Genetics of Nicotine Addiction

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Financial Disclosure

- Patent on genetic variants that predict addiction – “Markers for Addiction”.
- Consultant for Pfizer in 2008 for genetic studies for smoking cessation.

- Funding of studies is through the National Institutes of Health

Model of Nicotine Dependence - A many step process

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Never Use

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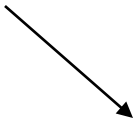
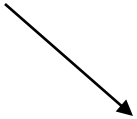


Initiation
First puff – First cigarette

Model of Nicotine Dependence - A many step process

Never Use



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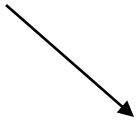
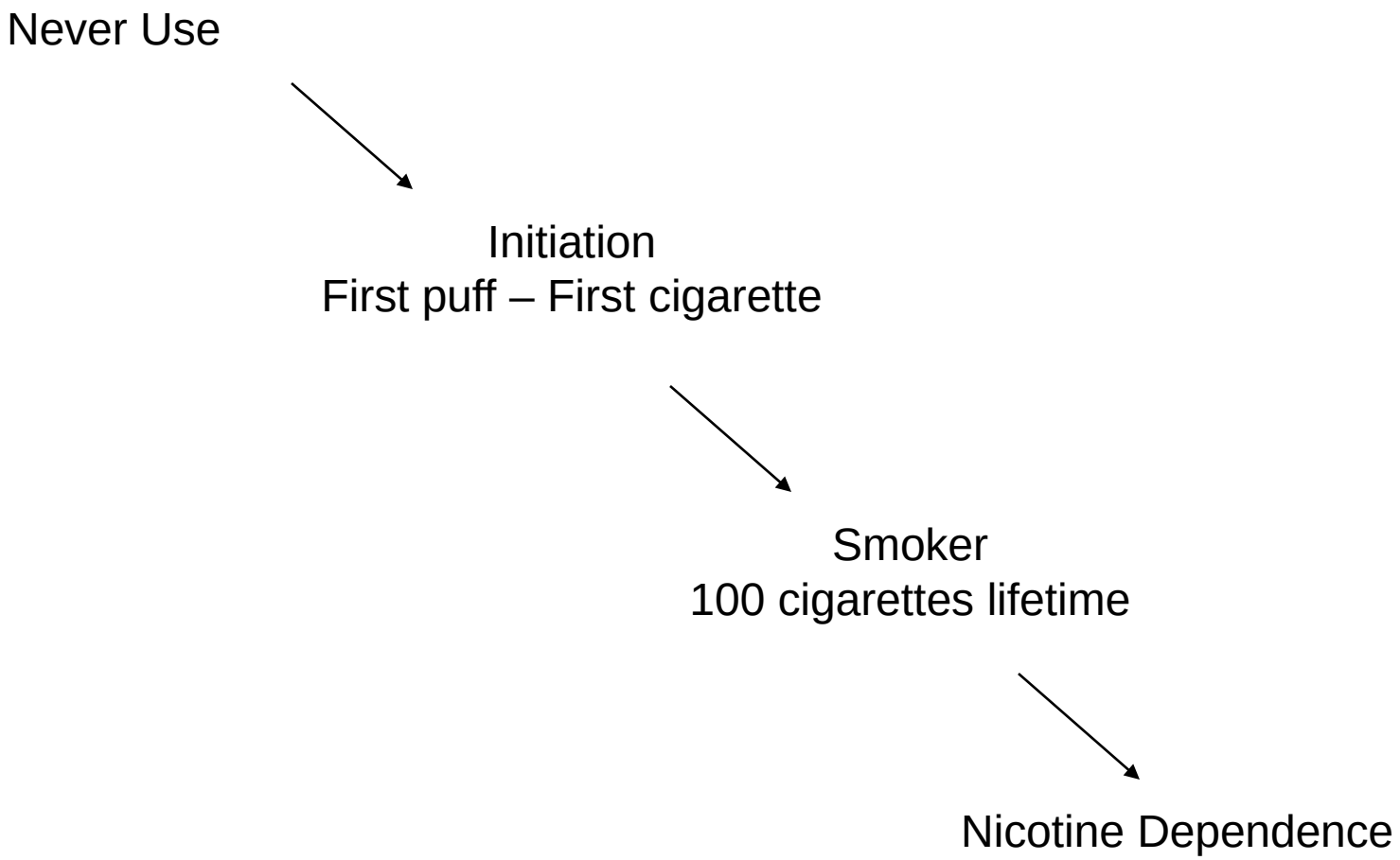


Smoker
100 cigarettes lifetime

Model of Nicotine Dependence - A many step process



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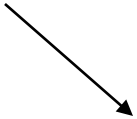

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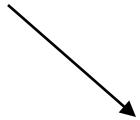

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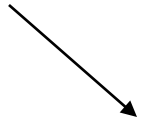

Nicotine Dependence

Environmental and genetic factors influence each step in the development of dependence.

Model of Nicotine Dependence - A many step process

Never Use

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First puff – First cigarette

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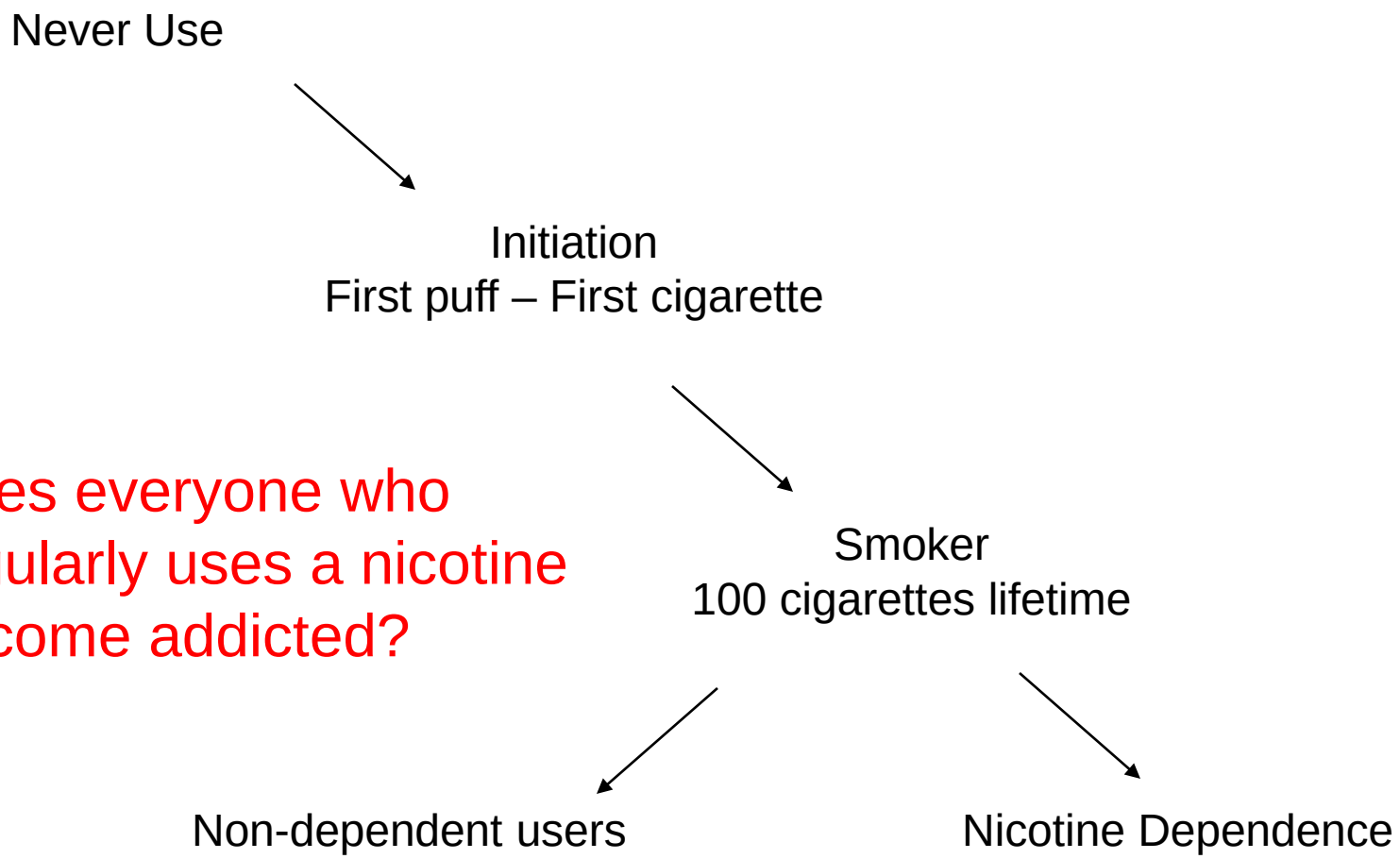
100 cigarettes lifetime

Nicotine Dependence

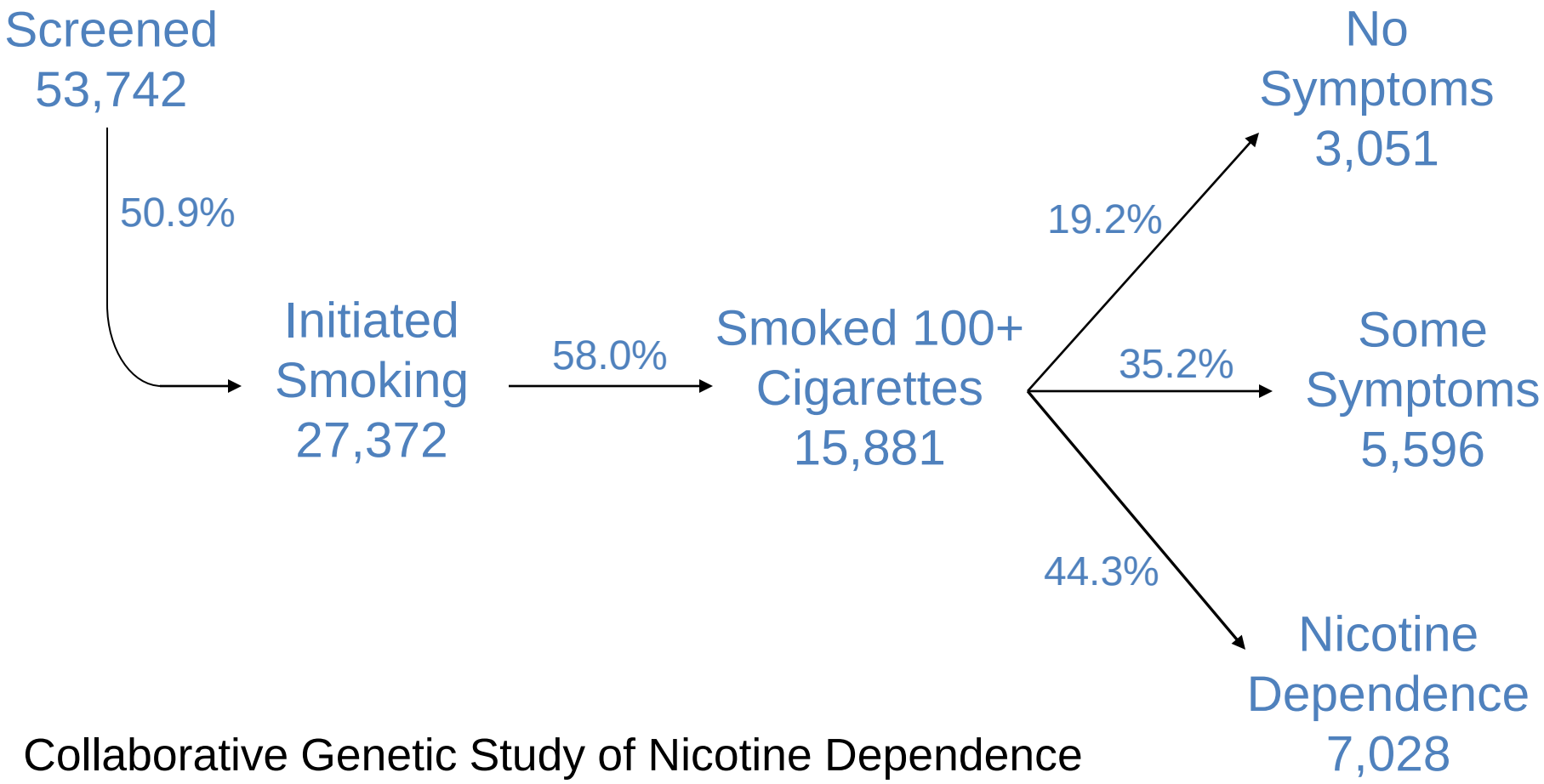
Does everyone who regularly uses a nicotine become addicted?

Model of Nicotine Dependence - A many step process



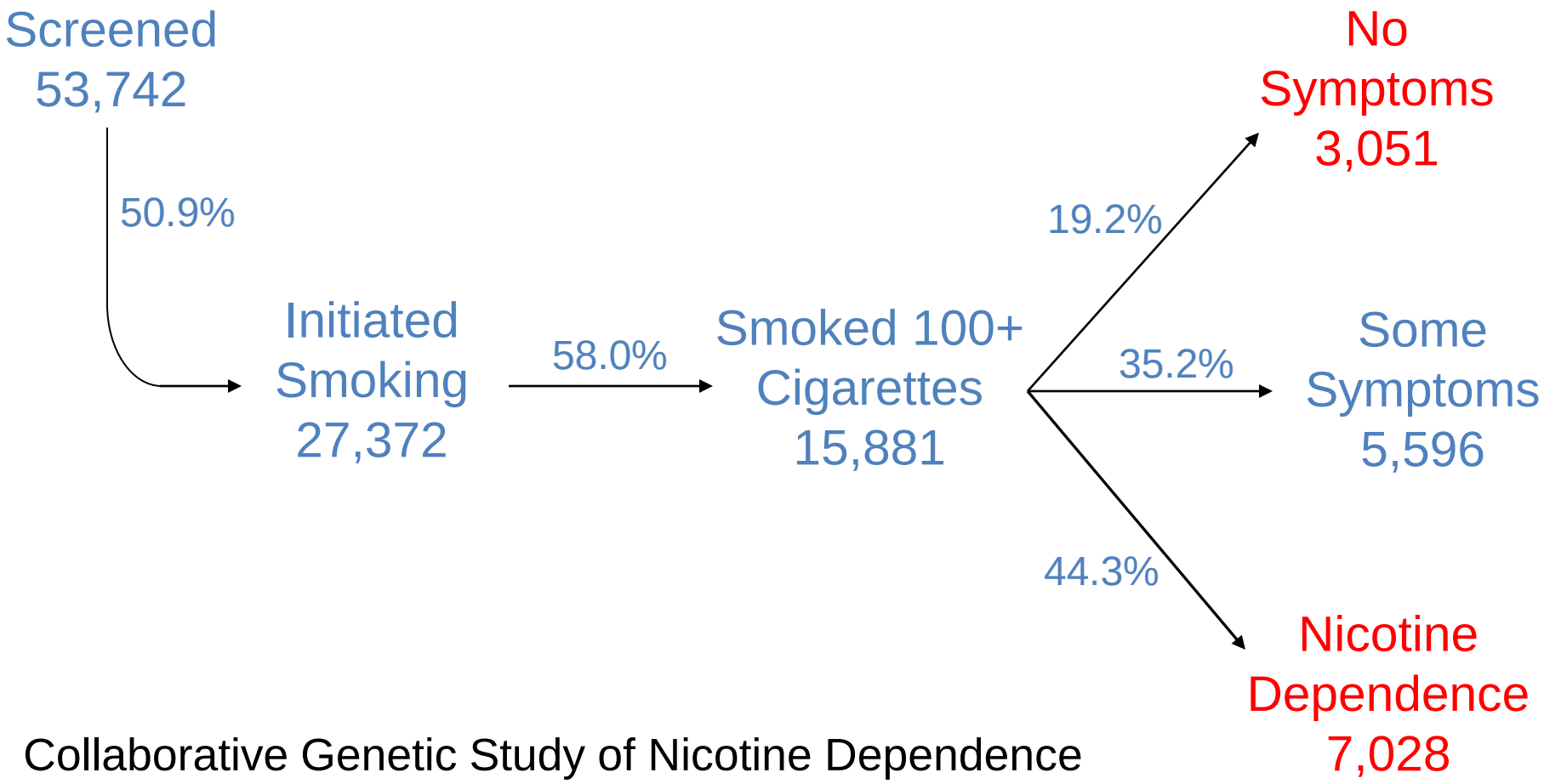
Does everyone who regularly uses a nicotine become addicted?

U.S. Population Screening and Nicotine Dependence



Collaborative Genetic Study of Nicotine Dependence

U.S. Population Screening and Nicotine Dependence



Collaborative Genetic Study of Nicotine Dependence

nature genetics

Sequence variants at *CHRNB3–CHRNA6* and *CYP2A6* affect smoking behavior

Thorgeirsson et al., 2010

Smoking is a common risk factor for many diseases[1]. We conducted genome-wide association meta-analyses for the number of cigarettes smoked per day (CPD) in smokers ($n = 31,266$) and smoking initiation ($n = 46,481$) using samples from the ENGAGE Consortium. In a second stage, we tested selected SNPs with *in silico* replication in the Tobacco and Genetics (TAG) and Glaxo Smith Kline (Ox-GSK) consortia cohorts ($n = 45,691$ smokers) and assessed some of those in a third sample of European ancestry ($n = 9,040$). Variants in three genomic regions associated with CPD ($P < 5 \times 10^{-8}$), including previously identified SNPs at 15q25 represented by rs1051730[A] (effect size = 0.80 CPD, $P = 2.4 \times 10^{-69}$), and SNPs at 19q13 and 8p11, represented by rs4105144[C] (effect size = 0.39 CPD, $P = 2.2 \times 10^{-12}$) and rs6474412-T (effect size = 0.29 CPD, $P = 1.4 \times 10^{-8}$), respectively. Among the genes at the two newly associated loci are genes encoding nicotine-metabolizing enzymes (*CYP2A6* and *CYP2B6*) and nicotinic acetylcholine receptor subunits (*CHRNB3* and *CHRNA6*), all of which have been highlighted in previous studies of smoking and nicotine dependence[2–4]. Nominal associations with lung cancer were observed at both 8p11 (rs6474412[T], odds ratio (OR) = 1.09, $P = 0.04$) and 19q13 (rs4105144[C], OR = 1.12, $P = 0.0006$).

Smoking behavior and nicotine dependence are considered to be influenced by genetics[5]. Although environmental influences play a strong role in the initiation of smoking[6], the heritability of smoking persistence, smoking quantity and nicotine dependence has been high in most twin studies[6,7]. Sequence variants within a cluster of genes on chromosome 15q25 that encode nicotinic acetylcholine receptors (nAChRs) have recently been shown to associate with CPD[8,9], nicotine dependence[3,8] and smoking-related diseases such as lung cancer[8,10,11], peripheral arterial disease (PAD)[8] and chronic obstructive pulmonary disease (COPD)[12].

To search for additional common variants associated with smoking behavior, we performed meta-analyses of genome-wide association (GWA) studies, mainly using samples of European ancestry from the ENGAGE consortium (see URLs) and focusing on two smoking phenotypes: CPD and smoking initiation. The smoking initiation analysis was performed with a total of 30,431 ever-smokers and 16,050 never-smokers, using data from 12 GWA studies: Corogene, deCODE,

nature genetics

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Genome-wide meta-analyses identify multiple loci associated with smoking behavior

Furberg et al., 2010

The Tobacco and Genetics Consortium*

Consistent but indirect evidence has implicated genetic factors in smoking behavior[1,2]. We report meta-analyses of several smoking phenotypes within cohorts of the Tobacco and Genetics Consortium (n = 74,053). We also partnered with the European Network of Genetic and Genomic Epidemiology (ENGAGE) and Oxford-GlaxoSmithKline (Ox-GSK) consortia to follow up the 15 most significant regions (n > 140,000). We identified three loci associated with number of cigarettes smoked per day. The strongest association was a synonymous 15q25 SNP in the nicotinic receptor gene *CHRNA3* (rs1051730[A], β = 1.03, standard error (s.e.) = 0.053, $P = 2.8 \times 10^{-73}$). Two 10q25 SNPs (rs1329650[G], β = 0.367, s.e. = 0.059, $P = 5.7 \times 10^{-10}$; and rs1028936[A], β = 0.446, s.e. = 0.074, $P = 1.3 \times 10^{-9}$) and one 9q13 SNP in *EGLN2* (rs3733829[G], β = 0.333, s.e. = 0.058, $P = 1.0 \times 10^{-8}$) also exceeded genome-wide significance for cigarettes per day. For smoking initiation, eight SNPs exceeded genome-wide significance, with the strongest association at a nonsynonymous SNP in *BDNF* on chromosome 11 (rs6265[C], odds ratio (OR) = 1.06, 95% confidence interval (CI) 1.04–1.08, $P = 1.8 \times 10^{-8}$). One SNP located near *DBH* on chromosome 9 (rs3025343[G], OR = 1.12, 95% CI 1.08–1.18, $P = 3.6 \times 10^{-8}$) was significantly associated with smoking cessation.

nature genetics

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Meta-analysis and imputation refines the association of 15q25 with smoking quantity

Liu et al., 2010

Smoking is a leading global cause of disease and mortality[1]. We established the Oxford-GlaxoSmithKline study (Ox-GSK) to perform a genome-wide meta-analysis of SNP association with smoking-related behavioral traits. Our final data set included 41,150 individuals drawn from 20 disease, population and control cohorts. Our analysis confirmed an effect on smoking quantity at a locus on 15q25 ($P = 9.45 \times 10^{-19}$) that includes *CHRNA5*, *CHRNA3* and *CHRNB4*, three genes encoding neuronal nicotinic acetylcholine receptor subunits. We used data from the 1000 Genomes project to investigate the region using imputation, which allowed for analysis of virtually all common SNPs in the region and offered a fivefold increase in marker density over HapMap2 (ref. 2) as an imputation reference panel. Our fine-mapping approach identified a SNP showing the highest significance, rs55853698, located within the promoter region of *CHRNA5*. Conditional analysis also identified a secondary locus (rs6495308) in *CHRNA3*.

Smoking behavior and nicotine dependence are multifactorial traits with substantial genetic influences[3]. There is an urgent need to better understand the molecular neurobiology of nicotine dependence in order to design targeted, more effective therapies[4]. Recently, genome-wide association studies (GWAS) have established one locus associated with nicotine dependence and smoking quantity, which implicates a cluster of three genes, *CHRNA5*, *CHRNA3* and *CHRNB4* on chromosome 15q25, which encode neuronal nicotinic acetylcholine receptor subunits[5–9]. This locus is also associated with lung cancer[8,10,11], peripheral arterial disease[8] and chronic obstructive pulmonary disease and lung function[12].

Table 1 Association of markers in four chromosomal regions with CPD

	Allele					Combined[d]				
SNP	Effect	Other	Freq.	Chr.	Position	*n*	Effect (s.e.m.)	*P*	P_{het}	I^2
rs1051730	A	G	0.339	15q25	76,681,394	76,972	0.80 (0.05)	2.4×10^{-69}	0.035	32
rs6474412	T	C	0.784	8p11	42,669,655	84,956	0.29 (0.05)	1.4×10^{-8}	0.24	13
rs13280604	A	G	0.784	8p11	42,678,743	76,670	0.31 (0.05)	1.3×10^{-8}	0.24	14
rs215614	G	A	0.356	7p14	32,313,860	86,259	0.22 (0.04)	2.1×10^{-7}	0.018	34
rs215605	G	T	0.357	7p14	32,303,490	77,012	0.26 (0.04)	5.4×10^{-9}	0.12	22
rs7937	T	C	0.560	19q13	45,994,546	86,319	0.24 (0.04)	2.4×10^{-9}	0.45	1
rs1801272	A	T	0.961	19q13	46,046,373	66,380	0.68 (0.18)	1.1×10^{-4}	0.50	0
rs4105144	C	T	0.704	19q13	46,050,464	83,317	0.39 (0.06)	2.2×10^{-12}	0.51	0
rs7260329	G	A	0.687	19q13	46,213,478	86,092	0.20 (0.04)	5.5×10^{-6}	0.12	21

Thorgeirsson et al., 2010

Genetic Association with Cigarettes per Day
A Proxy for Nicotine Dependence

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Strongest associations are nicotinic receptors and nicotine metabolizing genes.

Thorgeirsson et al., 2010

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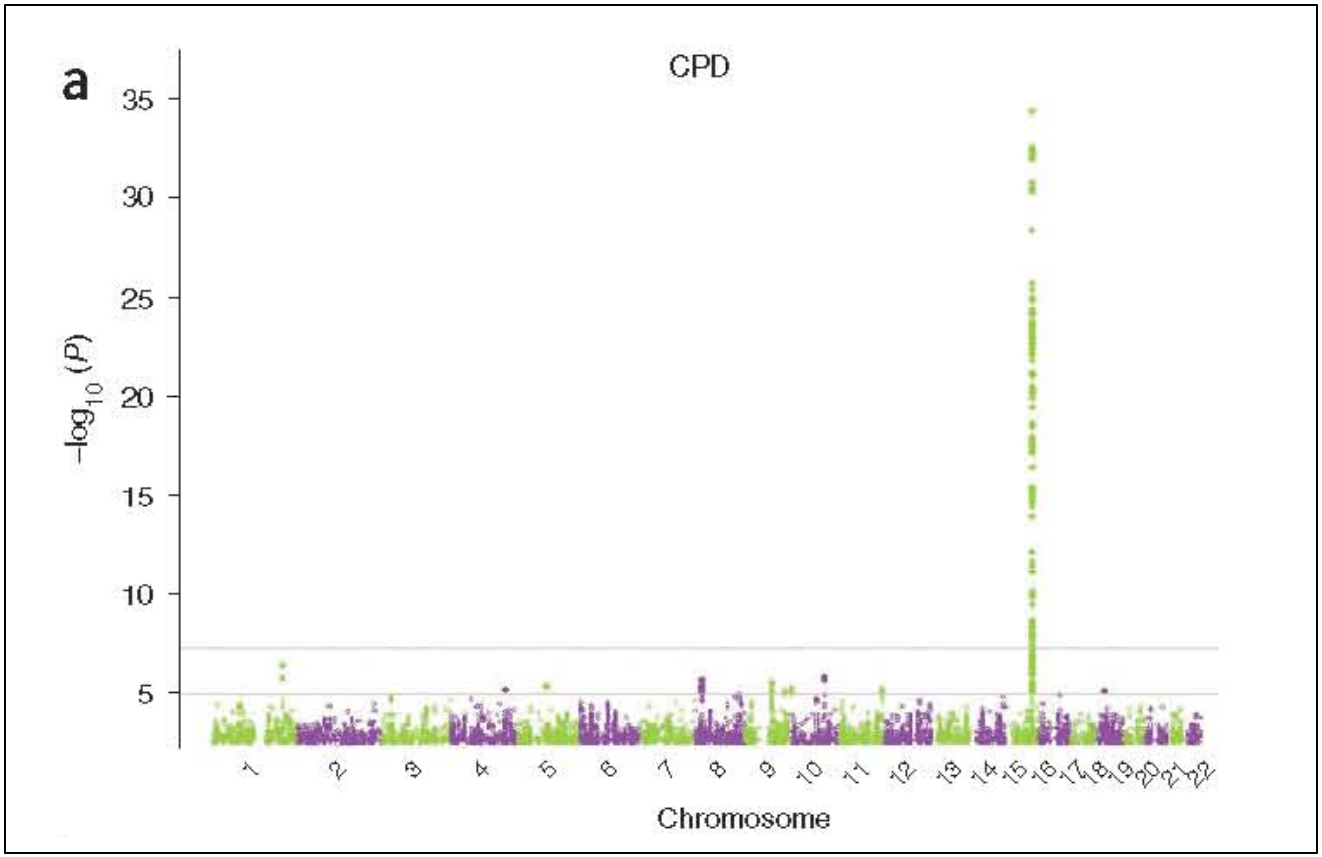
rs7260329	G	A	0.687	19q13	46,213,478	86,092	0.20 (0.04)	5.5×10^{-6}	0.12	21

rs1051730 Chromosome 15q25 N=76,972 Effect= 0.80 *p= 2.4 x 10^{-69}*

Thorgeirsson et al., 2010

Chromosome 15 – the strongest genetic risk

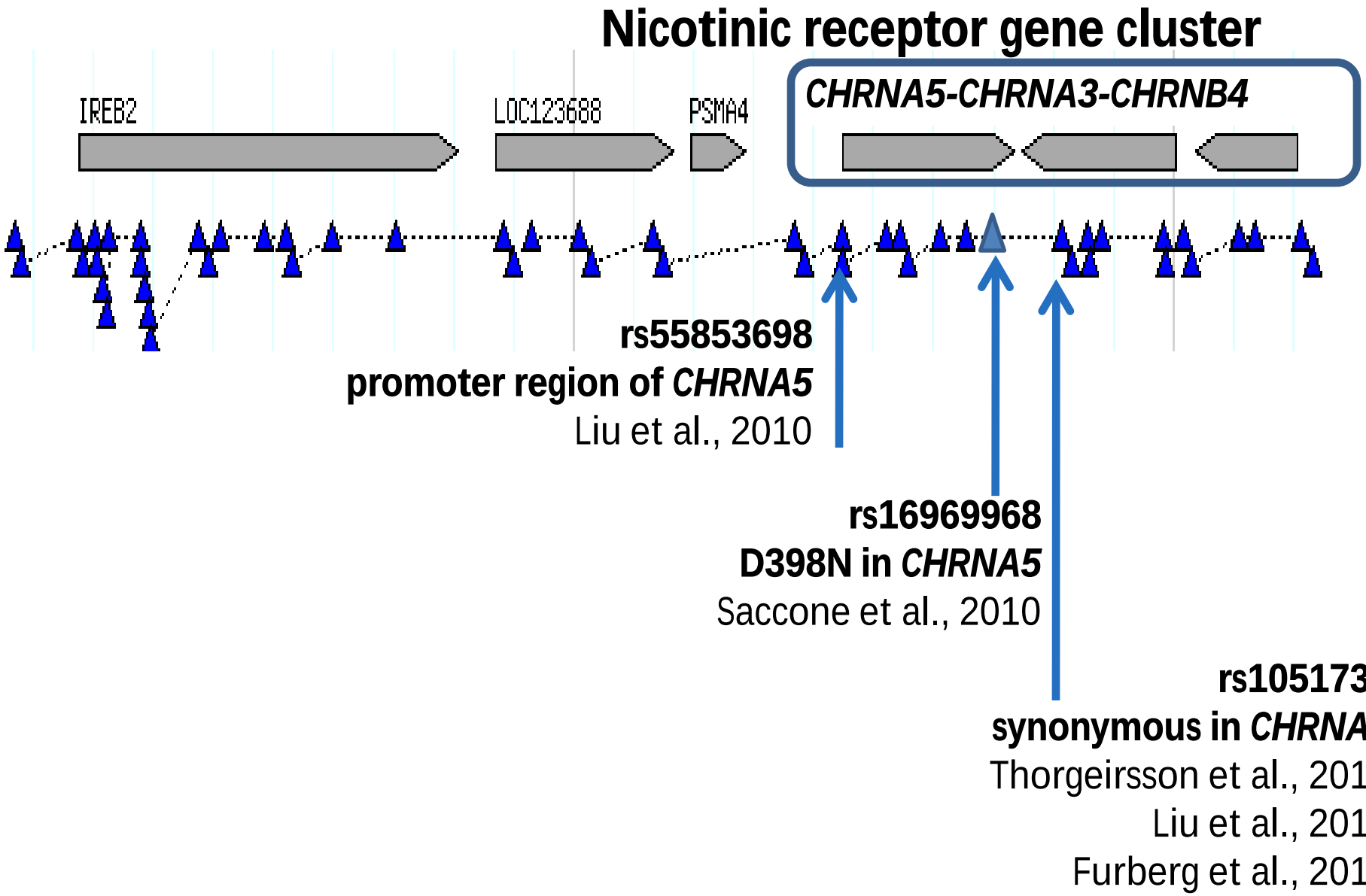
Genome Wide Association with Cigarettes per Day
A Proxy for Nicotine Dependence



TAG Consortium, 2010 Nature Genetics

Top meta-analysis results Locus A chromosome 15

52 SNPs correlated with rs16969968 ($r^2 \geq 0.7$) in 1000 Genomes CEU



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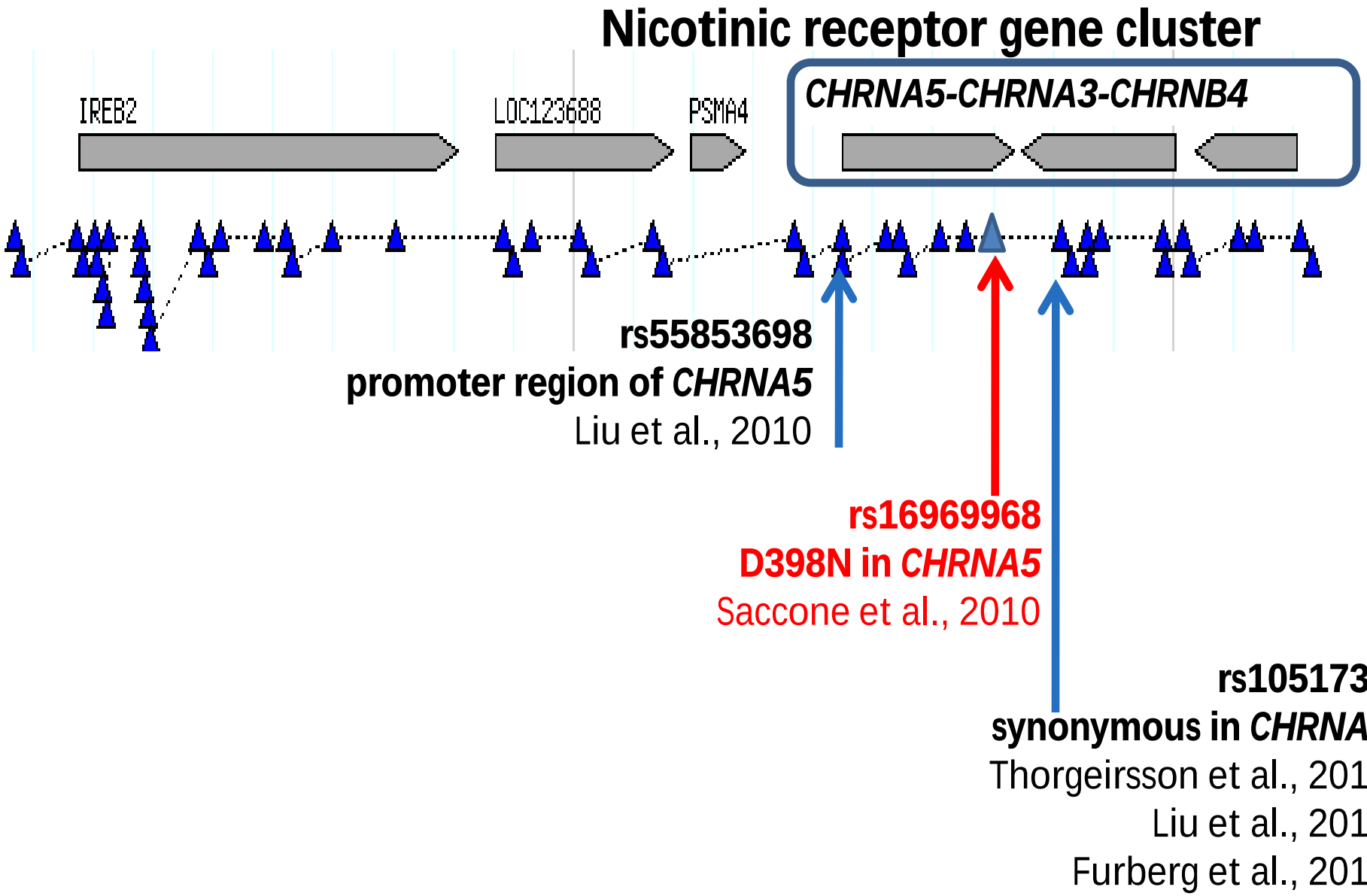
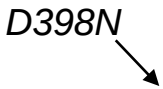


Comparative sequence analysis

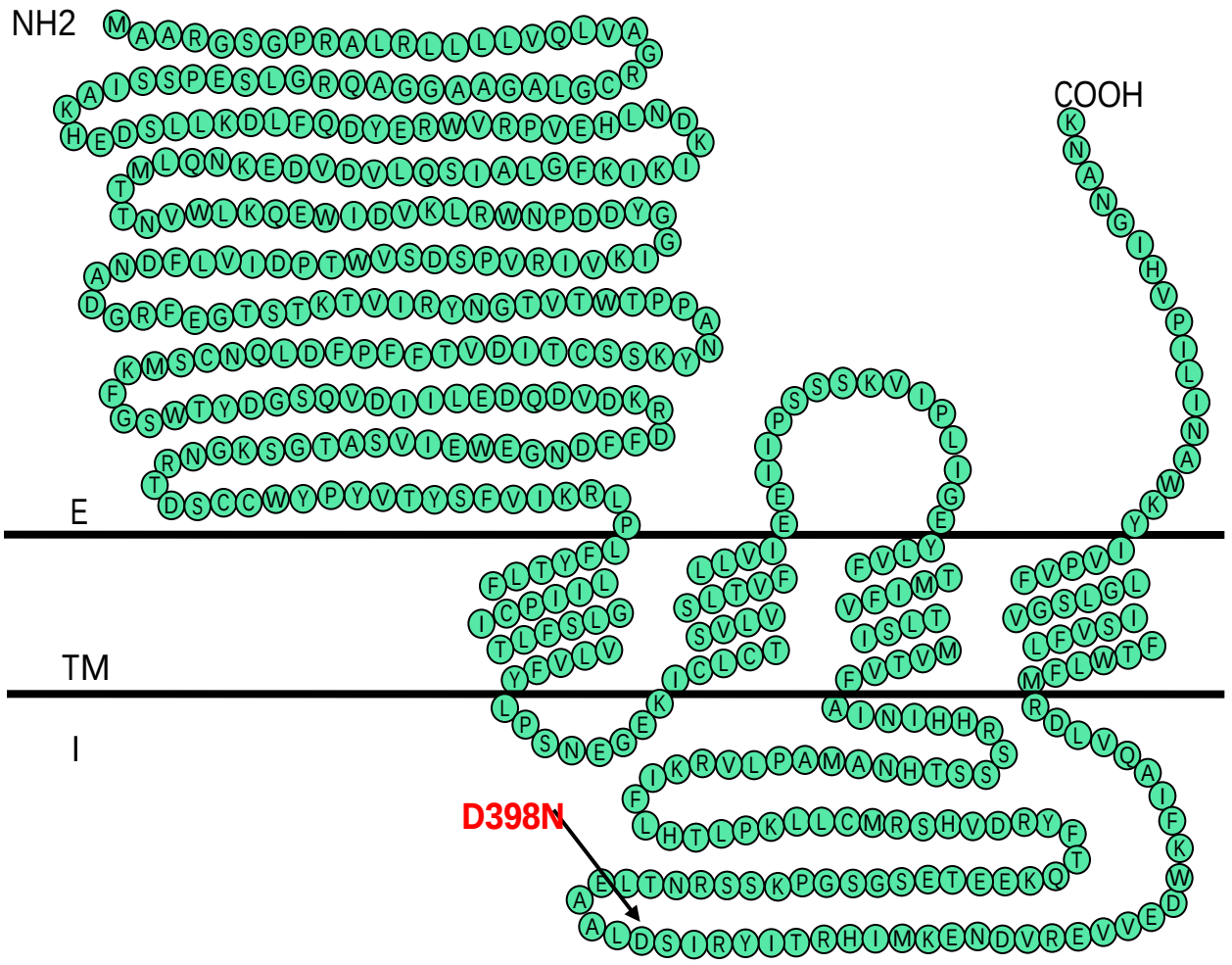
The amino acid change from aspartate to asparagine (D398N) in the •5 nicotinic receptor is caused by SNP rs16969968. It is a non-conservative change.

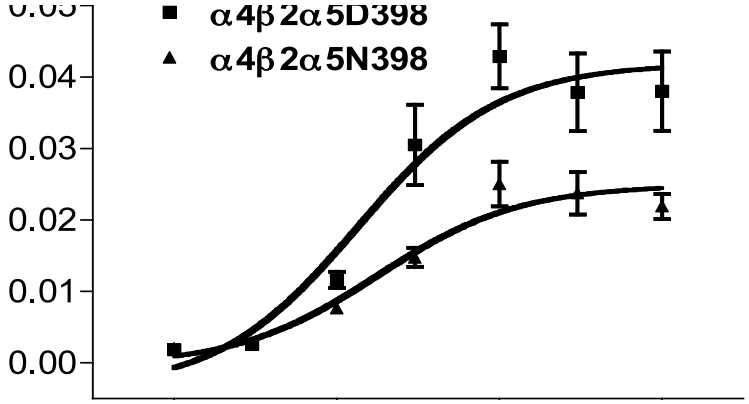


EETESGSGPKSSRNTLEAAL*D*SIRYITRHIMKENDVREVVEDW	**Homo sapiens**
EETESGSGPKSSRNTLEAALDSVRCITRHIMKENDVREVVEDW	Pan troglodytes
EQTGSGGGPESSRNTMEAALDSIRYITRHIVKENAVREVVEDW	Saimiri boliviensis
EEARSSRGPRSSRNALEAALDSVRYITRHVMKETDVREVVEDW	Bos taurus
REEAESGAGPKSRNTLEAALDCIRYITRHVVKENDVREVVEDW	Rattus norvegicus
REEAEKDGGPKSRNTLEAALDCIRYITRHVVKENDVREVVEDW	Mus musculus
EEKGNMSGSESSRNTLEAALDSIRYITRHVMKENEVREVVEDW	Gallus gallus

Bierut et al., 2008

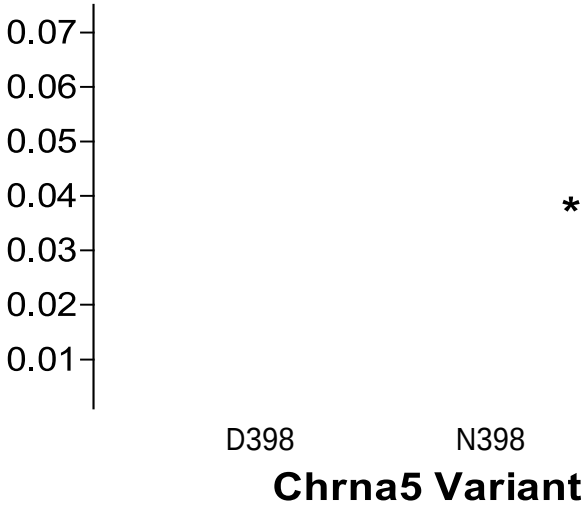
rs16969968 a non-synonymous coding change in the intracellular domain of CHRNA5





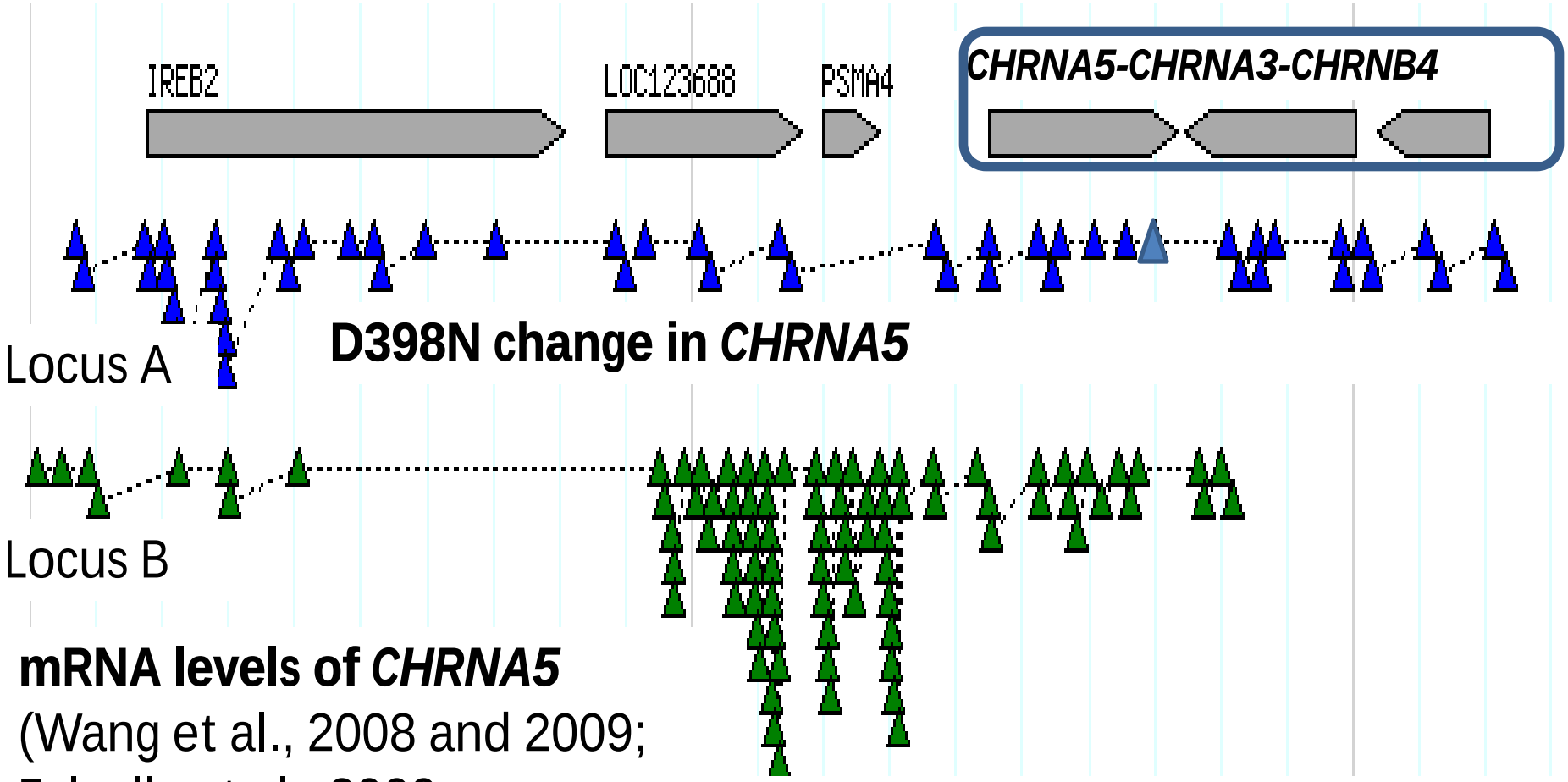
Response (L/L max)

The amino acid change alters receptor function.



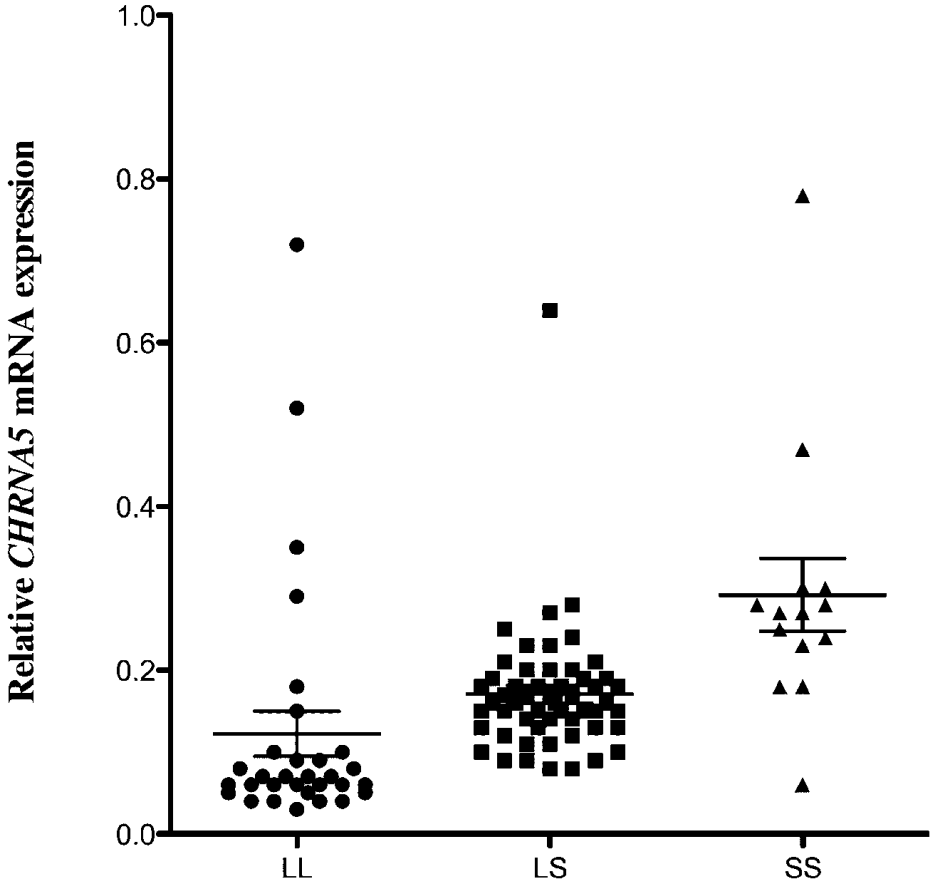
Bierut et al., 2008
From the laboratory of Jerry Stitzel

Targeted SNPs based on biological function



mRNA levels of *CHRNA5*
(Wang et al., 2008 and 2009;
Falvella et al., 2009;
Smith et al., 2010)

mRNA expression of CHRNA5
An endophenotype



Minor allele of rs588765 is associated with increased mRNA expression of *CHRNA5* in human frontal cortex.

This SNP explains 42% of the variance in mRNA expression.

Wang et al., 2009a
Wang et al., 2009b
From the lab of Alison Goate

$p=1.11x10^{-9}$

The bars represent mean ± SD of *CHRNA5* mRNA expression.

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Multiple Independent Loci at Chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD

ABSTRACT

Recently, genetic association findings for nicotine dependence, smoking behavior and smoking-related diseases converged to implicate the 15q25.1 region, which includes the CHRNA5-CHRNA3-CHRNB4 cholinergic nicotinic receptor subunit genes. In particular, association with the nonsynonymous CHRNA5 SNP rs16969968 and correlates has been replicated in several independent studies. Extensive genotyping of this region has suggested additional statistically distinct signals for nicotine dependence, tagged by r578776 and rs588765. As part of the consortium for Genetic Analysis of Smoking Phenotypes (CGASP), our goal was to elucidate the associations among these markers and dichotomous smoking quantity (heavy versus light smoking), lung cancer, and chronic obstructive pulmonary disease (COPD). We performed a meta-analysis across 34 datasets of

Saccone et al., 2010 in press

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ABSTRACT

Recently, genetic association findings for nicotine dependence, smoking behavior

Meta-analysis across 34 datasets
38,617 smokers who were assessed for cigarettes-per-day,
7,700 lung cancer cases and 5,914 lung-cancer-free controls, and
2,614 COPD cases and 3,568 COPD-free controls

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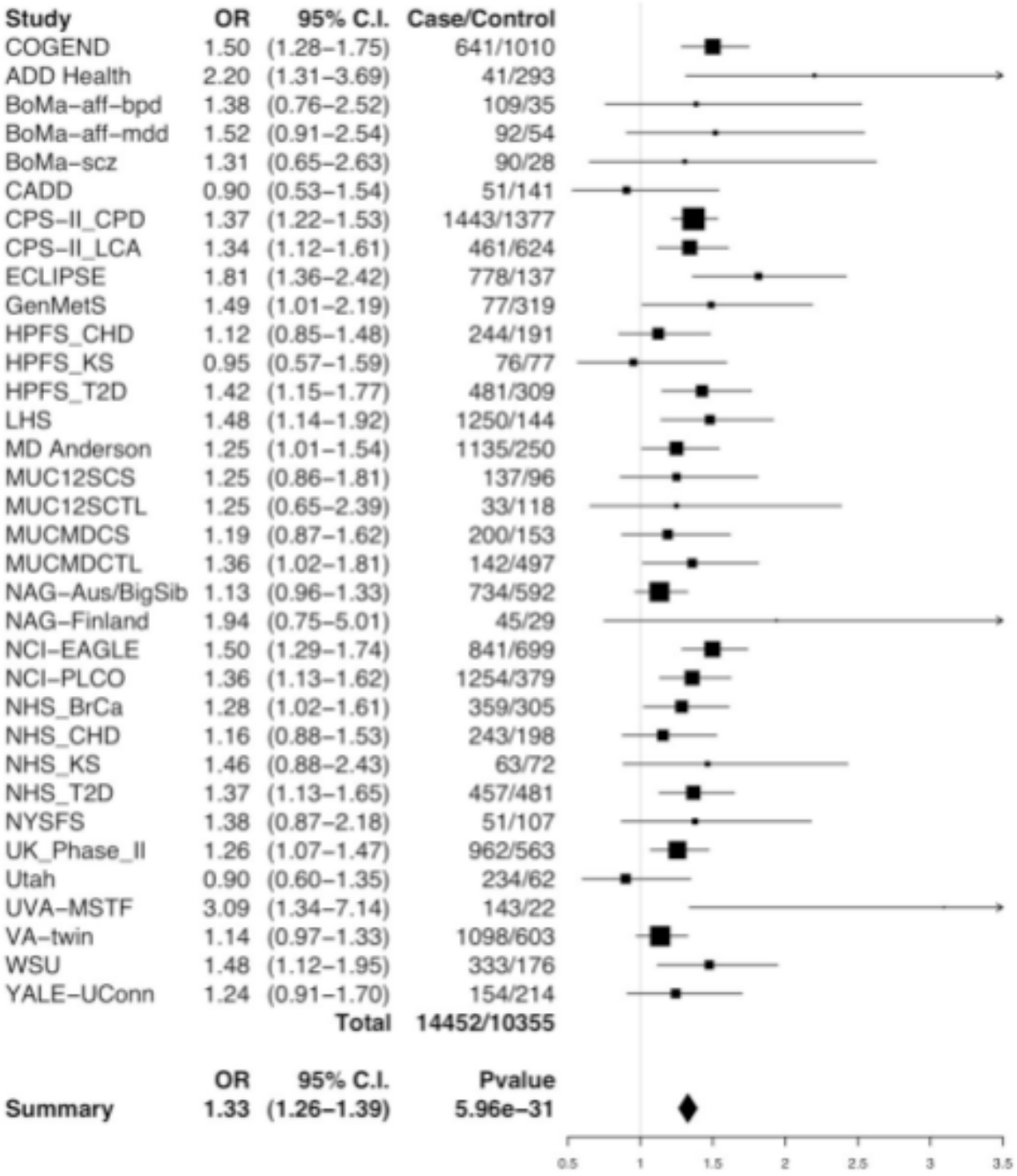
rs16969968	OR = 1.33	$p = 5.96 \times 10^{-31}$
rs588765	OR = 1.17	$p = 6.03 \times 10^{-9}$

Saccone et al., 2010



Similar genetic risk seen across studies recruited for a variety of conditions such as diabetes, hypertension, cancer, schizophrenia.

Saccone et al., 2010
Plos Genetics

Two distinct variants are associated with smoking

- Joint analysis:

  locus A (rs16969968): $p = 3.52 \times 10^{-36}$, OR = 1.47

  locus B (rs588765): $p = 6.03 \times 10^{-09}$, OR = 1.17

  “Genome-wide significant”

Two distinct variants are associated with smoking

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Two distinct variants are associated with smoking

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  locus A (rs16969968): p = 3.52 x 10^{-36}, OR = 1.47

  locus B (rs588765): p = 6.03 x 10^{-09}, OR = 1.17

  "Genome-wide significant"

- This biologically relevant locus has a distinct, highly significant effect on smoking; connects •*5*-mRNA levels to smoking behavior

Two distinct variants are associated with smoking

- Joint analysis:

  locus A (rs16969968): $p = 3.52 \times 10^{-36}$, OR = 1.47

  locus B (rs588765): $p = 6.03 \times 10^{-09}$, OR = 1.17

  "Genome-wide significant"

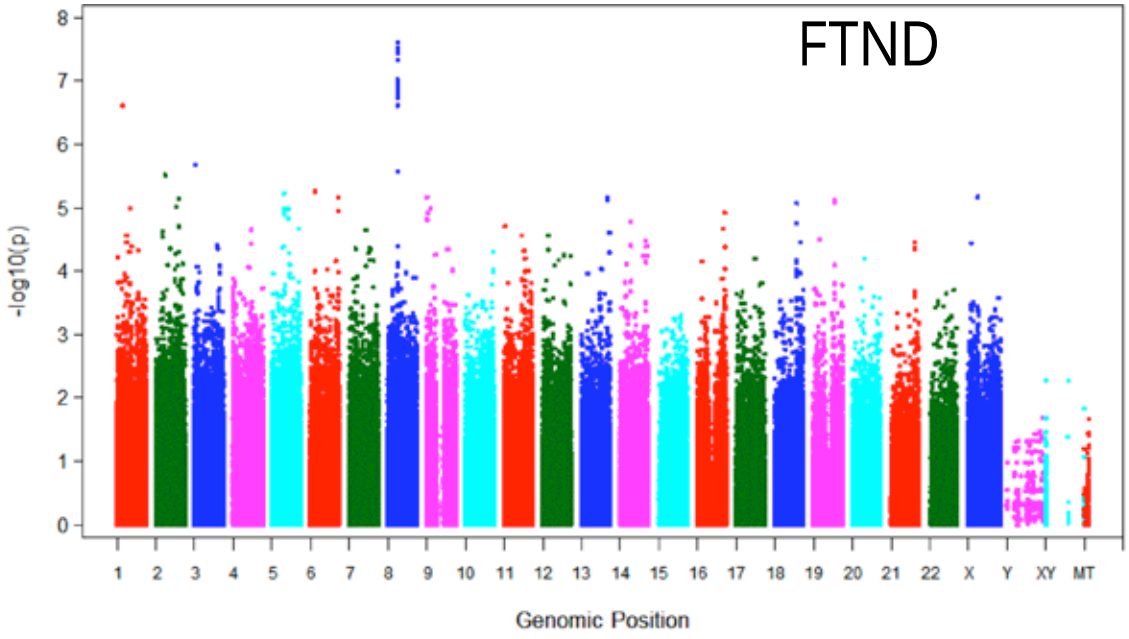
- This biologically relevant locus has a distinct, highly significant effect on smoking; connects •*5*-mRNA levels to smoking behavior

Lower smoking risk — Higher smoking risk

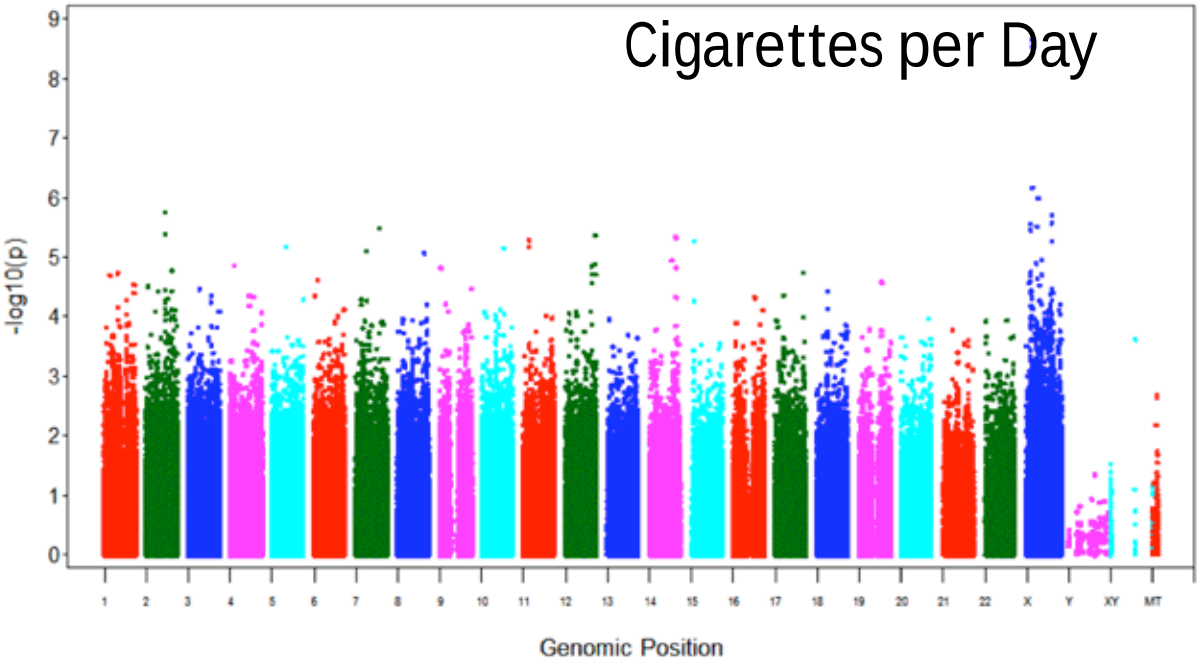
Lower • 5 mRNA level — Higher • 5 mRNA level

Other interesting facts

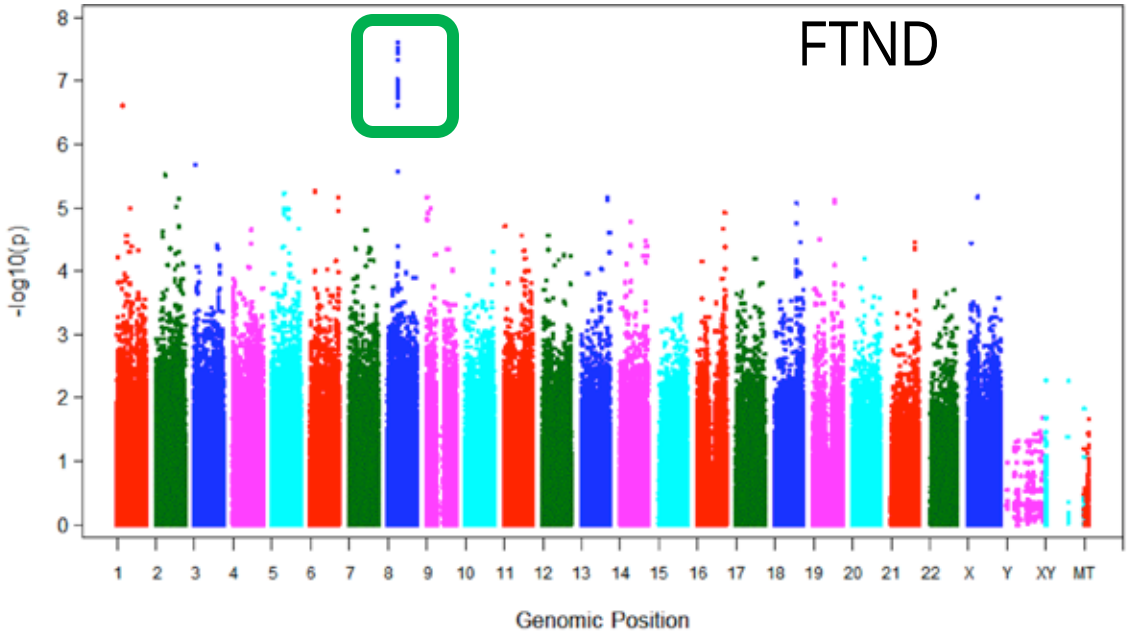
- This chromosome 15 region is related to the risk of cocaine dependence – but an opposite effect.
  - Grucza et al., 2008 and Sherva et al., 2010



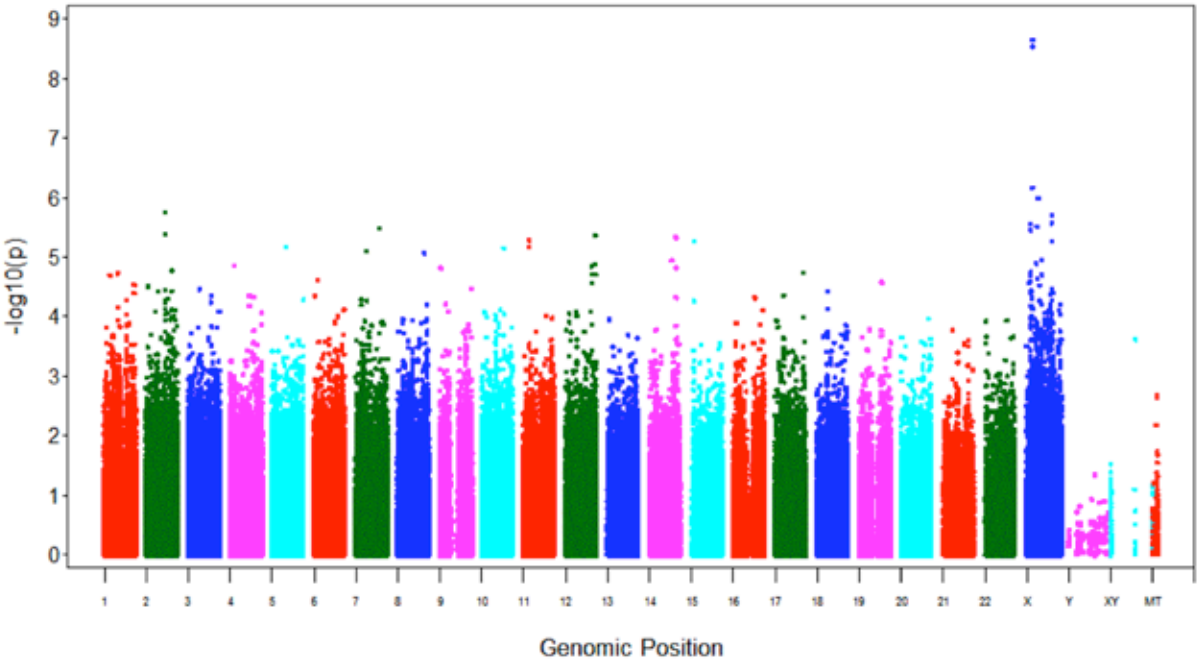
Phentoype Counts



From John Rice et al

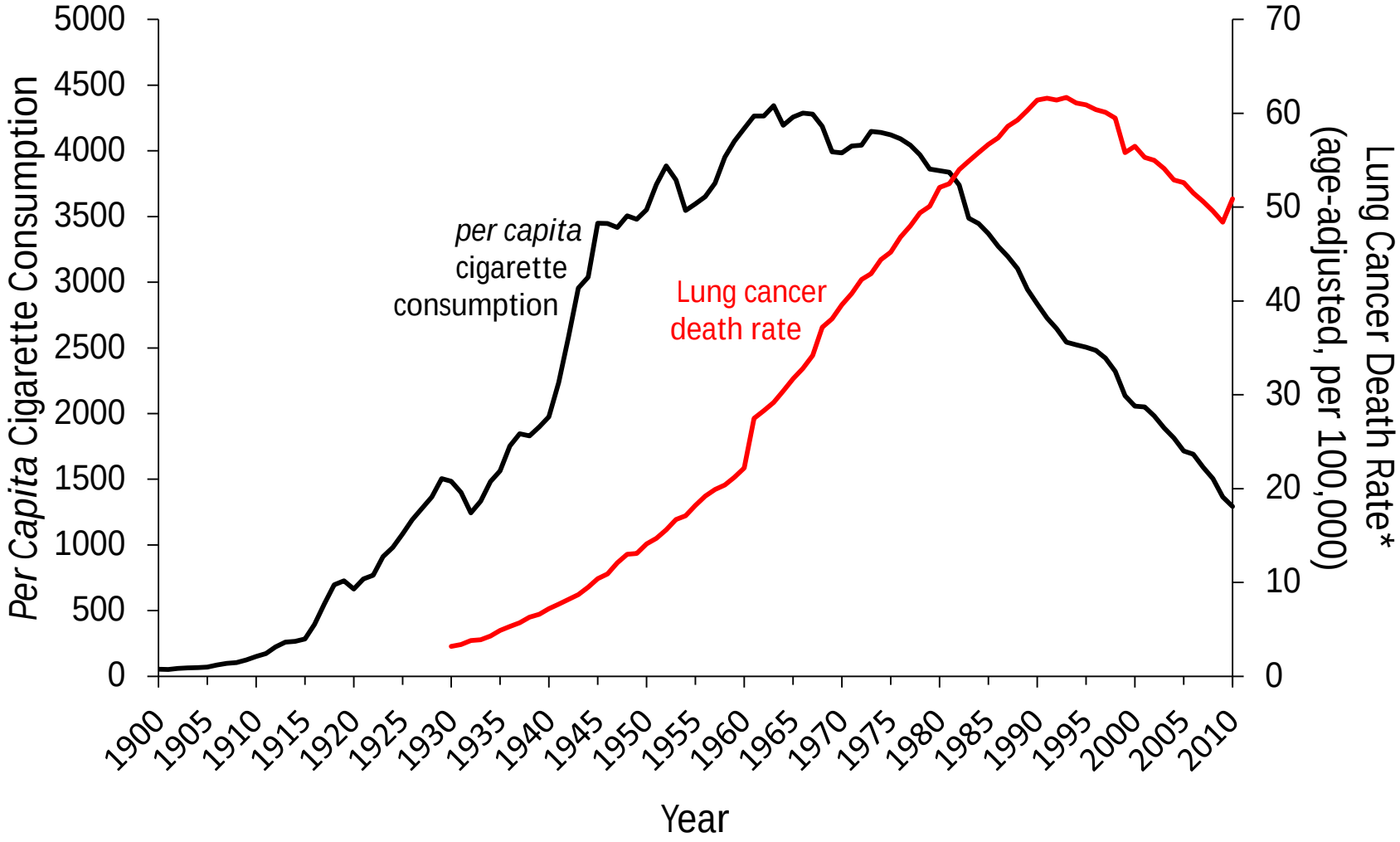


Phentoype Counts



From John Rice et al

US Cigarette Use vs. Lung Cancer Deaths, 1900 - 2010



Death rates sources: Public-use data files, National Vital Statistics System, National Center for Health Statistics, Centers for Disease Control and Prevention; and Jemal et al., CA Cancer J Clin, 2010. Cigarette consumption sources: Tobacco Outlook Report, Economic Research Service, US Department of Agriculture; and Alcohol and Tobacco Trade and Tax Bureau, US Department of Treasury.

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Nature, 2008

Thorgeir E. Thorgeirsson[1]*, Frank Geller[1]*, Patrick Sulem[1]*, Thorunn Rafnar[1]*, Anna Wiste[1,2], Kristinn P. Magnusson[1], Andrei Manolescu[1], Gudmar Thorleifsson[1], Hreinn Stefansson[1], Andres Ingason[1], Simon N. Stacey[1], Jon T. Bergthorsson[1], Steinunn Thorlacius[1], Julius Gudmundsson[1], Thorlakur Jonsson[1], Margret Jakobsdottir[1], Jona Saemundsdottir[1], Olof Olafsdottir[1], Larus J. Gudmundsson[1], Gyda Bjornsdottir[1], Kristleifur Kristjansson[1], Halla Skuladottir[3], Helgi J. Isaksson[4], Tomas Gudbjartsson[5], Gregory T. Jones[8], Thomas Mueller[9], Anders Gottsäter[10], Andrea Flex[11], Katja K. H. Aben[12,13], Femmie de Vegt[12], Peter F. A. Mulders[14], Dolores Isla[15], Maria J. Vidal[15], Laura Asin[16], Berta Saez[17], Laura Murillo[18], Thorsteinn Blondal[19], Halldor Kolbeinsson[6], Jon G. Stefansson[6], Ingunn Hansdottir[20], Valgerdur Runarsdottir[20], Roberto Pola[11,21], Bengt Lindblad[10], Andre M. van Rij[8], Benjamin Dieplinger[9], Meinhard Haltmayer[9], Jose I. Mayordomo[15,16,17], Lambertus A. Kiemeney[12,13,14], Stefan E. Matthiasson[22], Hogni Oskarsson[23], Thorarinn Tyrfingsson[20], Daniel F. Gudbjartsson[1], Jeffrey R. Gulcher[1], Steinn Jonsson[7], Unnur Thorsteinsdottir[1,22], Augustine Kong[1] & Kari Stefansson[1,22]

A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25

Nature, 2008

Rayjean J. Hung[1,2]*, James D. McKay[1]*, Valerie Gaborieau[1], Paolo Boffetta[1], Mia Hashibe[1], David Zaridze[3], Anush Mukeria[3], Neonilia Szeszenia-Dabrowska[4], Jolanta Lissowska[5], Peter Rudnai[6], Eleonora Fabianova[7], Dana Mates[8], Vladimir Bencko[9], Lenka Foretova[10], Vladimir Janout[11], Chu Chen[12], Gary Goodman[12], John K. Field[13], Triantafillos Liloglou[13], George Xinarianos[13], Adrian Cassidy[13], John McLaughlin[14], Geoffrey Liu[15], Steven Narod[16], Hans E. Krokan[17], Frank Skorpen[17], Maiken Bratt Elvestad[17], Kristian Hveem[17], Lars Vatten[17], Jakob Linseisen[18], Françoise Clavel-Chapelon[19], Paolo Vineis[20,21], H. Bas Bueno-de-Mesquita[22], Eiliv Lund[23], Carmen Martinez[24], Sheila Bingham[25], Torgny Rasmuson[26], Pierre Hainaut[1], Elio Riboli[20], Wolfgang Ahrens[27], Simone Benhamou[28,29], Pagona Lagiou[30], Dimitrios Trichopoulos[30], Ivana Holcátová[31], Franco Merletti[32], Kristina Kjaerheim[33], Antonio Agudo[34], Gary Macfarlane[35], Renato Talamini[36], Lorenzo Simonato[37], Ray Lowry[38], David I. Conway[39], Ariana Znaor[40], Claire Healy[41], Diana Zelenika[42], Anne Boland[42], Marc Delepine[42], Mario Foglio[42], Doris Lechner[42], Fumihiko Matsuda[42], Helene Blanche[43], Ivo Gut[42], Simon Heath[43], Mark Lathrop[42,43] & Paul Brennan[1]

Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1

Nature Genetics, 2008

Christopher I Amos[1], Xifeng Wu[1], Peter Broderick[2], Ivan P Gorlov[1], Jian Gu[1], Timothy Eisen[3], Qiong Dong[1], Qing Zhang[1], Xiangjun Gu[1], Jayaram Vijayakrishnan[2], Kate Sullivan[2], Athena Matakidou[2], Yufei Wang[2], Gordon Mills[4], Kimberly Doheny[5], Ya-Yu Tsai[5], Wei Vivien Chen[1], Sanjay Shete[1], Margaret R Spitz[1,6] & Richard S Houlston[2,6]

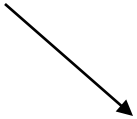
GENOMICS

When the smoke clears ...

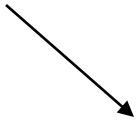
Stephen J. Chanock and David J. Hunter

Cessation-
The Final Step

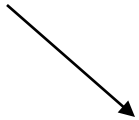
Never Use



Initiation
First puff – First cigarette



Smoker
100 cigarettes lifetime



Nicotine Dependence

Washington University

Laura Jean Bierut
Kathleen Bucholz
LiShiun Chen
Alison Goate
Sarah Hartz
Anthony Hinrichs
Pamela Madden
John Rice
Nancy Saccone
Scott Saccone
Jen Wang
Sarah Bertelsen
Sherri Fisher
Louis Fox
Tracey Richmond
Jaime Strickland

GENEVA Project

Funded by the
National Institute on Alcohol Abuse and Alcoholism
National Institute of Drug Abuse
National Cancer Institute
National Human Genome Research Institute

Michigan State University

Naomi Breslau

Research Triangle Institute

Eric Johnson

University of Minnesota

Dorothy Hatsukami

University of Michigan

Ovide Pomerleau

SRI International

Gary Swan

Queensland Australia

Nicholas Martin
Grant Montgomery

Perlegen Sciences

Dennis Ballinger
Karel Konvicka

American Cancer Society

Victoria Stevens

State University of New York Health Sciences Center – Brooklyn

Bernice Porjesz

Indiana University

Howard Edenberg
Tatiana Foroud
John Nurnberger, Jr.

University of California, San Diego

Marc Schuckit

University of Connecticut

Victor Hesselbrock

University of Iowa

Samuel Kuperman
John Kramer

Rutgers University

Jay Tischfield

Southwest Foundation

Laura Almasy

Phenotypic and genetic data are available to qualified investigators through the NIDA Genetics Consortium and dbGaP.