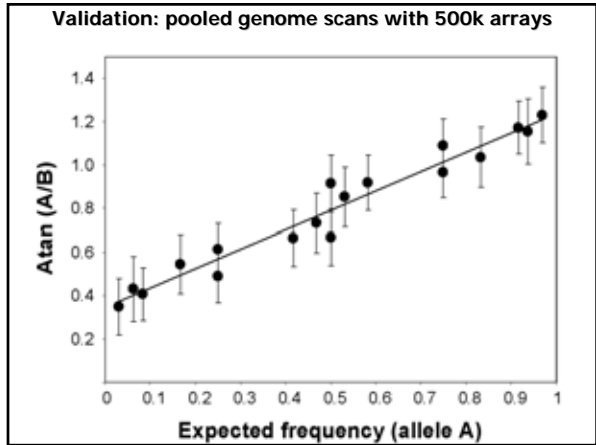
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So: How do we carry out a "whole genome association" genome scan

**Ingredients for whole genome association**

- Genotyping
- Subjects
- Data handling
- Statistical approaches

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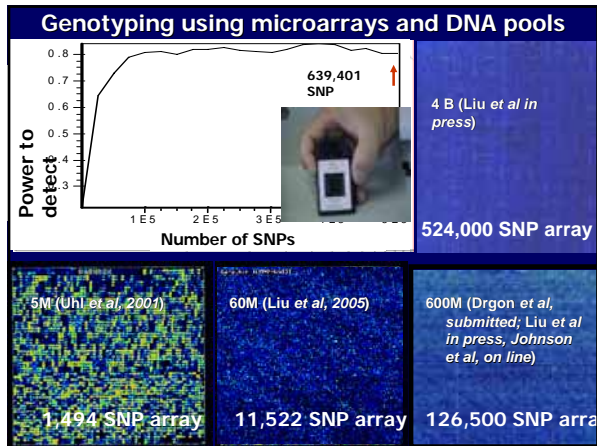
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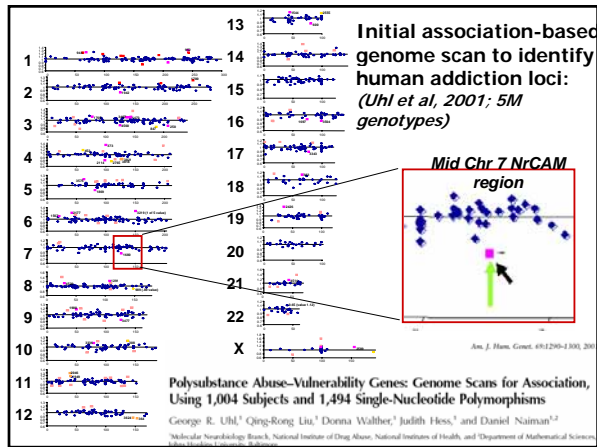
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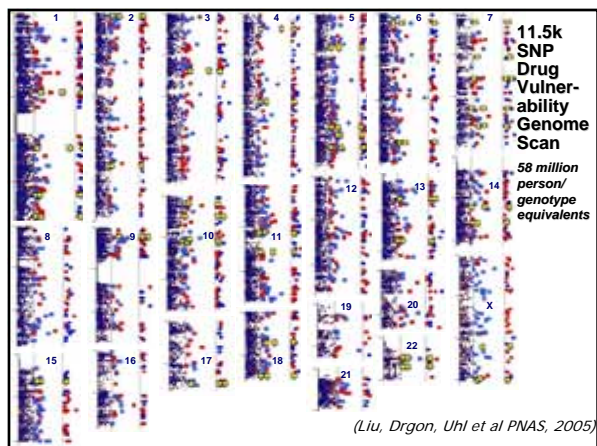
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### Subjects

- 1) **NIDA** ( $n = 1460$ ) "Abusers" Heavy peak lifetime use of and/or DSM dependence on at least one illegal addictive substance vs "Control" No significant lifetime use of any addictive substance, legal or illegal (*European-, African-American*)
- 2) **COGA** ( $n = 280$ ) "Abuser" Alcohol dependent proband, most with illegal substance abuse/ dependence vs "Control" Unrelated individual with no abuse/ dependence (*European-American*)
- 3) **JGIDA** ( $n = 200$ ) "Abuser" Methamphetamine dependent proband, most IV with amphetamine psychosis vs "Control" Unrelated individual from same prefectures with no substance abuse histories (*Japanese*)
- 4) **Duke** ( $n = 260$ ) "Abusers" Heavy peak lifetime use of and DSM dependence on nicotine Successful vs unsuccessful abstainers (*European-American*)

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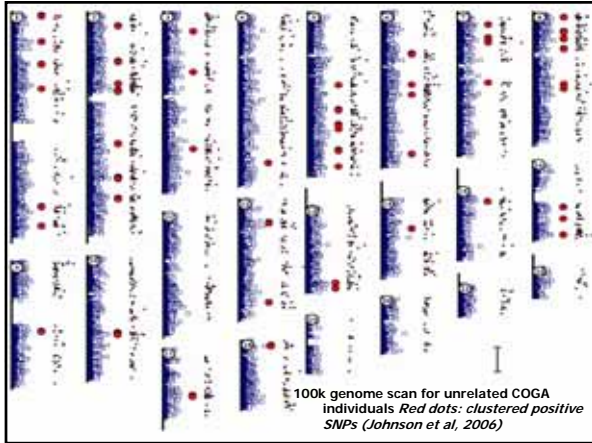
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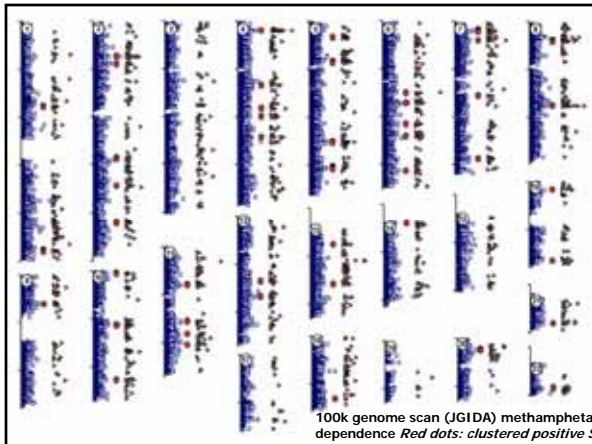
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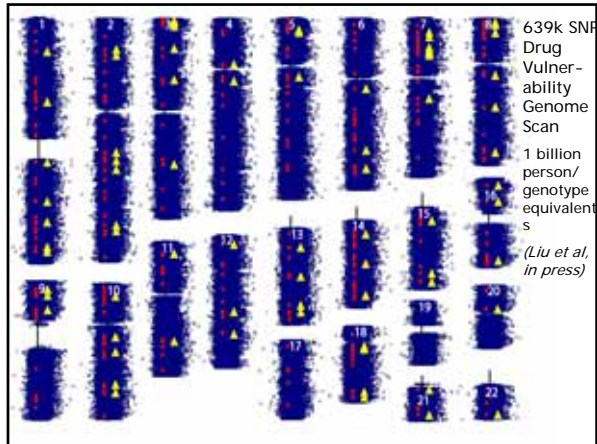
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**Ingredients for whole genome association**

Genotyping  
Subjects  
Data handling  
Statistical approaches

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**Analyses** (increasing numbers of repeated comparisons with denser genotyping)

**1.5k arrays** (Uhl et al, Am J Human Gen 2001): Nominal significance with internal replication (require same SNPs to display outlier p value and abuser/control difference in both European and African-American samples). Monte Carlo simulations, chromosomal clustering (1+Mb)

**Convergence with linkage data** (Uhl et al, Trends in Genetics 2002): Monte Carlo simulations, chromosomal clustering (1+Mb)

**10k arrays** (Liu et al, PNAS 2005): Nominal significance with internal replication (require same SNPs to display outlier p value in both European and African-American samples). Monte Carlo simulations, chromosomal clustering (0.1 Mb)

**100k arrays** (Johnson et al, 2006): Nominal significance with chromosomal clustering (0.1 Mb) in annotated genes. Convergence with 100k data from NIDA and IGIDA

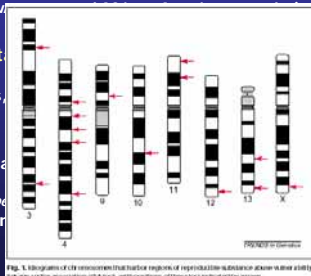


FIG. 1. Histograms of chromosomes that have regions of replication-silencing observed using linkage and/or association (PSAs), with positions of denser SNPs indicated by arrows.

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Clustered positive results from several different samples overlap much more than expected by chance

|         | NIDA EA | NIDA AA        | JGIDA          | COGA           |
|---------|---------|----------------|----------------|----------------|
| NIDA EA |         | 102<br><0.0001 | 122<br><0.0001 | 118<br><0.0001 |
| NIDA AA |         |                | 30<br><0.0001  | 20<br><0.0001  |
| JGIDA   |         |                |                | 25<br><0.0001  |
| COGA    |         |                |                |                |

(n)   P<0.0001

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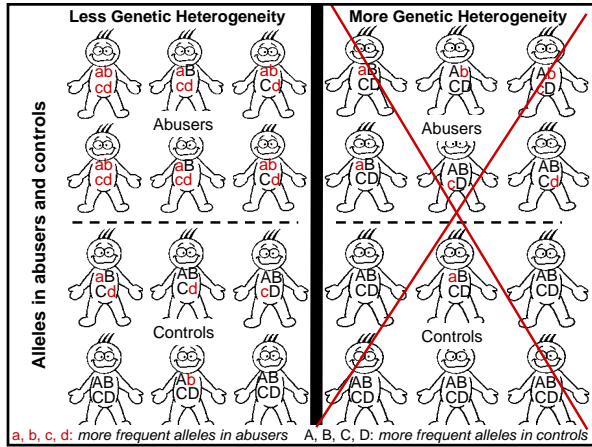
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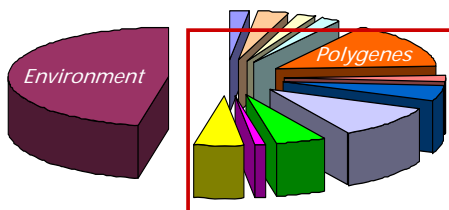
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Current working hypotheses about underlying genetic architecture




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**Ingredients for whole genome association**  
 Genotyping  
 Subjects  
 Data handling  
 Statistical approaches

600k arrays (Liu et al, in press)

Nominal significance with internal replication (same SNPs display outlier p values in both European- and African-American samples)

Chromosomal clustering (0.1 Mb)

Convergence with 100k JGIDA

COGA data in annotated genes

Primary Monte Carlo simulations

Secondary permutation analyses

False false discovery rate corrections for gene identification

Thus: we can apply relatively stringent criteria for identified genes

- 1) **NIDA (639K)** At least three SNPs within 0.1 Mb of each other that each reach nominal  $p < 0.05$  in both NIDA EuAM and NIDA AfAM samples and lie within an annotated gene
- 2) **COGA (128k)** At least one SNP within 0.1Mb of NIDA clustered positive SNP with nominal  $p < 0.05$
- 3) **JGIDA (128k)** At least one SNP within 0.1Mb of NIDA clustered positive SNP with nominal  $p < 0.05$

$$I = \frac{\bar{X}_{\text{NIDA}} - \bar{X}_{\text{COGA}}}{\sqrt{\frac{(\sigma_{\text{NIDA}}^2 - 10^4 \sigma_{\text{COGA}}^2) + (\sigma_{\text{NIDA}}^2 - 10^4 \sigma_{\text{COGA}}^2)}{n_{\text{NIDA}} + n_{\text{COGA}} - 2}} \times \sqrt{\frac{1}{n_{\text{NIDA}}} + \frac{1}{n_{\text{COGA}}}}}$$

| Gene/Cluster | Class | Chr | bp          | p Rose | P NIDA  | P COGA  | PROT   | EPH11L         | 0.00189 |
|--------------|-------|-----|-------------|--------|---------|---------|--------|----------------|---------|
| CDMD2        | CAM   | 1   | 34,204,028  | 0.004  | 0.00055 | ELMO1   | PROT   | 6,181,412,222  | 0.00045 |
| LRP1B a      | CAM   | 2   | 140,790,957 | 0.0185 | 0.00329 | JGIDA   | PROT   | 7,36,840,767   | 0.00045 |
| LRP1B b      | CAM   | 2   | 142,478,887 | 0.016  | 0.00367 | SORCS1  | PROT   | 10,108,468,878 | 0.01056 |
| CNTN6        | CAM   | 3   | 1,280,415   | 0.001  | 0.00059 | MICALCL | PROT   | 11,12,241,526  | 0.009   |
| CNTN4        | CAM   | 3   | 3,075,787   | 0.009  | 0.00267 | MCTP2   | PROT   | 15,92,656,554  | 0.0115  |
| LRN1         | CAM   | 3   | 3,765,691   | 0      | 0.00066 | IMPACT  | PROT   | 18,20,182,039  | 0.0007  |
| CTNND2       | CAM   | 4   | 62,110,385  | 0.0145 | 0.00267 | DDK6    | PROT   | 18,65,456,774  | 0.00047 |
| TRIO         | CAM   | 5   | 14,191,248  | 0.0065 | 0.00044 | NAB1    | PROT   | 20,23,246,296  | 0.0008  |
| BA3          | CAM   | 6   | 69,765,171  | 0.0155 | 0.00078 | CRM1    | REC    | 2,36,424,664   | 0.00045 |
| SEMA3C       | CAM   | 7   | 80,111,952  | 0.0025 | 0.00120 | GPR154  | REC    | 3,6,934,982    | 0.0006  |
| CSMD1a       | CAM   | 8   | 3,184,850   | 0.002  | 0.00063 | HRH4    | REC    | 18,20,260,986  | 0.0007  |
| CSMD1b       | CAM   | 8   | 3,655,990   | 0.0015 | 0.00095 | TF      | TF     | 7,18,877,145   | 0.013   |
| CSMD1c       | CAM   | 8   | 3,885,737   | 0      | 0.00009 | PERD1L  | TF     | 7,18,877,145   | 0.013   |
| SGC2         | CAM   | 8   | 14,393,368  | 0      | 0.00005 | CND1    | TF     | 8,88,431,975   | 0.0125  |
| PTFRD        | CAM   | 9   | 8,510,837   | 0.002  | 0.00047 | NFB     | TF     | 9,14,190,005   | 0.0006  |
| LRN6C5       | CAM   | 9   | 29,153,017  | 0.0025 | 0.00118 | ERT     | TF     | 12,75,889,008  | 0.0004  |
| CTNNA3       | CAM   | 10  | 67,807,778  | 0.015  | 0.00112 | NPAS3   | TF     | 14,32,886,303  | 0.0005  |
| CNTN5        | CAM   | 11  | 99,293,263  | 0.0065 | 0.00065 | ENF47   | TF     | 18,70,633,914  | 0.016   |
| ANKR1B       | CAM   | 12  | 97,868,771  | na     | 0.00336 | NR1P1   | TF     | 21,15,243,812  | 0.0095  |
| POSTN        | CAM   | 13  | 36,957,218  | 0.0055 | 0.00014 | QJAP1   | CHA    | 1,144,373,120  | 0.013   |
| PCDH9B       | CAM   | 13  | 66,841,174  | 0.0175 | 0.00349 | KCNQ3   | CHA    | 8,133,172,472  | 0.005   |
| CDM13a       | CAM   | 16  | 81,421,161  | na     | 0.00359 | TRPC4   | CHA    | 13,37,010,413  | 0.0055  |
| CDM13b       | CAM   | 16  | 81,647,004  | 0.003  | 0.00198 | KCNM5   | CHA    | 14,62,388,345  | na      |
| DISCAM       | CAM   | 21  | 40,304,081  | 0.0085 | 0.0007  | RVE3    | CHA    | 15,31,619,712  | 0.003   |
| TTLL7        | ENZ   | 1   | 83,968,756  | 0.01   | 0.00343 | SLC9A8  | TRANSF | 3,144,621,080  | 0.0165  |
| ACRF         | ENZ   | 1   | 144,373,120 | 0.013  | 0.00184 | SLC9A9  | TRANSF | 3,144,621,080  | 0.0165  |
| PTGS2        | ENZ   | 1   | 183,326,925 | na     | 0.00214 | XRR5    | TRANSF | 8,6,650,733    | 0.0005  |
| BAR          | ENZ   | 1   | 203,813,122 | 0.0055 | 0.00024 | KRR4    | TRANSF | 8,56,387,673   | 0.0045  |
| SIPAL12      | ENZ   | 1   | 228,796,685 | 0.0005 | 0.00040 | BCC4    | TRANSF | 13,94,600,083  | 0.011   |
| CPH1         | ENZ   | 2   | 30,911,219  | na     | 0.00140 | ALSCR19 | DIS    | 2,205,600,773  | 0.023   |
| PHF3         | ENZ   | 3   | 60,583,757  | 0.017  | 0.00279 | THYB1   | DIS    | 7,33,369,755   | 0.01    |
| UST          | ENZ   | 5   | 58,461,253  | 0.0125 | 0.00329 | AAA1    | DIS    | 7,34,383,589   | 0.01    |
| POSD4        | ENZ   | 6   | 149,285,788 | 0.0035 | 0.00046 | ENL     | DIS    | 22,44,348,854  | 0.0165  |
| ENK          | ENZ   | 7   | 14,210,001  | 0.02   | 0.00112 | ACTN2   | STR    | 1,233,147,888  | 0       |
| CHN2         | ENZ   | 7   | 29,145,188  | 0.008  | 0.00007 | OC50    | STR    | 8,133,172,472  | 0.005   |
| POEC1        | ENZ   | 7   | 31,545,014  | 0.004  | 0.00024 | AKAP13  | STR    | 15,83,590,525  | 0.009   |
| CAMK1D       | ENZ   | 10  | 12,881,298  | 0.0315 | 0.00315 | RBM53   | OTHER  | 3,29,413,504   | 0.01    |
| FRS31B       | ENZ   | 10  | 52,485,930  | 0.0065 | 0.00029 | RP3     | OTHER  | 7,7,377,316    | 0.0005  |
| PRKG1b       | ENZ   | 10  | 52,986,399  | 0.0025 | 0.00214 | HHLA1   | OTHER  | 8,133,172,472  | 0.005   |
| PRKG1c       | ENZ   | 10  | 53,405,302  | 0.014  | 0.00259 | DEFB1   | OTHER  | 8,6,650,733    | 0.0005  |
| HPSE2L       | ENZ   | 10  | 100,743,717 | 0.012  | 0.00314 | TOP14   | OTHER  | 13,101,764,771 | 0.007   |
| P2P          | ENZ   | 12  | 93,143,898  | 0.0175 | 0.00144 | AZP1    | OTHER  | 16,6,603,645   | 0.0025  |
| SERPINA2     | ENZ   | 14  | 93,825,872  | 0.0085 | 0.00065 | DSRPL1A | OTHER  | 18,20,182,039  | 0.007   |
| SERPINA1     | ENZ   | 14  | 93,825,872  | 0.0085 | 0.00065 |         |        |                |         |
| USP31        | ENZ   | 16  | 22,804,931  | 0.012  | 0.00183 |         |        |                |         |
| CHST3        | ENZ   | 18  | 22,731,652  | 0.004  | 0.00378 |         |        |                |         |

## What about convergence with nicotine dependence?

- NIDA (n = 1460)** "Abusers" Heavy peak lifetime use of and/or DSM dependence on at least one illegal addictive substance vs "Control" No significant lifetime use of any addictive substance, legal or illegal (*European-, African-American*)
- COGA (n = 280)** "Abuser" Alcohol dependent proband, most with illegal substance abuse/ dependence vs "Control" Unrelated individual with no abuse/ dependence (*European-American*)
- JGIDA (n = 200)** "Abuser" Methamphetamine dependent proband, most IV with amphetamine psychosis vs "Control" Unrelated individual from same prefectures with no substance abuse histories (*Japanese*)
- Duke (n = 260)** "Abusers" Nicotine cessation trial par who are heavy peak lifetime users and DSM dependent nicotine vs NIDA controls (*European American*)

| Genes that contain clustered positive SNPs from four prior abuser vs control comparisons | Gene/Cluster | Class | Chr | bp          | p Rosio | JGIDA   | EPBTL2   | PROT   | 6  | 131121823   | 0.0006 | 0.00193 |
|--|--------------|-------|-----|-------------|---------|---------|----------|--------|----|-------------|--------|---------|
|  | CSMD2        | CAM   | 1   | 34,234,029  | 0.004   | 0.00025 | ELMO1    | PROT   | 7  | 36,940,767  | 0.0045 | 0.00249 |
|  | LRFB1b       | CAM   | 2   | 140,790,957 | 0.0165  | 0.00329 | JGIDA    | PROT   | 10 | 108,456,878 | 0.0155 | 0.00169 |
|  | LRFB1b       | CAM   | 2   | 142,478,867 | 0.016   | 0.00367 | SOCS1    | PROT   | 11 | 12,241,526  | 0.009  | 0.00115 |
|  | CNTN6        | CAM   | 3   | 1,290,415   | 0.001   | 0.00059 | MICAL2   | PROT   | 15 | 92,656,564  | 0.0115 | 0.00215 |
|  | CNTN4        | CAM   | 3   | 1,075,735   | 0.009   | 0.00257 | MCTP2    | PROT   | 18 | 20,182,039  | 0.007  | 0.00071 |
|  | LRN1         | CAM   | 3   | 3,760,591   | 0       | 0.00007 | DOG5     | PROT   | 20 | 23,246,296  | 0.008  | 0.00083 |
|  | CTNND2       | CAM   | 4   | 62,110,865  | 0.0145  | 0.00369 | NAPB     | PROT   | 2  | 36,424,664  | 0.0015 | 0.00045 |
|  | TRIO         | CAM   | 5   | 11,209,205  | 0.006   | 0.00166 | GRM1     | REC    | 2  | 133,101,796 | 0.007  | 0.00077 |
|  | BAI2         | CAM   | 6   | 89,760,171  | 0.0155  | 0.00444 | GRM7     | REC    | 3  | 160,400,048 | 1      | 0.00005 |
|  | SEMA3C       | CAM   | 7   | 80,115,052  | 0.0025  | 0.00120 | GPR154*  | REC    | 7  | 34,363,589  | 0.01   | 0.00133 |
|  | CSMD1a       | CAM   | 8   | 3,184,850   | 0.002   | 0.00083 | HRM4*    | REC    | 18 | 20,280,986  | 0.007  | 0.00097 |
|  | CSMD1b       | CAM   | 8   | 3,653,950   | 0.0015  | 0.00055 | TWIST1*  | TF     | 7  | 18,877,145  | 0.013  | 0.00203 |
|  | CSMD1c       | CAM   | 8   | 3,885,737   | 0       | 0.00009 | FERD3L*  | TF     | 7  | 18,877,145  | 0.013  | 0.00202 |
|  | SOX2         | CAM   | 8   | 14,393,366  | 0       | 0.00006 | CND31    | TF     | 8  | 88,431,075  | 0.0125 | 0.00248 |
|  | PTPRD        | CAM   | 9   | 8,310,837   | 0.002   | 0.00047 | NEB      | TF     | 9  | 14,190,005  | 0.006  | 0.00074 |
|  | LRINRC5      | CAM   | 9   | 29,153,017  | 0.0025  | 0.00118 | EPF7     | TF     | 12 | 75,889,008  | 0.004  | 0.00025 |
|  | CTNNA3       | CAM   | 10  | 67,807,779  | 0.015   | 0.00112 | NPA33    | TF     | 14 | 32,886,303  | 0.0055 | 0.00101 |
|  | CNTN5        | CAM   | 11  | 99,293,253  | 0.0055  | 0.00045 | ZNF407   | TF     | 18 | 70,633,914  | 0.016  | 0.00036 |
|  | ANKK1B       | CAM   | 12  | 97,658,771  | na      | 0.00336 | NR1*     | TF     | 21 | 15,243,912  | 0.0095 | 0.00077 |
|  | POSTN        | CAM   | 13  | 36,367,218  | 0.0055  | 0.00194 | GJAS*    | CHA    | 1  | 144,373,120 | 0.013  | 0.00184 |
|  | PCDH9S       | CAM   | 13  | 66,841,174  | 0.0175  | 0.00349 | KCNQ3*   | CHA    | 8  | 133,172,472 | 0.005  | 0.00114 |
|  | CDH13        | CAM   | 16  | 81,421,101  | na      | 0.00358 | TRPC4*   | CHA    | 13 | 37,020,413  | 0.0055 | 0.00114 |
|  | CDH13b       | CAM   | 16  | 84,470,044  | 0.003   | 0.00198 | KCNH5    | CHA    | 14 | 62,388,345  | na     | 0.00377 |
|  | DSCAM        | CAM   | 21  | 40,304,081  | 0.0285  | 0.00007 | RVR3     | CHA    | 15 | 31,919,712  | 0.002  | 0.00021 |
|  | TLL1         | ENZ   | 1   | 83,966,756  | 0.01    | 0.00349 | SLC9A9   | TRANSF | 3  | 144,821,080 | 0.0165 | 0.00328 |
|  | ACPF6*       | ENZ   | 1   | 144,373,120 | 0.013   | 0.00184 | SLC9A9   | TRANSF | 3  | 144,821,080 | 0.0165 | 0.00328 |
|  | PTGSE        | ENZ   | 1   | 183,326,925 | na      | 0.00214 | SLC9A9   | TRANSF | 3  | 144,821,080 | 0.0165 | 0.00328 |
|  | DAF          | ENZ   | 1   | 203,813,122 | 0.0255  | 0.00024 | SLC9A9   | TRANSF | 3  | 144,821,080 | 0.0165 | 0.00328 |
|  | SIPAL12      | ENZ   | 1   | 228,796,888 | 0.0095  | 0.00040 | KRR4*    | TRANSF | 8  | 56,387,673  | 0.0045 | 0.00029 |
|  | CAPN13       | ENZ   | 2   | 30,911,219  | na      | 0.00140 | ABCC4    | TRANSF | 13 | 94,600,083  | 0.011  | 0.0035  |
|  | CPII         | ENZ   | 2   | 211,223,231 | 0.0175  | 0.00330 | AL3SCR19 | DIS    | 2  | 205,600,773 | 0.023  | 0.00232 |
|  | FHT          | ENZ   | 3   | 60,583,757  | 0.017   | 0.00279 | PTH1     | DIS    | 7  | 33,369,755  | 0.01   | 0.00250 |
|  | PDE4D        | ENZ   | 5   | 58,481,253  | 0.0125  | 0.00329 | AAH1*    | DIS    | 7  | 34,363,589  | 0.01   | 0.00125 |
|  | LIST         | ENZ   | 6   | 149,293,788 | 0.0035  | 0.00046 | E46L     | DIS    | 22 | 44,434,684  | 0.0165 | 0.00069 |
|  | DGKB         | ENZ   | 7   | 14,210,001  | 0.02    | 0.00112 | ACTN2    | STR    | 1  | 233,147,888 | 0      | 0.00016 |
|  | CHN2         | ENZ   | 7   | 29,145,188  | 0.008   | 0.00007 | OCYP*    | STR    | 8  | 133,172,472 | 0.005  | 0.00114 |
|  | PDEC1C       | ENZ   | 7   | 31,648,914  | 0.004   | 0.00204 | AKAP13   | STR    | 15 | 83,690,625  | 0.009  | 0.00221 |
|  | CAMK1D       | ENZ   | 10  | 12,881,208  | 0.0315  | 0.00115 | RBM5     | OTHER  | 3  | 29,413,504  | 0.01   | 0.00022 |
|  | PRKG1a       | ENZ   | 10  | 52,485,930  | 0.0065  | 0.00299 | RPAS     | OTHER  | 7  | 7,377,316   | 0.006  | 0.00016 |
|  | PRKG1b       | ENZ   | 10  | 52,986,059  | 0.0025  | 0.0014  | HHLA1*   | OTHER  | 8  | 133,172,472 | 0.005  | 0.00114 |
|  | PRKG1c       | ENZ   | 10  | 53,403,302  | 0.014   | 0.00239 | DEFB1*   | OTHER  | 8  | 6,620,733   | 0.0005 | 0.00063 |
|  | HRPE2L       | ENZ   | 10  | 100,743,717 | 0.012   | 0.00314 | FGF14    | OTHER  | 13 | 101,764,771 | 0.007  | 0.00317 |
|  | PZP          | ENZ   | 12  | 9,141,868   | 0.0175  | 0.00144 | OSBPL1A  | OTHER  | 18 | 20,182,038  | 0.007  | 0.00071 |
|  | HRPE2L       | ENZ   | 14  | 93,825,972  | 0.0065  | 0.0005  |          |        |    |             |        |         |
|  | SERPINA2*    | ENZ   | 14  | 93,825,872  | 0.0085  | 0.0005  |          |        |    |             |        |         |
|  | SERPINA1*    | ENZ   | 14  | 93,824,931  | 0.012   | 0.00163 |          |        |    |             |        |         |
|  | USP1*        | ENZ   | 18  | 22,304,853  | 0.024   | 0.00324 |          |        |    |             |        |         |
|  | KHST9        | ENZ   | 18  | 22,291,853  | 0.024   | 0.00324 |          |        |    |             |        |         |

- ### Whole genome association studies
- MNB/NIDA Polysubstance dependent vs controls (639k SNPs): African American: European American:
  - COGA Alcohol dependent vs controls (100k SNPs):
  - JGIDA Methamphetamine dependent vs controls (639k SNPs)
  - Duke Nicotine dependent vs MNB/NIDA controls (520k SNPs)
  - Duke Nicotine quit success vs nonsuccess (520k SNPs)



### Initial Molecular Genetics of Smoking Cessation Success

2311 nominally-significant SNPs

These nominally-positive SNPs cluster more than anticipated by chance (*Monte Carlo p < 0.0001*)

Genes identified by these clustered positive SNPs overlap with genes identified for nicotine and other substance dependence genes (*eg CDH13*)

Nominates interesting gene groups never identified in abuser/nonabuser comparisons (*eg CRH-related genes*)

[Need replication]

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### Implications

Quantitative modeling for effects of genotyping on clinical trial design/costs

What might identification of specific gene classes tell us about addiction:

- Many cell adhesion related genes

- Potential implications for different brains in addicts

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### Model for effects of genotyping on clinical trial costs and power

**Data:**

0.5 heritability for quit success tx trial

little evidence for large G x E environment

allele frequencies from 1 quit success study

calculated power 0.45 - .9 genetic

and

about 0.1 of smokers quit about 0.2 of tx smokers quit components

genetic = env influences

**Assumptions:**

0.5 genetic influence on

additive genetic +

these can represent all

genotyping can assess 0.5 of influences

threshold model for quit success tx effects

set threshold so that genetic and environmentally derived match these figures

use the variance of components to

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**Build two subpopulations:**

a) 100,000 Genetic quitters: Each gets 2311 "quitter" genotypes and 2311 "environmental" features selected at random

b) 100,000 Genetic nonquitters: Each gets 2311 "nonquitter" genotypes and 2311 "environmental" features selected at random

**Assess distribution of  $\chi^2$  values for the difference between treatment and placebo for 100,000 trials of three types:**

a) Randomly selected participants (average 0.1: 0.9 genetic quitters:nonquitters)

b) Half-maximal genetic stratification (average 0.25:0.5 genetic quitters: nonquitters)

c) Completely genetic stratification (average 0.5 : 0.5 genetic quitters : nonquitters)

Assume that treatment effects are such that 0.1 of individuals quit with placebo and 0.2 quit with active treatment

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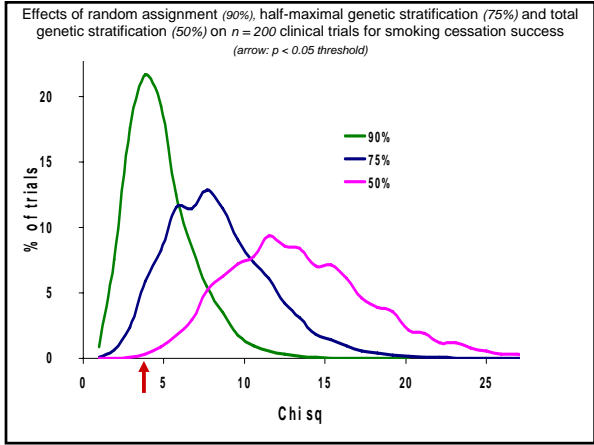
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**What might this mean for the costs of clinical trials?**

**Example:**  $n = 200$ , 0.9 power for trial stratified on the basis of assays for 0.5 of total genetic influences on quit success

$n = 450$  gives matching 0.9 power for conventional design

**Results:** Savings are maximized when pools of potential subjects are available for genotype-based stratification at little additional recruiting cost and when trial costs are large

(When  $n = 1000$ /group, both designs have ca 1 power. When  $n = 20$ /group, stratification increases power substantially, but both designs are underpowered)

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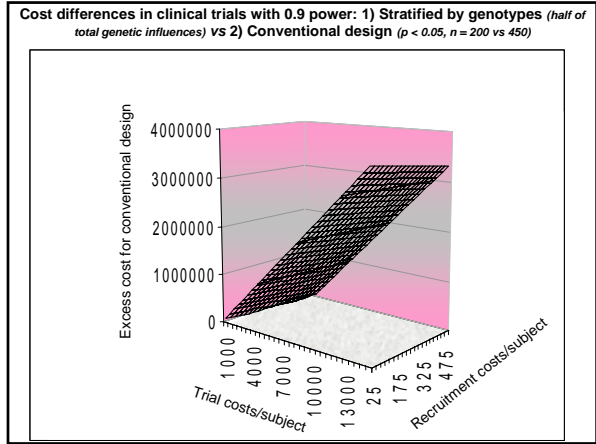
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**Implications**

Quantitative modeling for effects of genotyping on clinical trial design/costs

What can identification of specific gene classes tell us about addiction:

Many cell adhesion related genes

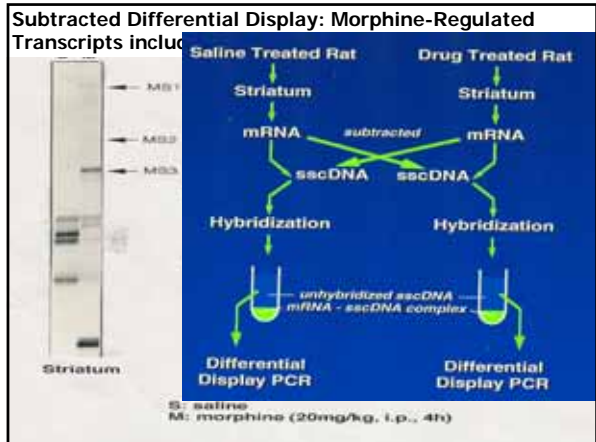
Potential implications for different brains in addiction

**Not just the usual suspects.**

| Gene/Cluster | Class   | Chr | bp        | p Rose | p Value  | Gene      | Class  | Chr | bp        | p Value |         |
|--------------|---------|-----|-----------|--------|----------|-----------|--------|-----|-----------|---------|---------|
| EPH11E       | PROT    | 6   | 121121822 | 0.0005 | 0.00189  | ELMO1     | PROT   | 7   | 36840767  | 0.0045  | 0.00243 |
| JM2A         | PROT    | 10  | 10846878  | 0.0156 | 0.00169  | SORCS1    | PROT   | 10  | 10846878  | 0.0156  | 0.00169 |
| Rose         | MICALCL | 11  | 12241526  | 0.009  | 0.00115  | MICALCL   | PROT   | 11  | 12241526  | 0.009   | 0.00115 |
| LRP1B a      | CAM     | 2   | 140790367 | 0.0185 | 0.00329  | MCTP2     | PROT   | 15  | 92666554  | 0.0115  | 0.00219 |
| LRP1B b      | CAM     | 2   | 140790367 | 0.0185 | 0.00329  | IMPACT2   | PROT   | 18  | 20182039  | 0.007   | 0.0007  |
| CNTN6        | CAM     | 3   | 1280415   | 0.001  | 0.00059  | DDK6      | PROT   | 18  | 65456774  | 0.015   | 0.00047 |
| CNTN4        | CAM     | 3   | 3075787   | 0.009  | 0.00267  | NARB      | PROT   | 20  | 23246296  | 0.008   | 0.00063 |
| LRN1         | CAM     | 3   | 3765691   | 0      | 0.00166  | CRM1      | REC    | 2   | 36424664  | 0.0015  | 0.00045 |
| LRN3         | CAM     | 4   | 62110385  | 0.0145 | 0.00389  | GPR39     | REC    | 2   | 13310178  | 0.007   | 0.00077 |
| CTNND2       | CAM     | 5   | 11206205  | 0.006  | 0.00166  | GFGR like | REC    | 2   | 150490048 | 1       | 0.00000 |
| TRIO         | CAM     | 5   | 14191248  | 0.0065 | 0.00044  | GRM7      | REC    | 3   | 6394382   | 0.006   | 0.00289 |
| BA3          | CAM     | 6   | 69765171  | 0.0155 | 0.00078  | GABRG1    | REC    | 4   | 45363501  | 0.01    | 0.00154 |
| SEMA3C       | CAM     | 7   | 80111352  | 0.0025 | 0.00120  | GPR154*   | REC    | 7   | 34383589  | 0.01    | 0.00123 |
| CSDM1a       | CAM     | 8   | 3184850   | 0.002  | 0.00053  | HRH4*     | REC    | 18  | 20280386  | 0.007   | 0.0007  |
| CSDM1b       | CAM     | 8   | 3655390   | 0.0015 | 0.00095  | TWIST1*   | TF     | 7   | 18877145  | 0.013   | 0.00202 |
| CSDM1c       | CAM     | 8   | 3885737   | 0      | 0.00009  | FERD1L    | TF     | 7   | 18877145  | 0.013   | 0.00202 |
| SGC2         | CAM     | 8   | 14393368  | 0      | 0.00005  | CND1      | TF     | 7   | 18877145  | 0.013   | 0.00202 |
| PFPRD        | CAM     | 9   | 8310837   | 0.002  | 0.00047  | NEB       | TF     | 9   | 14190005  | 0.006   | 0.00274 |
| LRN6C3       | CAM     | 9   | 29153017  | 0.0025 | 0.00118  | EFTF      | TF     | 12  | 75889008  | 0.004   | 0.00052 |
| CTNNA3       | CAM     | 9   | 67807778  | 0.015  | 0.00112  | NPAS3     | TF     | 14  | 32886303  | 0.0065  | 0.00101 |
| CNTN5        | CAM     | 11  | 99293263  | 0.0065 | 0.00055  | DNF407    | TF     | 18  | 70533914  | 0.016   | 0.00036 |
| ANKS1B       | CAM     | 12  | 97888771  | na     | 0.00336  | NR1P1     | TF     | 21  | 15243812  | 0.0095  | 0.00077 |
| PCDH9        | CAM     | 13  | 36957218  | 0.0055 | 0.00014  | QJAS1*    | CHA    | 1   | 144373120 | 0.013   | 0.00184 |
| CDM13a       | CAM     | 13  | 6684174   | 0.0175 | 0.00349  | KCNQ3*    | CHA    | 8   | 133172472 | 0.005   | 0.00114 |
| CDM13b       | CAM     | 16  | 81467004  | 0.003  | 0.00198  | TRPC4*    | CHA    | 13  | 37010413  | 0.0055  | 0.00014 |
| DISCAM       | CAM     | 21  | 40304081  | 0.0085 | 0.0007   | KCNH5     | CHA    | 14  | 62388345  | na      | 0.00377 |
| TTL7         | ENZ     | 1   | 83068756  | 0.01   | 0.00343  | RVE3      | CHA    | 15  | 31619712  | 0.003   | 0.00021 |
| ACRF*        | ENZ     | 1   | 144373120 | 0.013  | 0.00184  | SLC9A9    | TRANS* | 3   | 144621080 | 0.0165  | 0.00328 |
| PTGS2        | ENZ     | 1   | 183326925 | na     | 0.00214  | SLC9A9    | TRANS* | 3   | 144621080 | 0.0165  | 0.00328 |
| DAP          | ENZ     | 1   | 203813122 | 0.0055 | 0.00024  | XKR5*     | TRANS* | 8   | 6650733   | 0.0005  | 0.00063 |
| SIPAL12      | ENZ     | 1   | 228796685 | 0.0005 | 0.00040  | XKR4*     | TRANS* | 8   | 56387873  | 0.0045  | 0.00029 |
| CAPN13       | ENZ     | 2   | 30911219  | na     | 0.00140  | ABCC4     | TRANS* | 13  | 94600083  | 0.011   | 0.0005  |
| CPB1         | ENZ     | 2   | 211226231 | 0.0175 | 0.00320  | ALX2CR19  | DIS    | 2   | 205600773 | 0.023   | 0.00232 |
| PHF3         | ENZ     | 3   | 60583757  | 0.017  | 0.00329  | THYB1     | DIS    | 7   | 33369755  | 0.01    | 0.00250 |
| USP44        | ENZ     | 5   | 58461253  | 0.0125 | 0.00046  | AAA1*     | DIS    | 7   | 34383589  | 0.01    | 0.00123 |
| PCSK9        | ENZ     | 6   | 149285788 | 0.0035 | 0.00112  | ENL       | DIS    | 22  | 44434864  | 0.0165  | 0.00069 |
| ANKB         | ENZ     | 7   | 3154501   | 0.02   | 0.00112  | ACTN2     | STR    | 1   | 233147888 | 0       | 0.00016 |
| CHN2         | ENZ     | 7   | 29145188  | 0.008  | 0.00007  | OC50*     | STR    | 8   | 133172472 | 0.006   | 0.00114 |
| ROSC1        | ENZ     | 7   | 3154501   | 0.004  | 0.00004  | AKAP13    | STR    | 15  | 83590525  | 0.009   | 0.00221 |
| CAMK1D       | ENZ     | 10  | 12881298  | 0.0315 | 0.00315  | RBMS3     | OTHER  | 3   | 29413504  | 0.01    | 0.00022 |
| PRKG1b       | ENZ     | 10  | 52486399  | 0.0065 | 0.000214 | RP3       | OTHER  | 7   | 7377316   | 0.0065  | 0.00018 |
| PRKG1c       | ENZ     | 10  | 52486399  | 0.0025 | 0.000214 | HHLA1*    | OTHER  | 8   | 133172472 | 0.006   | 0.00114 |
| PRKG1d       | ENZ     | 10  | 52486399  | 0.014  | 0.00259  | DEFB1*    | OTHER  | 8   | 6650733   | 0.0005  | 0.00063 |
| HPSE2*       | ENZ     | 10  | 100743717 | 0.012  | 0.00314  | TOP14     | OTHER  | 13  | 101764771 | 0.007   | 0.0001  |
| PPP1R12B     | ENZ     | 12  | 93405362  | 0.0175 | 0.0014   | AZP1      | OTHER  | 16  | 6603465   | 0.0025  | 0.00171 |
| SERPINA2*    | ENZ     | 14  | 93405362  | 0.0085 | 0.0005   | OSBPL1A   | OTHER  | 18  | 20182039  | 0.007   | 0.0007  |
| SERPINA1*    | ENZ     | 16  | 22804931  | 0.012  | 0.00183  |           |        |     |           |         |         |
| USP31        | ENZ     | 18  | 25791652  | 0.004  | 0.00328  |           |        |     |           |         |         |
| CHST3        | ENZ     | 18  | 25791652  | 0.004  | 0.00328  |           |        |     |           |         |         |








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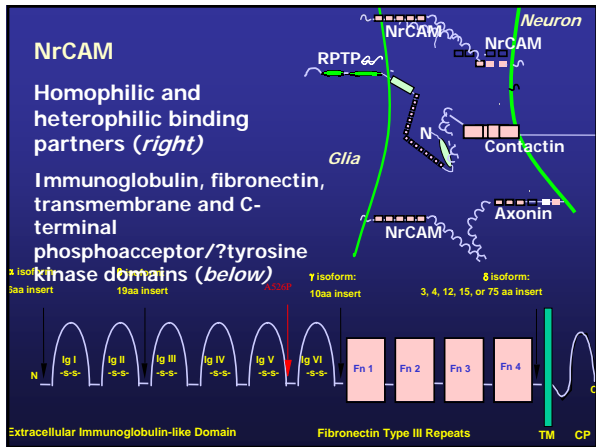
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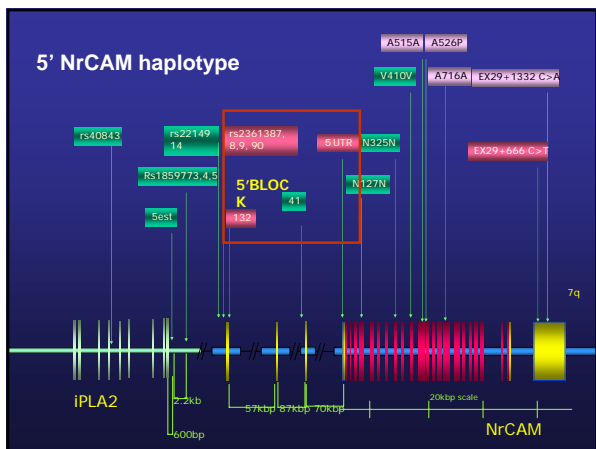
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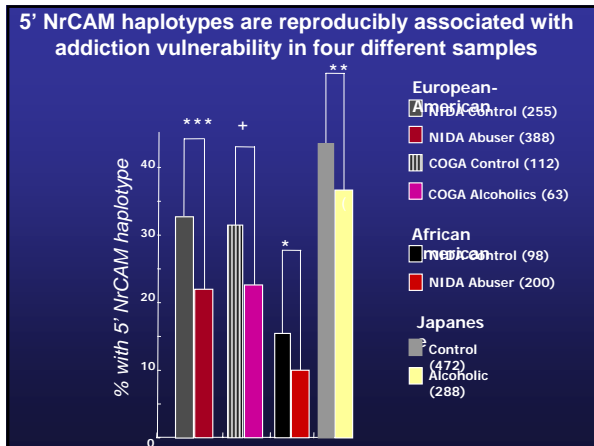
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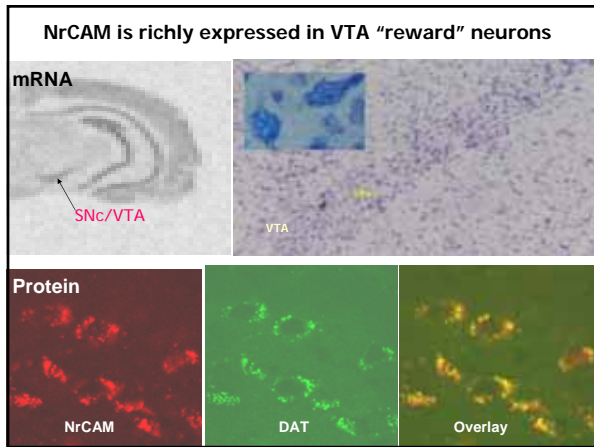
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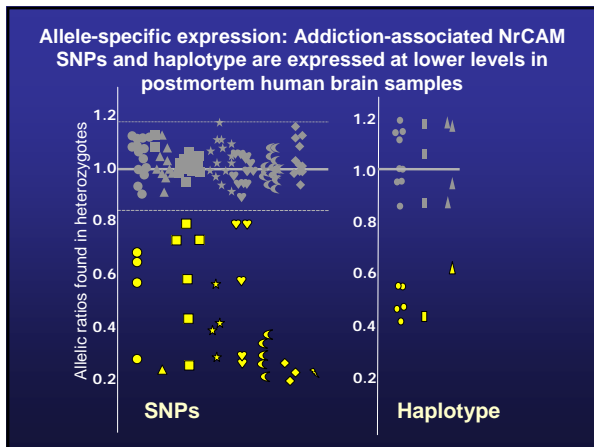
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**What does this mean for the clinician/researcher**

Now is a good time to collect DNA and appropriate consents from unrelated addicted and control individuals *(esp for phenotypes for which there is good evidence for heritability)*

Now is a good time to consider using genotype-based stratification for clinical trials

We will probably have to wade through a lot of noise to understand the small signals from this sort of work

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**What does this mean for the clinician**

Genotype based diagnosis and therapeutics for addictions will come of age within your practicing lifetime

The low costs of genotyping and the favorable cost/benefit considerations will increase use of personalized medicine based on genetic individual differences

*Current concerns re confidentiality and insurability need to be addressed*

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Sobering features of the current environment for association studies of illegal and legal addictive behaviors

Increasingly-powerful databases

Spotty legal protections re employability, insurability, nondiscrimination

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**Armed Forces Institute of Pathology**

**The Department of Defense DNA Registry**

**Military DNA reference database: 4,900,000 specimens as of 10/06 (D Boyer, personal communication)**

**Overview**

The identification of the American and foreign who have made the ultimate sacrifice in service to our nation has long been a high priority for the United States. Identification of deceased military personnel, whether they come from recent combat operations, peacekeeping missions, training exercises, or through other military activities in homeland operations, is essential to our country's history and the respect and honor that we owe to our fallen service members. It is also a key element in the identification and recovery of human remains and the closure of the grieving process for the families and loved ones of our fallen service members.

The United States has always been at the forefront of the scientific and technological advances in the identification of human remains. From the early days of forensic anthropology, to the use of dental records, to the use of fingerprints, to the use of DNA, we have always been at the forefront of the scientific and technological advances in the identification of human remains. In the past few years, the use of DNA has become a key element in the identification and recovery of human remains. In the past few years, the use of DNA has become a key element in the identification and recovery of human remains.

The system for mass identification of military personnel from World Wars I and II, Korea, and Vietnam has continued to improve, using the most advanced techniques in forensic anthropology, anthropology, and radiology. In the past few years, the use of DNA has become a key element in the identification and recovery of human remains. In the past few years, the use of DNA has become a key element in the identification and recovery of human remains.

In 1995, the Office of the Armed Forces Medical Director (AFMD) was established at the Armed Forces Institute of Pathology (AFIP) to provide the Department of Defense and other Federal agencies with the most advanced in forensic medicine. Since the early 1990s, new technologies have been incorporated into the field of forensic medicine. However, it was not until the late 1990s that the use of DNA in forensic medicine was becoming the primary method for the identification of the remains of military personnel. In 1998, the Department of Defense established the Department of Defense DNA Registry, which is the most advanced forensic medical laboratory, and the most advanced in the world. It is the most advanced in the world. It is the most advanced in the world.

In the fall of 2005, the Department of Defense established a DNA Reference Database (DRDB) to provide a central repository for the remains of military personnel. The DRDB is the most advanced in the world. It is the most advanced in the world.

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Liberal Politics: U.S.

## Senate Passes Genetic Privacy Act

Liberal Politics: U.S. Blog

[Main](#) | [Will Bush's Campaign Finance Cooffers Make Him Unbeatable?](#) »

October 17, 2003

### Senate Passes Genetic Privacy Act

Congress moved closer to protecting our [genetic privacy](#) last week when the Senate passed the [Genetic Privacy Act](#) in a 95 to 0 vote. The bi-partisan bill would prohibit insurance companies from using one's genetic predisposition to determine eligibility or to set rates and bar employers from basing employment decisions on genetic information. While Bush has indicated that he would sign the bill if and when it comes to him, the House of Representatives has yet to put the legislation on its agenda. Supporters of the legislation believe that House members are more beholden to lobbyists for the insurance industry and are dragging their hills on this issue as a result.

The Senate vote is historic because it is the first federal attempt to set genetic privacy standards. Educate yourself about this important issue [here](#) and [here](#).

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House hearings, but no floor schedule

### GENETIC NON-DISCRIMINATION: EXAMINING THE IMPLICATIONS FOR WORKERS AND EMPLOYERS

#### HEARING

BEFORE THE  
SUBCOMMITTEE ON EMPLOYER-EMPLOYEE RELATIONS  
OF THE  
COMMITTEE ON EDUCATION AND THE WORKFORCE  
U.S. HOUSE OF REPRESENTATIVES  
ONE HUNDRED EIGHTH CONGRESS  
SECOND SESSION

July 22, 2004

Serial No. 108-71

Printed for the use of the Committee on Education and the Workforce

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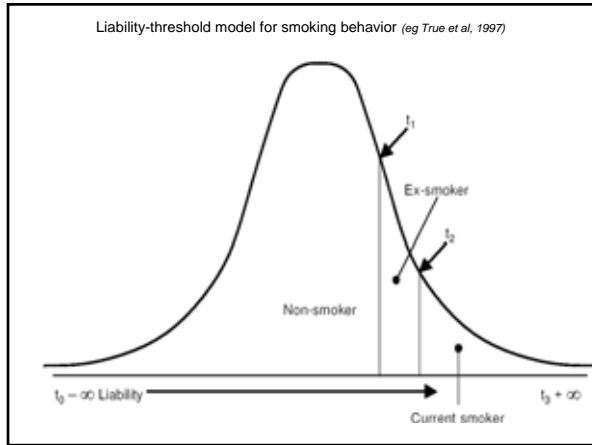
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