Genetics of Nicotine Addiction

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St. Louis, Missouri
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
Model of Nicotine Dependence - A many step process

Never Use
Model of Nicotine Dependence - A many step process

Never Use

Initiation
First puff – First cigarette
Model of Nicotine Dependence - A many step process

Never Use

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime
Model of Nicotine Dependence - A many step process

Never Use

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime

Nicotine Dependence
Model of Nicotine Dependence - A many step process

Never Use → Initiation → Smoker → Nicotine Dependence

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime

Nicotine Dependence

Environmental and genetic factors influence each step in the development of dependence.
Model of Nicotine Dependence - A many step process

Never Use

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime

Nicotine Dependence

Does everyone who regularly uses a nicotine become addicted?
Model of Nicotine Dependence - A many step process

Never Use

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime

Does everyone who regularly uses a nicotine become addicted?

Non-dependent users

Nicotine Dependence
U.S. Population Screening and Nicotine Dependence

Screened 53,742

50.9%

Initiated Smoking 27,372

58.0%

Smoked 100+ Cigarettes 15,881

19.2%

No Symptoms 3,051

35.2%

Some Symptoms 5,596

44.3%

Nicotine Dependence 7,028

Collaborative Genetic Study of Nicotine Dependence
U.S. Population Screening and Nicotine Dependence

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Nicotine Dependence 7,028

Collaborative Genetic Study of Nicotine Dependence
Sequence variants at CHRNβ3–CHRNA6 and CYP2A6 affect smoking behavior
Thorgeirsson et al., 2010

Smoking is a common risk factor for many diseases1. 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 GlaxoSmithKline (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 × 10^-8), including previously identified SNPs at 15q25 represented by rs1051730[A] (effect size = 0.80 CPD, P = 2.4 × 10^-62), and SNPs at 19q13 and 8p11, represented by rs4105144[C] (effect size = 0.39 CPD, P = 2.2 × 10^-12) and rs6474412[T] (effect size = 0.29 CPD, P = 1.4 × 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 (CHRNβ3 and CHRNA6), all of which have been highlighted in previous studies of smoking and nicotine dependence2-4. 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 genetics5. Although environmental influences play a strong role in the initiation of smoking5, the heritability of smoking persistence, smoking quantity and nicotine dependence has been high in most twin studies6,7. Sequence variants within a cluster of genes on chromosome 15q25 that encode nicotinic acetylcholine receptors (nAChRs) have recently been shown to associate with CPD8,9, nicotine dependence5,8 and smoking-related diseases such as lung cancer8,10,11, 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,
Sequence variants at CHRNA3–CHRNB3 and CYP2A6 affect smoking behavior

Thorgeirsson et al., 2010

Smoking is a common risk factor for many diseases. We conducted genome-wide association meta-analyses for the number of cigarettes smoked per day (n = 98,335) and smoking status (n = 97,667) from 11 European and North American cohorts. Genes in the CHRNA3/CHRNB3 and CYP2A6 loci were previously observed at both 8p11 (rs64774412[T], odds ratio (OR) = 1.09, \( P = 0.006 \)) and 19q13 (rs4105444[C], OR = 1.13, \( P = 0.0006 \)).

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

Furberg et al., 2010

Consistent but indirect evidence has implicated genetic factors in smoking behavior. 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], \( \beta = 1.03 \), standard error (s.e.) = 0.053, \( P = 2.8 \times 10^{-7} \)). Two 10q25 SNPs (rs1329650[G], \( \beta = 0.367 \), s.e. = 0.059, \( P = 5.7 \times 10^{-10} \), and rs1028936[A], \( \beta = 0.446 \), s.e. = 0.074, \( P = 1.3 \times 10^{-9} \)) and one 9q13 SNP in EGLN2 (rs3733829[G], \( \beta = 0.333 \), 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, \( P = 3.6 \times 10^{-6} \)) was significantly associated with smoking cessation.
Sequence variants at *CHRN*B3–*CHRNA*6 and *CYP2A6* affect smoking behavior

Smoking is a common risk factor for many diseases\(^1\). We conducted genome-wide association meta-analyses for the smoking status (\(n = 11,768\)) and smoking quantity (\(n = 7,432\)) from 20 studies in the Tobacco and Genetics Consortium (TGC*). Our meta-analyses identified novel variants associated with smoking status and the number of cigarettes smoked per day. Specifically, we observed an association of the variant rs410544149, located in the promoter region of *CHRN*A5. The conditional analysis also identified a secondary locus (rs6495308) in *CHRN*A3.

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

The Tobacco and Genetics Consortium*  

Consists of members of the Tobacco and Genetics Consortium Network and Oxford Genetics Network. The 15 members of the consortium have defined genotyping protocols and obtained high-quality genotype data from 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 *CHRN*A5, *CHRN*A3 and *CHRN*B4, 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 *CHRN*A5. Conditional analysis also identified a secondary locus (rs6495308) in *CHRN*A3.

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

Liu et al., 2010
### Table 1 Association of markers in four chromosomal regions with CPD

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect</th>
<th>Other</th>
<th>Freq.</th>
<th>Chr.</th>
<th>Position</th>
<th>$n$</th>
<th>Effect (s.e.m.)</th>
<th>$\rho$</th>
<th>$\rho_{het}$</th>
<th>$\rho$</th>
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<tbody>
<tr>
<td>rs1051730</td>
<td>A</td>
<td>G</td>
<td>0.339</td>
<td>15q25</td>
<td>76,681,394</td>
<td>76,972</td>
<td>0.80 (0.05)</td>
<td>$2.4 \times 10^{-69}$</td>
<td>0.03532</td>
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<tr>
<td>rs6474412</td>
<td>T</td>
<td>C</td>
<td>0.784</td>
<td>8p11</td>
<td>42,669,655</td>
<td>84,956</td>
<td>0.29 (0.05)</td>
<td>$1.4 \times 10^{-8}$</td>
<td>0.2413</td>
<td></td>
</tr>
<tr>
<td>rs13280604</td>
<td>A</td>
<td>G</td>
<td>0.784</td>
<td>8p11</td>
<td>42,678,743</td>
<td>76,670</td>
<td>0.31 (0.05)</td>
<td>$1.3 \times 10^{-8}$</td>
<td>0.2414</td>
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</tr>
<tr>
<td>rs215614</td>
<td>G</td>
<td>A</td>
<td>0.356</td>
<td>7p14</td>
<td>32,313,860</td>
<td>86,259</td>
<td>0.22 (0.04)</td>
<td>$2.1 \times 10^{-7}$</td>
<td>0.01834</td>
<td></td>
</tr>
<tr>
<td>rs215605</td>
<td>G</td>
<td>T</td>
<td>0.357</td>
<td>7p14</td>
<td>32,303,490</td>
<td>77,012</td>
<td>0.26 (0.04)</td>
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<td>0.1222</td>
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<tr>
<td>rs7937</td>
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<td>C</td>
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<td>45,994,546</td>
<td>86,319</td>
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<td>$2.4 \times 10^{-9}$</td>
<td>0.451</td>
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<tr>
<td>rs1801272</td>
<td>A</td>
<td>T</td>
<td>0.961</td>
<td>19q13</td>
<td>46,046,373</td>
<td>66,380</td>
<td>0.68 (0.18)</td>
<td>$1.1 \times 10^{-4}$</td>
<td>0.500</td>
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<tr>
<td>rs4105144</td>
<td>C</td>
<td>T</td>
<td>0.704</td>
<td>19q13</td>
<td>46,050,464</td>
<td>83,317</td>
<td>0.39 (0.06)</td>
<td>$2.2 \times 10^{-12}$</td>
<td>0.510</td>
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<tr>
<td>rs7260329</td>
<td>G</td>
<td>A</td>
<td>0.687</td>
<td>19q13</td>
<td>46,213,478</td>
<td>86,092</td>
<td>0.20 (0.04)</td>
<td>$5.5 \times 10^{-6}$</td>
<td>0.1221</td>
<td></td>
</tr>
</tbody>
</table>

Thorgeirsson et al., 2010
Genetic Association with Cigarettes per Day
A Proxy for Nicotine Dependence

<table>
<thead>
<tr>
<th>SNP</th>
<th>Effect</th>
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<th>Position</th>
<th>Combined$^d$ Effect (s.e.m.)</th>
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<tr>
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Strongest associations are nicotinic receptors and nicotine metabolizing genes.

Thorgeirsson et al., 2010
Genetic Association with Cigarettes per Day
A Proxy for Nicotine Dependence

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<td>0.24   14</td>
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<tr>
<td>rs15511</td>
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<td>0.855</td>
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<td>32,818,950</td>
<td>88,255</td>
<td>0.32 (0.01)</td>
<td>$5.1 \times 10^{-7}$</td>
<td>0.01838</td>
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</table>

rs1051730    Chromosome 15q25  N=76,972  Effect= 0.80  $p= 2.4 \times 10^{-69}$

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

Nicotinic receptor gene cluster

$CHRNA5$-$CHRNA3$-$CHRNB4$

rs55853698 promoter region of $CHRNA5$
Liu et al., 2010

rs16969968 D398N in $CHRNA5$
Saccone et al., 2010

rs1051730 synonymous in $CHRNA3$
Thorgeirsson et al., 2010
Liu et al., 2010
Furberg et al., 2010
Top meta-analysis results Locus A chromosome 15
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**Nicotinic receptor gene cluster**

- **rs16969968**
  - D398N in **CHRNA5**
  - Saccone et al., 2010

- **rs55853698**
  - promoter region of **CHRNA5**
  - Liu et al., 2010

- **rs1051730**
  - synonymous in **CHRNA3**
  - Thorgeirsson et al., 2010
  - Liu et al., 2010
  - Furberg et al., 2010
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.

\[ D398N \]

```
Homo sapiens
EETESGSGPKSSRNTLEAALDSIRYITRHIMKENDVREVVEDW

Pan troglodytes
EETESGSGPKSSRNTLEAALDSVRCITRHIMKENDVREVVEDW

Saimiri boliviensis
EQTGSGGGPESRNTMEAALDSIRYITRHIVKENAVREVVEDW

Bos taurus
EEARSSRGPRSSRNALAEALDSVRYITRHVMKETDVREVVEDW

Rattus norvegicus
REEAESGAGPKSRNTLEAALDCIRYITRHVVKENDVREVVEDW

Mus musculus
REEAEKDGGPKSRNTLEAALDCIRYITRHVVKENDVREVVEDW

Gallus gallus
EEKGNMSGSESSRNTLEAALDSIRYITRHVMKENEVREVVEDW
```

Bierut et al., 2008
rs16969968 a non-synonymous coding change in the intracellular domain of CHRNA5
The amino acid change alters receptor function.

Bierut et al., 2008
From the laboratory of Jerry Stitzel
Targeted SNPs based on biological function

D398N change in CHRNA5

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

\( p = 1.11 \times 10^{-9} \)

The bars represent mean ± SD of CHRNA5 mRNA expression.
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
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, signals for nicotine dependence, tagged by rs578776 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 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.

Meta-analysis across 34 datasets
Sacco et al., 2010 in press
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 rs578776 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.

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

<table>
<thead>
<tr>
<th>SNP</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs16969968</td>
<td>1.33</td>
<td>5.96 x 10^{-31}</td>
</tr>
<tr>
<td>rs588765</td>
<td>1.17</td>
<td>6.03 x 10^{-9}</td>
</tr>
</tbody>
</table>

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

- 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

- 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
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
Lower \( 5\) mRNA level

Higher smoking risk
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
From John Rice et al
US Cigarette Use vs. Lung Cancer Deaths, 1900 - 2010

Per Capita Cigarette Consumption

Lung Cancer Death Rate

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

Thorgeir E. Thorgeirsson*, Frank Geller*, Patrick Sulem*, Thorunn Rafnar*, Anna Wiste1,2,
Kristinn P. Magnusson1, Andrei Manolescu, Guðmar Thorleifsson, Hreinn Stefansson, Andres Ingason,
Simon N. Stacey†, Jon T. Berghorsson, Steinunn Thorlacius, Julius Gudmundsson, Thorlakur Jonsson,
Margret Jakobsdottir, Jóna Saemundsdottir, Olof Olafsdottir, Larus J. Gudmundsson, Gyda Bjornsdottir†,
Kristelínur Kristjansdottir, Halla Skuladóttir, Hélgi J. Isaksson, Tomas Gudbjartsson, Gregory T. Jones†,
Thomas Mueller, Anders Gottsäter†, Andrea Flex†, Katja K. H. Aben1,13,14, Femmie de Vegt†, Peter F. A. Mulders1,4,
Dolores Isla15, María J. Vidal15, Laura Asín15, Berta Saez15, Laura Murillo15, Theresa Bloude16,
Hallgar Kolbeinsdottir, Jon G. Stefansson†, Ingum Hansdottir†, Valgerdur Runarsdottir†, Roberto Pola1,2,11,
Bengt Lindblad19, Andre M. van Rij†, Benjamin Dieplinger†, Meinhard Haltmayer†, Jose I. Mayordomo1,16,17,
Lambertus A. Kiemeneij12,13,14, Stefan E. Matthiasson15, Hogni Oskarsson23, Thorarinn Tyrifjörgnsson19,
Daniel F. Gudbjartsson†, Jeffrey R. Gulcher†, Steinn Jonsson, Unnur Thorsteinsdottir1,22, Augustine Kong†
& Kari Stefansson1,22

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

Rayjean J. Hung1,2,*, James D. McKay1,*, Valerie Gaborieau1, Paolo Buffet1, Mia Hashibe1, David Zaridze3,
Anush Mukeria1, Neelima Szeszenia-Dabrowska1, Jolanta Lisowska1, Peter Rudnai, Eleonora Fabianova,
Dana Mates1, Vladimir Bencko, Lenka Foretova1,6, Vladimir Janout1, Chu Chen1, Gary Goodman1,2, John K. Field3,
Triantafillos Liloglou1, George Xinaros1,3, Adrian Cassidy1, John McLaughlin1, Geoffrey Liu1,3, Steven Narod1,6,
Hans E. Krokan1, Frank Skorpen17, Maiken Bratt Elvestad17, Kristian Hveem17, Lars Vatten17, Jakob Linseisen18,
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Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1

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Nature Genetics, 2008
Cessation - The Final Step

Never Use

Initiation
First puff – First cigarette

Smoker
100 cigarettes lifetime

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