Personalized Genetic Approaches to Tobacco Cessation

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Acknowledgements & Disclosure

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• **Funding for BEACON Study:** Funded by DA027331 (PI: David) from NIDA. Extant genotyping funded by CA071358 (PI: Swan) from NCI & the Pharmacogenetics of Nicotine Addiction & Treatment program (DA02083) (PI: Lerman) from NIDA.

• **Acknowledgements to:** Drs. Andrew Bergen, Wei-Qing Chen, Charles Eaton, Helena Furberg, Joel Killen, Caryn Lerman, Jennifer McClure, Marcus Munafò, Mike Murphy, Raymond Niaura, David Strong, Gary Swan, Marcia Stefanick, Rachel Tyndale, and the STOMP, BEACON & Cancer Research UK General Practice Research Group study teams.
Stopping smoking works.

34,439 Male British Male Doctors

1.3 Million UK Women

“Take the big causes seriously because you can avoid a lot more deaths by moderate reduction in a big cause than you can by a small reduction in a little cause.”

Sir Richard Peto

Smoking cessation treatment does not work well.

Three Main Points

1. Smoking cessation treatments have major room for improvement.
2. Pharmacogenomics has potential to improve effectiveness of smoking cessation, identify high-risk smokers & inform drug discovery.
3. Must first address translational gaps from cell to society.
Sally

- A 38 year old woman with asthma, hyperlipidemia, depression & a family history of early onset heart disease, presents with cough & dyspnea.
- Smoked a pack per day for 25 years.
- Tried quitting “cold turkey” but felt irritable and couldn’t concentrate; she tried nicotine gum but it didn’t work.
- She is wants to stop smoking again but wonders if it is too late for her to benefit from quitting and if she ever can quit.
- How can we help Sally to stop smoking?
Best Evidence: The Five A’s Framework

• **USPHS Tobacco Use Treatment Guidelines (2008)**, US Preventive Services Task Force (2009) & Joint Commission **Core Measures (2012)** promote the “5-As”.
  - [http://www.ahrq.gov/path/tobacco.htm](http://www.ahrq.gov/path/tobacco.htm)
  - [http://www.uspreventiveservicestaskforce.org/uspstf/uspstbac2.htm](http://www.uspreventiveservicestaskforce.org/uspstf/uspstbac2.htm)
  - [http://www.jointcommission.org/core_measure_sets.aspx](http://www.jointcommission.org/core_measure_sets.aspx)

• **Ask** each patient about tobacco use—Document this in the patient’s record.

• **Advise** each smoker to quit—Make advice strong and positive.

• **Assess** each smoker’s willingness to make a quit attempt.

• **Assist** each smoker to make a quit attempt.

• **Arrange** follow-up—In your office, either with you or with an allied health professional, or through community services, accessed through [www.smokefree.gov](http://www.smokefree.gov), [http://www.cdc.gov/tobacco/campaign/tips/](http://www.cdc.gov/tobacco/campaign/tips/), [http://www.nhs.uk/smokefree](http://www.nhs.uk/smokefree) or other websites.
Assist each smoker to make a quit attempt.

• Offer medication & refer to counseling:
• Counseling effective in person or by telephone.
• Drug treatments increase the chance of success of a quit attempt (compared to placebo):
  – Nicotine replacement therapy (gum, patch, tablet, lozenge, inhaler, or nasal spray) almost doubles chance of success.
  – Bupropion SR, an antidepressant, approximately doubles a smoker’s chance of success.
  – Varenicline, a partial agonist of the $\alpha4\beta2$ nicotinic receptor, nearly triples the chance of success, vs. placebo, & more effective than bupropion or nicotine replacement.
Personalized treatments are needed.

Should we genotype Sally?

- We can personalize treatment for Sally using patient-centered, empirical medicine and emphasize that the hazards of smoking & benefits of stopping smoking are large \(^1,^2\) but...

- Efficacy of best “one-size-fits-all” treatments is low \(^3-^5\).

- Genetic factors influence smoking behavior, nicotine pharmacology \(^6-^12\) & smoking cessation \(^13-^15\).

- In theory, genotyping Sally could help further personalize her treatments to guide drug selection & dose.

Not quite yet for smoking cessation, but more than 120 FDA drug labels for pharmacogenetic tests.

- Examples include abacavir & carbamazepine (HLAB); citalopram, clopidogrel & omeprazole (CYP2C19); crizotinib (ALK); tamoxifen (ER); warfarin (CYP2C9 & VKORC1): [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)
- Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing algorithms.
• 10-19% inherited disease genes not covered to accepted standards.
• Genotype concordance high for previously known SNPs (99-100%) but low for small insertion/deletions (53-59%).
• Average 54 minutes clinician time (range 5-223 minutes/variant) & reclassified 69% disease causing in mutation databases to variants of uncertain or lesser significance.
• Whole genome sequencing has limited clinical utility for routine preventive screening.

Translational Gaps to Fill in Smoking Cessation
Personalized Medicine Research

• Generate better evidence including clinical utility.
• Prospective trials.
• Research in non-European ancestry patients.
• Identify/validate drug response biomarkers.
• Find the “missing heritability”.
• Relative value proposition of pharmacogenomics.
• Clinical implementation science.

Nicotine Addiction Neurobiology & Pharmacology

- Nicotine crosses blood-brain barrier, binds $\alpha_4\beta_2$ & $\alpha_7$ nicotinic acetylcholine receptors, increasing burst firing of dopamine in the nucleus accumbens, prefrontal cortex. Modulated by GABA & glutamate.
- Nicotine stimulates serotonin release, mediates nicotine withdrawal & behavioral sensitization.
- $\alpha_5$ nicotinic acetylcholine receptors inhibit nicotine self-administration by activation of the habenulo-interpeduncular pathway in mice.

Examples of Nicotine Addiction Candidate Genes

Nicotine & Brain Reward Centers & Functional Magnetic Resonance Imaging

Smoking cues, activate brain reward & memory regions \(^1\), correlated with craving \(^2\), nicotine dopamine & pathway genotypes \(^3-5\).

Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: Analysis of pooled data from two clinical trials

Sean P. David, David R. Strong, Marcus R. Munafò, Richard A. Brown, Elizabeth E. Lloyd-Richardson, Paul E. Wilesoy, Eden A. Evins, Peter G. Shields, Caryn Lerman, Raymond Naïura

Received 22 October 2006; accepted 5 February 2007

We analyzed pooled data from two comparable randomized placebo-controlled clinical trials of bupropion pharmacotherapy for smoking cessation for which data on DRD2 Taq1A genotype were available. A total of 722 smokers across the two trials were randomized to 10 weeks of sustained-release bupropion hydrochloride or placebo. General estimating equation analysis demonstrated a significant gene × drug interaction (R²=0.07, SE=0.34, p<.009). Smokers with the A2/A2 genotype using bupropion were more than three times as likely, relative to placebo, to be abstinent at end of treatment (35.2% vs. 15.1%; OR=3.25, 95% CI 2.08-5.28) and at 6 months of follow-up (26.7% vs. 12.2%; OR=2.81, 95% CI 1.66-4.77), which was attenuated by 12 months (16.3% vs. 10.7%; OR=1.70, 95% CI 0.95-3.05). We found no significant benefit of bupropion relative to placebo on smoking cessation outcomes at any time point in participants with A1/A1 or A1/A2 genotypes. These data suggest that bupropion may be effective for smoking cessation only in a subgroup of smokers with the DRD2 Taq1A2/A2 genotype.

Introduction

Despite major recent public health gains, fewer than 10% of smokers who attempt to quit remain abstinent after years of follow-up (Yudkin et al., 2003), and among persistent smokers, approximately half, or 5 million annually worldwide, die prematurely (Peto et al., 1996). Bupropion, nicotine replacement therapy (NRT), and varenicline are the three first-line, FDA-approved, pharmacological interventions for smoking cessation (Foulds, 2006; Schnoll & Lerman, 2006). Despite the efficacy of these interventions, 70%–80% of patients relapse within 12 months of attempting to quit smoking (Hurt et al., 1997; Jorenby et al., 1999). Therefore, attention has focused increasingly on the prospect of tailored medicine as a means of identifying subgroups of smokers most likely to respond to specific pharmacotherapies, thereby increasing smoking cessation efficacy (Munafò, Shields, Berrettini, Patterson, & Lerman, 2005).

Approximately 50% of the variance in risk for nicotine dependence is attributable to genetic factors (Li, Cheng, Ma, & Swan, 2003). Bupropion has demonstrated dopamine and norepinephrine reuptake and nicotinic acetylcholine receptor antagonist activity of pharmacogenetic and genomic investigations of smoking cessation and its translation to primary care.

Review

Pharmacogenetics of Smoking Cessation in General Practice: Results From the Patch II and Patch in Practice Trials

Sean P. David, M.D., S.M., D.P.H.,1,2 Elaine C. Johnston, Ph.D.,1,3 Michael Churchman, Ph.D.,1,3 Paul Aveyard, M.D., Ph.D.,4 Michael F.G. Murphy, M.B. B.Chir.,5 & Marcus R. Munafò, Ph.D.6

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Abstract

Introduction: Cigarette smoking remains the leading cause of preventable death worldwide. However, the efficacy of first-line pharmacotherapies remains low, particularly in primary care practice where most smokers seek and receive treatment. These observations reinforce the notion that ‘one size fits all’ smoking cessation therapies may not be optimal. Therefore, a translational research effort was launched by the Imperial Cancer Research Fund (later Cancer Research UK) General Practice Research Group, which led a decade-long research enterprise that examined the influence of pharmacological hypothesis-driven research into genetic influences on drug response for smoking cessation with transdermal nicotine replacement therapy in general practice.

Methods: New and previously published smoking cessation gene association results of 30 candidate gene polymorphisms generated for participants in two transdermal nicotine replacement clinical trials based in UK general practices, which employed an intention to analyze approach.

Results: By high bar, one of the polymorphisms (COMT Val158Met) was robust to correction for multiple comparisons. Moreover, future research directions are outlined; and lessons learned as well as best practice models for designing, analyzing, and translating results into clinical practice are proposed.

Conclusions: The results and lessons learned from this general practice-based pharmacogenetic research programme provide transportable insights at the transition to the second generation doi: 10.1038/ntr.2011.36

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**ANKK1/DRD2 Genotype & Bupropion**

RCT of Bupropion: Pooled Data \(^1\) from Brown University \(^2\) & University of Pennsylvania \(^3\) Trials (\(N = 722\))

Biochemically-verified End of Treatment (12-week) Abstinence

\[
\text{OR} = 1.15; \quad \text{OR} = 3.25; \\
(95\% \text{ CI } 0.58-2.29) \quad (95\% \text{ CI } 2.00-5.28)
\]

Gene x Drug Interaction:

\(P = 0.009\)

Dopamine D2 Receptor ("**DRD2**")
- "**ANKK1**" gene
- rs1800497 ("Taq1A")
- A1 ("T" or "A")
- A2 ("C" or "G")

Stanford University School of Medicine, March 20th, 2014

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1. David et al., *Nicotine Tob Res*. 2007 Dec;9(12):1251-7;  
**ANKK1/DRD2 Genotype & Nicotine Patch**

Nicotine Replacement Therapy (NRT) RCT Patch II Trial \(^1\) \((N = 749)\)

University of Oxford

**Biochemically-verified End of Treatment (12-week) Abstinence**

\(OR = 2.44;\) (95% CI 1.31-4.54)

\(OR = 1.52;\) (95% CI 0.89-2.60)

Gene x Drug Interaction: \(P = 0.04\)

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**DRD4 Genotype & Bupropion**

RCT of Bupropion (N = 331)

Brown University

Biochemically-verified End of Treatment (12-week) Abstinence

\[ OR = 1.79; \quad (95\% \text{ CI } 1.06-3.02) \]

\[ OR = 5.70; \quad (95\% \text{ CI } 2.39-13.62) \]

Gene x Drug Interaction: \[ P = 0.005 \]

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![Bar chart showing abstinence rates for different genotypes and drug conditions.](chart.png)

Dopamine D4 Receptor (**DRD4**) gene
Exon III VNTR

- **S/S**: "Long" (L); ≥ 7 repeats
- **S/L or L/L**: "Short" (S); < 7 repeats

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**COMT Genotype & Nicotine Patch**

**Patch II Trial (N = 755)** ¹

**University of Oxford**

Biochemically-verified End of Treatment (12-week) Abstinence

\[ \text{OR} = 2.44; \quad (95\% \text{ CI} 1.31-4.54) \]
\[ \text{OR} = 1.52; \quad (95\% \text{ CI} 0.89-2.60) \]

**Gene x Drug Interaction:**

- **Patch II:** \( P = 0.05 \)
- **PiP:** \( P = 0.001 \)

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**Replication Patch in Practice (PiP) Trial (N = 889)** ²⁻³


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**Catechol-O-methyl transferase (COMT) gene:**

- rs4680 ("val¹⁰⁸/¹⁰⁵met")
- A ("met") “low activity”
- G ("val") “normal activity”

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[Graph showing comparison of nicotine patch and placebo patch for different genotypes: A/A vs. A/G or G/G]
Influence of a dopamine pathway additive genetic efficacy score on smoking cessation: results from two randomized clinical trials of bupropion

Sean P. David,1,2,3,* David R. Strong,4,* Adam M. Leventhal,5 Molly A. Lancaster,5 John E. McGeary,6 Marcus R. Munafò,7 Andrew W. Bergen,2 Gary E. Swan,2 Neal L. Benowitz,9 Rachel F. Tyndale,10 David V. Conti,5 Richard A. Brown,8 Caryn Lerman11 & Raymond Niaura8,12

Stanford University School of Medicine, Center for Education and Research in Family and Community Medicine, Division of General Medical Disciplines, Department of Medicine, Stanford, CA, USA; SRI International, Center for Health Sciences, Menlo Park, CA, USA; Alpert Medical School of Brown University, Department of Family Medicine, Providence, RI, USA; University of California, San Diego, Division of Behavioral Medicine, Department of Family and Preventive Medicine, La Jolla, CA, USA; Keck School of Medicine of University of Southern California, Department of Preventive Medicine, Los Angeles, CA, USA; Providence VA Medical Center, Providence, RI, USA, University of Bristol, Department of Experimental Psychology, Bristol, UK; Alpert Medical School of Brown University, Department of Psychiatry and Human Behavior, Providence, RI, USA; University of California, San Francisco (UCSF), Division of Clinical Pharmacology, Departments of Medicine and Bioengineering and Therapeutic Sciences, San Francisco, CA, USA; University of Toronto, Departments of Psychiatry, Pharmacology and Toxicology, Centre for Addiction and Mental Health, Toronto, ON, Canada; Perelman School of Medicine, University of Pennsylvania, Department of Psychiatry, Philadelphia, PA, USA; and American Legacy Foundation, Schroeder Center for Tobacco and Policy Studies, Johns Hopkins Bloomberg School of Public Health, Department of Health, Behavior and Society, Baltimore, MD, USA.
Table 1 Characteristics of randomized clinical trials of bupropion combined in pooled analyses.

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (Brown trial) (n = 356)</th>
<th>Study 2 (Penn/PNAT trial) (n = 436)</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline measures</strong></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>Bupropion (n = 175) 88 (50.3%)</td>
<td>Placebo (n = 181) 89 (49.2%)</td>
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<tr>
<td></td>
<td>Bupropion (n = 235) 126 (54%)</td>
<td>Placebo (n = 201) 110 (55%)</td>
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<tr>
<td>Age</td>
<td>Bupropion (n = 175) 45.8 (10.9%)</td>
<td>Placebo (n = 181) 46.0 (10.8%)</td>
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<td>Bupropion (n = 235) 44.6 (11.8%)</td>
<td>Placebo (n = 201) 44.7 (11.2%)</td>
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<tr>
<td>FTND</td>
<td>Bupropion (n = 175) 6.2 (1.7%)</td>
<td>Placebo (n = 181) 6.2 (1.8%)</td>
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<td></td>
<td>Bupropion (n = 235) 5.1 (2.1%)</td>
<td>Placebo (n = 201) 5.2 (2.2%)</td>
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<td>Bupropion (n = 175) 24.2 (9.3%)</td>
<td>Placebo (n = 181) 25.2 (10.3%)</td>
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<td>Bupropion (n = 235) 21.4 (9.0%)</td>
<td>Placebo (n = 201) 21.9 (9.7%)</td>
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<td><strong>Genotype</strong></td>
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<td>AA</td>
<td>Bupropion (n = 175) 4.1 (1.4)</td>
<td>Placebo (n = 181) 4.4 (1.3)</td>
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<td>Bupropion (n = 235) 4.3 (1.4)</td>
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<tr>
<td>DRD2 rs1800497</td>
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<tr>
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<td>Bupropion (n = 175) 10 (6%)</td>
<td>Placebo (n = 181) 13 (7%)</td>
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<td>Bupropion (n = 235) 11 (5%)</td>
<td>Placebo (n = 201) 10 (5%)</td>
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<td>Bupropion (n = 175) 79 (45%)</td>
<td>Placebo (n = 181) 65 (36%)</td>
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<td>Bupropion (n = 235) 78 (33%)</td>
<td>Placebo (n = 201) 54 (27%)</td>
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<td>Bupropion (n = 175) 86 (49%)</td>
<td>Placebo (n = 181) 103 (57%)</td>
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<td>Placebo (n = 181) 0</td>
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<td>DRD4 VNTR</td>
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<td>Placebo (n = 181) 113 (62%)</td>
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<td>Bupropion (n = 235) 164 (70%)</td>
<td>Placebo (n = 201) 124 (62%)</td>
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<td>SL</td>
<td>Bupropion (n = 175) 44 (25%)</td>
<td>Placebo (n = 181) 48 (27%)</td>
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<td>Bupropion (n = 235) 51 (22%)</td>
<td>Placebo (n = 201) 60 (30%)</td>
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<td>Bupropion (n = 175) 2 (1%)</td>
<td>Placebo (n = 181) 8 (4%)</td>
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<td>Placebo (n = 201) 9 (4%)</td>
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<td>Bupropion (n = 175) 13 (8%)</td>
<td>Placebo (n = 181) 12 (7%)</td>
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<td>Bupropion (n = 235) 12 (5%)</td>
<td>Placebo (n = 201) 8 (4%)</td>
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<td>Placebo (n = 181) 38 (21%)</td>
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<td>Placebo (n = 181) 48 (26%)</td>
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<tr>
<td></td>
<td>Bupropion (n = 235) 69 (29%)</td>
<td>Placebo (n = 201) 48 (24%)</td>
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<td>Bupropion (n = 175) 10 (6%)</td>
<td>Placebo (n = 181) 5 (3%)</td>
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<td></td>
<td>Bupropion (n = 235) 15 (6%)</td>
<td>Placebo (n = 201) 26 (13%)</td>
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<tr>
<td>SLC6A3 VNTR</td>
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<tr>
<td>**</td>
<td>Bupropion (n = 175) 73 (42%)</td>
<td>Placebo (n = 181) 93 (51%)</td>
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<td>9*</td>
<td>Bupropion (n = 175) 53 (30%)</td>
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<td>99</td>
<td>Bupropion (n = 175) 14 (8%)</td>
<td>Placebo (n = 181) 11 (6%)</td>
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<td>Bupropion (n = 235) 95 (40%)</td>
<td>Placebo (n = 201) 71 (35%)</td>
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<td>Bupropion (n = 175) 35 (20%)</td>
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<tr>
<td></td>
<td>Bupropion (n = 235) 8 (3%)</td>
<td>Placebo (n = 201) 9 (5%)</td>
</tr>
</tbody>
</table>

Values represent means (standard deviation) or frequencies (%). All genotypes were in approximate Hardy–Weinberg equilibrium. AGES = additive genetic efficacy scale; FTND = Fagerström Test for Nicotine Dependence [44]; VNTR = variable number of tandem repeats; CPD = cigarettes per day; PNAT = Pharmacogenetics of Nicotine Addiction Treatment. * SLC6A3 non-9 allele.
Table 2  Cox proportional hazards of time to first lapse and logistic regression models for biochemically verified point prevalence abstinence, genotype and Additive Genetic Efficacy Scale AGES scores in combined analyses (n = 792).

<table>
<thead>
<tr>
<th></th>
<th>Time to first smoking lapse</th>
<th>Abstinence at end of treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>Beta (SE)</td>
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<tr>
<td>Baseline covariates</td>
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<tr>
<td>Age</td>
<td>1.01</td>
<td>0.01 (0.14)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.52</td>
<td>0.42 (0.10)</td>
</tr>
<tr>
<td>FTND</td>
<td>1.48</td>
<td>0.14 (0.03)</td>
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<tr>
<td>*BT</td>
<td>1.31</td>
<td>0.27 (0.14)</td>
</tr>
<tr>
<td>Drug</td>
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<td>-0.56 (0.10)</td>
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<tr>
<td>Site (SD, n = 4)</td>
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<td>0.13</td>
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<tr>
<td>Genotype</td>
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<tr>
<td>DRD2 rs1800497&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.25 (0.09)</td>
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<td>COMT rs4680&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0.02 (0.07)</td>
</tr>
<tr>
<td>SLC6A3 VNTR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.89</td>
<td>-0.11 (0.08)</td>
</tr>
<tr>
<td>AGES</td>
<td>1.10</td>
<td>0.09 (0.04)</td>
</tr>
<tr>
<td>AGES × drug&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td>-0.18 (0.07)</td>
</tr>
</tbody>
</table>

AGES = additive genetic efficacy scale; BT = behavioral treatment; FTND = Fagerström Test for Nicotine Dependence (FTND) [44]; VNTR = variable number of tandem repeats; drug = bupropion versus placebo; SD = standard deviation of effect of study recruitment site; SE = standard error. | AGES × drug = effects evaluated in models including planned covariates, counseling condition and lower order terms. <sup>a</sup>Individual genes were entered as a block in models without AGES scores. <sup>b</sup>SLC6A3 non-9 allele.
Time to First Smoking Lapse

- AGES main effect
  Hazard ratio [HR] = 1.29, (95% confidence interval [CI] = 1.06-1.14)
  $P = 0.009$

- DRD4 VNTR main effect
  HR = 1.29, (95% CI = 1.17-1.41)
  $P = 0.0073$

- AGES x bupropion Interaction
  $\beta$ standard error = -0.18(0.07)
  $P = 0.016$

*Figure 1* Displays the risk for lapse among smokers receiving bupropion or placebo as additive genetic efficacy scales (AGES) scores increase. Grey regions represent 95% confidence limits.
CHRNA5-A3-B4 & Smoking Cessation

- In RCT of $N = 1073$ smokers randomized to placebo, nicotine replacement therapy (NRT) patch, NRT lozenge, bupropion, NRT patch & nicotine lozenge, or bupropion & nicotine lozenge $^1$, rs16969968-rs680244 haplotype predicted drug response for smoking cessation, similar or related results for at least five other trials $^2,3,4,5,6$.

- Number needed to treat for NRT was 2.9 for CYP2A6 fast metabolizers (71%) vs. >1000 for CYP2A6 slow metabolizers (29%) $^7$.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Effect on Abstinence at End of Treatment$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Interaction of haplotype and intervention$^d$</td>
<td></td>
</tr>
<tr>
<td>Haplotype 1 and active treatment</td>
<td>Reference</td>
</tr>
<tr>
<td>Haplotype 2 and active treatment</td>
<td>1.83</td>
</tr>
<tr>
<td>Haplotype 3 and active treatment</td>
<td>3.12</td>
</tr>
</tbody>
</table>

Meta-Analysis of *CHRNA5-A3-B4* & Smoking Cessation

- Bergen et al., 2012 conducted pooled regression analyses of *CHRNA5-A3-B4* SNPs from 8 RCTs (*N* = 2,633).
- **Rs588765 & rs1051730**: Reduced abstinence placebo at end of treatment (EOT) & 6-months for increased abstinence NRT (6-months).

Genes in Multiple Pathways & Smoking Cessation
Efficacy & Side-Effects

• **ANKK1, DRD2, DRD4 & SLC6A3** (dopamine transporter), bupropion & nicotine replacement therapy [NRT])
  \(1^-7\).

• NRT & bupropion (**CYP2A6**) (nicotine metabolism) \(5^-7\).

• Bupropion \(8\), NRT \(9\), combination bupropion + NRT \(10\) & varenicline \(11\) (**CHRNQ2, CHRNA4, CHRNA7, CHRNA5-CHRNA3-CHRNB4**), varenicline transporter (**SLC22A2**) \(12\), **CYP2B6** \(12^-13\) (bupropion metabolism) & serotonin (**HTR3B**) \(12\).

1. Lerman et al., *Health Psychol*. 2003 Sep;22(5):541-8;  
3. David et al., *Nicotine Tob Res*. 2007 Dec;9(12):1251-7;  
5. Lerman et al., *Neuropsychopharmacology*. 2006 Jan;31(1):231-42;  
ORIGINAL ARTICLE

Molecular Genetics of Successful Smoking Cessation
Convergent Genome-Wide Association Study Results

George R. Uhl, MD, PhD; Qiqi, Rong Liu, PhD; Tomas Ordog, PhD; Catherine Johnson, MS; Donna Walther, MS; Jed E. Rose, PhD; Sean P. David, MD; Ray Nair, PhD; Garry Lerman, PhD

Context: Smoking remains a major public health problem. Twin studies indicate that the ability to quit smoking is substantially heritable, with genetics that overlap modestly with the genetics of vulnerability to dependence on addictive substances.

Objectives: To identify replicated genes that facilitate smokers’ abilities to achieve and sustain abstinence from smoking (hereinafter referred to as quit-success genes) found in more than 2 genome-wide association (GWA) studies of successful vs unsuccessful abstainers, and, secondarily, to nominate genes for selective involvement in smoking cessation success with bupropion hydrochloride vs nicotine replacement therapy (NRT).

Design: The GWA results in subjects from 3 centers, with secondary analyses of NRT vs bupropion responders.

Setting: Outpatient smoking cessation trial participants from 3 centers.

Participants: European American smokers who successfully vs unsuccessfully abstained from smoking with biochemical confirmation in a smoking cessation trial using NRT, bupropion, or placebo (N=305).

Main Outcome Measures: Quit-success genes, reproducibly identified by clustered nominally positive single-nucleotide polymorphisms (SNPs) in more than 2 independent samples with significant P values based on Monte Carlo simulation trials. The NRT-selective genes were nominated by clustered SNPs that display much larger t values for NRT vs placebo comparisons. The bupropion-selective genes were nominated by bupropion-selective results.

Results: Variants in quit-success genes are likely to alter cell adhesion, enzymatic, transcriptional, structural, and DNA, RNA, and protein-handling functions. Quit-success genes are identified by clustered nominally positive SNPs from more than 2 samples and are unlikely to represent chance observations (Monte Carlo P < .0005). These genes display moderate overlap with genes identified in GWA studies of dependence on addictive substances and memory.

Conclusions: These results support polygenic genetics for success in abstinence from smoking, overlap with genetic but non-addictive substance dependence and memory, and nominate gene variants for selective influences on therapeutic responses to bupropion vs NRT. Molecular genetics should help match the types and intensities of anti-smoking treatments with the smokers most likely to benefit from them.

Arch Gen Psychiatry. 2008;65(6):693-693

CIGARETTE SMOKING CONTINUES to contribute substantially to US morbidity and mortality, despite increasing stringent public health measures that make it more difficult and expensive to smoke. Smokers may thus now include many who have considered difficulty in achieving sustained abstinence from tobacco, despite the availability of therapeutic drugs that act at sites that include nicotinic receptors and monoamine transporters. Understanding the mechanisms that facilitate or impede smokers’ abilities to achieve and sustain abstinence from smoking could thus inform a major current US public health problem and augment understanding of mnemonic and other brain mechanisms that might influence abstinence. Understanding mechanisms that contribute to the abstinence-enhancing efficacy of specific therapeutic drugs could help match smokers with treatments that would be more likely to be effective for them.

Two studies suggest that 40% to 60% of individual differences in the ability to successfully quit smoking are heritable. Nicotine dependence is also heritable in ways that overlap substantially with vulnerability to dependence on nicotine and other addictive substances (10-14). For example, genes for two cell-adhesion molecules, CDH13 and CSMD1, are identified by clusters of such nominally significant SNPs in at least one or both of these traits that compare successful quitters with unsuccessful quitters and at least four of seven other samples that compare substance-dependent control individuals (Monte Carlo p < 0.001) to smokers.

In one of the largest reported trials of smoking cessation in primary care settings, Patch in Practice (PIP) study investigators studied the influence of different intensities of behavioral support on smoking cessation, aided by 15-mg nicotine patches. In smokers recruited at UK general practices in Buckinghamshire and Cheshire (8), we now report ‘homogeneity analyses’ of GWA data that compares individuals from this trial who were successful versus unsuccessful in achieving biochemically monitored 12-week abstinence. SNP from Affymetrix 6.0 Array (Affymetrix, CA, USA) studies of these samples identified many of the same chromosomal regions previously identified in other samples based on data for smoking cessation and vulnerability of smokers to physiological dependence on nicotine. We discuss the significant limitations of this dataset, including substantial limitations based on the modest number of successful quitters in this sample. We also discuss the ways in which the results may provide further insight into the mechanisms that contribute to smoking cessation and other addictive behaviors.
Genome-wide Association Studies of Bupropion & Nicotine Replacement Therapy (NRT)

“Successful vs. unsuccessful quitters” from Brown & Penn Bupropion Trials \(^1\); Penn & Duke Nicotine Replacement Trials \((N = 550)\); overlap 78 nominally significant clusters with Oxford PiP Trial \(^2\) \((N = 324)\).

Genes containing alleles with at least 2 samples: Cell adhesion: e.g., \textit{CLSTN2}, \textit{TEK}, \textit{CDH13}, \textit{PTPRT}; enzymes: e.g., \textit{PRKG1}, \textit{ALT9A}; transcriptional regulation; receptors; channels; transporters: e.g., \textit{THSD4}; protein processing; intracellular signaling; structural proteins: e.g., \textit{PARD3}; 41 NRT-specific, 66 non-specific, & 26 bupropion specific genes \(^1\). Overlap with candidate genes \textit{CYP2A7P1-CYP2B6} & \textit{NCAM1-TTC12-DRD2-ANKK1}.

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**CHRNA5-A3-B4 & CPD & Lung Cancer in European-Ancestry**

- **2007:** First GWAS smoking $^{1-2}$: Non-synonymous SNP (CHR\textit{NA5} rs16969968).
- **2008:** Lung Cancer association \textit{CHRNA3} rs1051730$^{3}$, widely replicated$^{4,5}$:
- **2010:** Meta-Analysis ($k = 34$) $^{3}$: Forest plot dichotomous CPD & \textit{CHRNA5} rs16969968:
  - CPD OR = 1.33 (95% CI = 1.26-1.39), $p = 5.96 \times 10^{-31}$.
  - Lung Cancer OR = 1.31 (95% CI = 1.24-1.38), $p = 1.99 \times 10^{-21}$.

Tobacco and Genetics (TAG) Consortium Genome-Wide Meta-Analyses (Meta-GWAS)

- **TAG Consortium**: \( n = 74,053 \) \( k = 16 \) & ENGAGE + Oxford-GSK \( n = 143,023 \).
- **Smoking initiation**: \( BDNF \) rs6265, \( p = 1.8 \times 10^{-8} \)
- **Cigarettes per day**: \( CHRNA3 \) rs1051730, \( p = 2.8 \times 10^{-73} \) & \( CHRNA5 \) rs16969968, \( p = 5.6 \times 10^{-72} \).
- **Smoking cessation**: \( DBH \) rs3025343, \( p = 3.6 \times 10^{-8} \).

Genome-wide meta-analyses of smoking behaviors in African Americans


The identification and exploration of genetic loci that influence smoking behaviors have been conducted primarily in populations of the European ancestry. Here we report results of the first genome-wide association study meta-analysis of smoking behavior in African Americans in the Study of Tobacco in Minority Populations Genetics Consortium (n = 32 389). We identified one non-coding single-nucleotide polymorphism (SNP; rs2036527[A]) on chromosome 15q25.1 associated with smoking quantity.
Study of Tobacco use in Minority Populations (STOMP) Genetics Consortium Studies & Methods

- **Aim:** We established STOMP Genetics Consortium to search for risk loci for smoking behaviors in African American & other minority populations.

- **Started Women’s Health Initiative (WHI) paper proposal (WHI MS984) for analysis of SHARe (8,208 African Americans) with limited statistical power for genome-wide association.

- **Organizational Structure:**
  - Liaison Working Group (lead authors & analysts from the SHARe [Bergen, Brown, David, Furberg, Wessel], CARe [Amidovic, Jorgenson, Kasberger] & Multiethnic Cohort Study [Chen, Haiman]) investigators.
  - Analytic Working Group & Writing Group.
  - Phenotype harmonization & analysis plan.

- Mostly volunteer effort, funding from NIH & host institutions.
- Added additional cohorts, 78 investigators & 50 institutions.
- P&P committee approval, dbGaP, data hosted at Broad Institute.
- Weekly to biweekly teleconferences >2 years.

STOMP Genetics Consortium: Studies ($N = 32,389$)

### Table 1: Descriptive characteristics of the 13 studies participating in the STOMP Consortium

<table>
<thead>
<tr>
<th>Study</th>
<th>$N$ (% female)</th>
<th>Age, mean (s.d.)</th>
<th>Ever smokers (%)</th>
<th>CPD, mean (s.d.)</th>
<th>AO6, mean (s.d.)</th>
<th>Former smokers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AABC</td>
<td>5061 (100)</td>
<td>56.6 (12.6)</td>
<td>47.2</td>
<td>11.9 (8.4)</td>
<td>23.3 (9.0)</td>
<td>58.8</td>
</tr>
<tr>
<td>AAPC</td>
<td>5556 (0)</td>
<td>63.7 (9.6)</td>
<td>68.7</td>
<td>14.6 (9.9)</td>
<td>23.2 (9.0)</td>
<td>64.9</td>
</tr>
<tr>
<td>CHS</td>
<td>801 (63.2)</td>
<td>72.9 (5.6)</td>
<td>51.2</td>
<td>13.9 (11.2)</td>
<td>19.0 (5.2)</td>
<td>66.8</td>
</tr>
<tr>
<td>CARe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>2916 (61.2)</td>
<td>54.1 (5.7)</td>
<td>52.2</td>
<td>14.4 (9.8)</td>
<td>19.5 (6.4)</td>
<td>28.1</td>
</tr>
<tr>
<td>CARDIA</td>
<td>953 (61.4)</td>
<td>24.4 (3.8)</td>
<td>39.2</td>
<td>11.8 (8.7)</td>
<td>17.3 (5.1)</td>
<td>4.6</td>
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<tr>
<td>CFS</td>
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<td>35.5 (19.8)</td>
<td>45.1</td>
<td>13.1 (10.3)</td>
<td>19.0 (5.5)</td>
<td>13.3</td>
</tr>
<tr>
<td>JHS</td>
<td>2145 (60.7)</td>
<td>55.2 (12.8)</td>
<td>33.2</td>
<td>14.9 (10.8)</td>
<td>19.3 (5.7)</td>
<td>17.0</td>
</tr>
<tr>
<td>MESA</td>
<td>1646 (54.7)</td>
<td>62.2 (10.1)</td>
<td>53.5</td>
<td>14.6 (18.2)</td>
<td>18.3 (5.4)</td>
<td>35.0</td>
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<tr>
<td>GeneSTAR</td>
<td>1175 (61.7)</td>
<td>47.4 (12.3)</td>
<td>57.2</td>
<td>11.5 (10.3)</td>
<td>18.3 (5.4)</td>
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<tr>
<td>HANDLS</td>
<td>918 (54.5)</td>
<td>48.6 (9.0)</td>
<td>65.4</td>
<td>15.7 (32.8)</td>
<td>17.4 (6.2)</td>
<td>29.0</td>
</tr>
<tr>
<td>Health ABC</td>
<td>1137 (57.2)</td>
<td>73.4 (2.9)</td>
<td>56.4</td>
<td>15.7 (12.6)</td>
<td>19.5 (7.0)</td>
<td>69.5</td>
</tr>
<tr>
<td>HyperGEN</td>
<td>1241 (67.3)</td>
<td>45.2 (13.3)</td>
<td>48.7</td>
<td>12.1 (9.8)</td>
<td>19.5 (5.5)</td>
<td>58.0</td>
</tr>
<tr>
<td>WHI (SHARe)</td>
<td>8208 (100)</td>
<td>61.6 (7.0)</td>
<td>50.6</td>
<td>11.5 (9.5)</td>
<td>20.5 (5.8)</td>
<td>39.1</td>
</tr>
</tbody>
</table>

- **13 Studies**: WHI SNP Health Association Resource (WHI SHARe, $n = 8,208$), African American GWAS consortia of Breast (AABC, $n = 5,061$) & Prostate Cancer (AAPC, $n = 5,556$), Candidate Gene Association Resource (CARe) Consortium (Atherosclerosis Risk in Communities [ARIC, $n = 2,916$] study, Cleveland Family Study [CFS, $n = 632$], Coronary Artery Risk Development in Young Adults [CARDIA, $n = 953$], Jackson Heart Study [JHS, $n = 2,145$], Multi-Ethnic Study of Atherosclerosis [MESA, $n = 1,646$]), Cardiovascular Health Study (CHS, $n = 801$), Healthy Aging in Neighborhoods across the Life Span Study (HANDLS, $n = 918$), Health ABC ($n = 1,137$), Genetic Study of Atherosclerosis Risk (GeneSTAR, $n = 1,175$) & Hypertension Genetic Epidemiology Network (HyperGEN, $n = 1,241$).
- **Additional details**: [http://www.nature.com/tp/journal/v2/n5/suppinfo/tp201241s1.html](http://www.nature.com/tp/journal/v2/n5/suppinfo/tp201241s1.html)

STOMP Genetics Consortium: Methods

• Phenotypes: Four smoking phenotypes previously shown to be heritable in African- & European Americans & used in other GWAS\textsuperscript{1-3}:
  – **Smoking initiation (SI)**: Ever Smokers (≥100 cig/lifetime) vs. Never Smokers (0-99 cig/lifetime).
  – **Age of SI (AOI)**: Age first tried smoking/first regular smoking.
  – **Smoking quantity (Cigarettes per Day)(CPD)**: Current & Former Smokers.
  – **Smoking Cessation (SC)**: Former vs. Current Smokers.

• Study-specific GWAS: Genotyped by Affy 6.0 or Illumina 1M or Omni-Quad, GW imputation (MACH, IMPUTE, BEAGLE, BIMBAM) 2 million SNPs, Principal Components Analysis, <20% admixture.

• Meta-analyses: fixed-effects, pooled inverse-variance-weighted \(\hat{\beta}\)-coefficients & Z-scores for each SNP; 2\textsuperscript{nd} genomic control correction (\(\lambda < 1.02\)); genome-wide \(\alpha<5 \times 10^{-8}\).

STOMP Genetics Consortium Results
Results: Manhattan Plots of SI, AOI, CPD & SC

Figure 1 Double genomic control (GC)-corrected Manhattan plots showing significance of association of all single-nucleotide polymorphisms (SNPs) for four smoking phenotypes. (a–d). SNPs plotted on the x axis according to their position on each chromosome against, on the y axis (shown as $-\log_{10} P$-value), the association with (a) smoking initiation (SI, ever vs never smokers), (b) age of SI, (c) cigarettes smoked per day, and (d) smoking cessation (former vs current smokers). Dotted red line indicates genome-wide significance threshold of $P < 5 \times 10^{-8}$.

STOMP Genetics Consortium

Results: Genome-Wide Significant SNP for Smoking Quantity (CPD)

- One SNP (CHRNA5 rs2036527 [A]) (chr15q25.1) was genome-wide significant for CPD.
- For every copy of the A allele, ~1 CPD increase in smoking quantity (explains 0.2% variance): Mean CPD for rs2036527 AA (14.6), AG (13.5); GG (12.8) CPD.

$\beta = 0.04$, s.e. 0.007, $P = 1.8 \times 10^{-8}$

• **Rs2036527** located 5' distal enhancer region of *CHRNA5* gene affecting expression in prefrontal cortex\(^1\)-\(^2\) & is associated lung cancer in African Americans\(^3\).

• **CPD:** Three modestly correlated SNPs \((r^2 = 0.32)\), at 15q25.1 w/in *PSMA4* (rs3813570), *CHRNA5* (rs667282) & *CHRNA3* (rs938682) genes, weakly correlated with rs2036527 \((r^2 = 0.04)\)

• **AOI:** Three SNPs in *SPOCK2* (rs1678618, rs1245577, rs1612028) (chr10q22.1).

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STOMP Genetics Consortium
Results: Overlap of STOMP (African ancestry) w/ TAG (European ancestry)

• Of top SNPs in TAG\(^1\), nominal associations with **CHRNA3**, **CHRNA5** (CPD) & **DBH** (SC) in STOMP\(^2\).

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SNP</th>
<th>Nearest Genes</th>
<th>Alleles*</th>
<th>n</th>
<th>Frequency</th>
<th>β</th>
<th>P-value</th>
<th>n</th>
<th>Frequency</th>
<th>β</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD</td>
<td>rs1051730</td>
<td>CHRNA3</td>
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<td>38</td>
<td>0.65</td>
<td>-1.021</td>
<td>2.8x10^{-75}</td>
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<td>0.88</td>
<td>0.025</td>
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<td>T/C</td>
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<td>1.8x10^{-4}</td>
<td>30</td>
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<td>0.42</td>
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<td>T/A</td>
<td>74</td>
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<td>-0.055</td>
<td>3.3x10^{-4}</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Ever vs. Never</td>
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<td>BDNF</td>
<td>T/A</td>
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<td>31</td>
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<td>-0.029</td>
<td>0.21</td>
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<td>T/G</td>
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<td>-0.058</td>
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<td>31</td>
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<td>0.21</td>
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<td>T/C</td>
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<td>0.23</td>
<td>-0.058</td>
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<td>-0.037</td>
<td>0.11</td>
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<td>BDNF</td>
<td>G/A</td>
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<td>31</td>
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<td>0.280</td>
<td>0.12</td>
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<td>BDNF</td>
<td>T/A</td>
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<td>0.010</td>
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<td>C/A</td>
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<td>4.9x10^{-4}</td>
<td>31</td>
<td>0.37</td>
<td>0.010</td>
<td>0.59</td>
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<td>Former vs. Current</td>
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<td>0.84</td>
<td>0.121</td>
<td>3.6x10^{-8}</td>
<td>11</td>
<td>0.97</td>
<td>-0.207</td>
<td>0.03</td>
</tr>
</tbody>
</table>

• **CHRNA3** rs1051730 & **CHRNA5** rs16969968 variants rare or non-polymorphic in African-ancestry populations.

# CHRNA5 rs2036527 & Lung Cancer in African Americans

Table 2. Top 10 directly genotyped SNP associations from the case-control analysis of lung cancer in African-Americans

<table>
<thead>
<tr>
<th>SNP</th>
<th>Position</th>
<th>Gene</th>
<th>Allele</th>
<th>MAF</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2036527</td>
<td>Chr15:78651615</td>
<td>6.3 kb upstream of CHRNA5</td>
<td>C/T</td>
<td>0.2102</td>
<td>1.34 (1.17–1.54)</td>
<td>2.0 × 10⁻⁵</td>
</tr>
<tr>
<td>rs17486278</td>
<td>Chr15:78867482</td>
<td>Intron 1 of CHRNA5</td>
<td>A/C</td>
<td>0.2802</td>
<td>1.31 (1.15–1.48)</td>
<td>2.7 × 10⁻⁵</td>
</tr>
<tr>
<td>rs16968968</td>
<td>Chr15:78882925</td>
<td>Exon 5 of CHRNA5 (missense Asp → Asn)</td>
<td>G/A</td>
<td>0.06008</td>
<td>1.57 (1.25–1.97)</td>
<td>1.1 × 10⁻⁴</td>
</tr>
<tr>
<td>rs7180002</td>
<td>Chr15:78873993</td>
<td>Intron 2 of CHRNA5</td>
<td>A/T</td>
<td>0.102</td>
<td>1.40 (1.17–1.68)</td>
<td>2.1 × 10⁻⁴</td>
</tr>
<tr>
<td>rs951266</td>
<td>Chr15:78878541</td>
<td>Exon 2 of CHRNA5</td>
<td>C/T</td>
<td>0.1031</td>
<td>1.39 (1.16–1.66)</td>
<td>2.8 × 10⁻⁴</td>
</tr>
<tr>
<td>rs17486195</td>
<td>Chr15:78865197</td>
<td>Intron 1 of CHRNA5</td>
<td>A/G</td>
<td>0.114</td>
<td>1.36 (1.14–1.61)</td>
<td>5.4 × 10⁻⁴</td>
</tr>
<tr>
<td>rs4243084</td>
<td>Chr15:78911672</td>
<td>Intron 1 of CHRNA3</td>
<td>C/T</td>
<td>0.1753</td>
<td>1.28 (1.11–1.48)</td>
<td>8.5 × 10⁻⁴</td>
</tr>
<tr>
<td>rs2735940</td>
<td>Chr15:1296486</td>
<td>1.3 kb upstream of TERT</td>
<td>T/C</td>
<td>0.479</td>
<td>0.82 (0.73–0.93)</td>
<td>1.1 × 10⁻³</td>
</tr>
<tr>
<td>rs4635969</td>
<td>Chr5:1308552</td>
<td>13.3 kb upstream of TERT</td>
<td>C/T</td>
<td>0.0328</td>
<td>0.81 (0.72–0.92)</td>
<td>1.2 × 10⁻³</td>
</tr>
<tr>
<td>rs17405217</td>
<td>Chr15:78731149</td>
<td>Intron 1 of IREB2</td>
<td>C/T</td>
<td>0.05842</td>
<td>1.43 (1.14–1.81)</td>
<td>2.5 × 10⁻³</td>
</tr>
</tbody>
</table>

*ordered by P value;  
*b: minor allele listed second;  
*c: MAF in controls only;  
*d: OR for each additional copy of the minor allele, estimated in a logistic regression model adjusted for: age, sex, study site, % sub-Saharan African ancestry, % European ancestry, and number of pack-years smoked;  
*e: P value in an allelic additive logistic regression model, adjusted for: age, sex, study site, % sub-Saharan African ancestry, % European ancestry, and number of pack-years smoked.

Table 4. Additive effects of (a) traumatic events, (b) neighborhood social cohesion and genetic risk on cigarette use in the Detroit Neighborhood Health Study.

| Environmental exposure | Genetic risk score | Cigarettes per day mean (95% CI) 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic life events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1 s.d. (n=685)</td>
<td>-1 s.d. (n=195)</td>
<td>10.91 (0.94, 11.89)</td>
</tr>
<tr>
<td>+1 s.d. (n=58)</td>
<td>+1 s.d. (n=58)</td>
<td>11.22 (10.44, 11.29)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>0.31 (-0.50, 0.60)</td>
</tr>
<tr>
<td>+1 s.d. (n=862)</td>
<td>-1 s.d. (n=295)</td>
<td>10.98 (0.97, 11.79)</td>
</tr>
<tr>
<td>+1 s.d. (n=102)</td>
<td>+1 s.d. (n=102)</td>
<td>12.20 (11.58, 12.52)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>1.22c (0.73, 1.61)</td>
</tr>
<tr>
<td>Interaction contrast</td>
<td></td>
<td>0.91d (0.23, 1.01)</td>
</tr>
<tr>
<td>Neighborhood social cohesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1 s.d. (n=520)</td>
<td>-1 s.d. (n=171)</td>
<td>09.48 (08.80, 10.56)</td>
</tr>
<tr>
<td>+1 s.d. (n=57)</td>
<td>+1 s.d. (n=57)</td>
<td>12.07 (11.88, 12.26)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>2.59c (1.70, 3.08)</td>
</tr>
<tr>
<td>+1 s.d. (n=1011)</td>
<td>-1 s.d. (n=317)</td>
<td>10.14 (9.44, 11.23)</td>
</tr>
<tr>
<td>+1 s.d. (n=102)</td>
<td>+1 s.d. (n=102)</td>
<td>10.22 (9.47, 10.18)</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>0.08 (-1.85, 2.03)</td>
</tr>
<tr>
<td>Interaction contrast</td>
<td></td>
<td>2.51c (1.05, 3.55)</td>
</tr>
</tbody>
</table>

aAdjusted for age, sex and ancestry using overdispersed Poisson regression.
bDifference between the mean for presence of high genetic risk versus low genetic risk, calculated on the mean (additive) scale using overdispersed Poisson regression with linear link function. cP-value <0.05. dDifference of the differences; additive interaction is indicated when the difference between the mean differences for the environmental exposure group versus the no-exposure group is significantly >0.

Figure 1. The interaction between genetic and environmental predictors of cigarette use in 399 individuals from the Detroit Neighborhood Health Study. (a) Genetic risk for smoking (GRS +1 s.d.) was greater for individuals who had experienced an increased number of traumatic events in their lifetimes. (b) Genetic risk for smoking (GRS +1 s.d.) was greater for individuals who lived in a neighborhood characterized by less social cohesion.

Myers et al., Translational Psychiatry (2013) 3, e290.
**CHRNA5 rs2636527 & Smoking Cessation in African Americans**

RCTs of NRT Patch (*N*=755) & Bupropion (*N*=540); Combined (*N*=1,295)

Zhu et al., 2014 (under review).

**Study 1**
NRT
38.8% A/A or A/G

**Combined Samples**
- **During treatment**
  - OR=0.42
  - (95% CI=0.27-0.67)
  - *P*<0.001
- **End of Treatment**
  - OR=0.55
  - (95% CI=0.36-0.82)
  - *P*=0.004.

**Study 2**
Bupropion
41.2% A/A or A/G
Communicating of genetic risk or drug response has potential behavioral impact.

- Genetic feedback (GF) to smokers with lung cancer \(^1\), \(^2\) or cardiovascular risk \(^3\) associated with greater perceived risk & motivation to quit smoking \(^1\)-\(^3\).
- GF about risk of addiction may influence smokers to choose medication over “will power”, regardless of whether or not is is combined with pharmacogenetic feedback \(^4\).
- Amongst smokers genotyped in a clinical trial of NRT, attributing nicotine dependence to genetic factors associated with lower perceived control but did not deter quit attempts \(^5\).
- Randomized clinical trial of GF + genetically-tailored (\textit{OPRM1 rs1799971}) vs. smoking quantity-tailored NRT dose – benefit genetically-tailored treatment on adherence & abstinence \(^6\).

What would it take to tailor drug treatment genomically for patients like Sally?

- Genomic biomarkers for smoking cessation & direct-to-consumer tests rapidly emerging 1-3.
- Genomic biomarkers of drug response, dose or side effects should be replicated, validated with high analytic validity & clinical utility 5.
- Prospective, implementation studies of feasibility real-world health care settings needed.

Original Investigation

Pharmacogenetic Smoking Cessation Intervention in a Health Care Setting: A Pilot Feasibility Study

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Received April 5, 2012; accepted June 19, 2012
Pharmacogenetic Feasibility Trial
Behaviorally-Enhanced Counseling for Nicotine Addiction (BEACON) Study

- **Setting:** Primary care patients in Group Health Cooperative.
- **Population:** Previously genotyped current smokers in Pharmacogenomics of Nicotine & Addiction (PNAT) program & newly recruited smokers prospectively genotyped.
- All received genetically tailored (ANIKK1 rs1800497) treatment: NRT for TT/TC (“A1A1/A1A2”) or bupropion for CC (“A2A2”) x 8 weeks.
- Standard behavioral counseling (BC) (pre-treatment, plus 2 follow-up support calls & written information about neurobiology of ND and “Clear the Air” from the National Cancer Institute)*.
- Randomized to standard behavioral counseling (BC) (telephone-based treatment without GF) vs. behaviorally enhanced treatment (BC + GF).
- GF group received “Understanding How Genes Influence Medications”.
- **Summative Interviews:** In-depth interviews of patients in Feasibility Trial.

*(http://www.smokefree.gov/pubs/clearing-the-air_acc.pdf)*
Personal Treatment Profile (ANKK1 rs1800497 A2/A2 genotype) & Medication Information

Understanding How Genes Influence Medications

Your genes can influence the way certain drugs work. The information below explains how this happens.

What is DNA?
DNA is found in every cell in the body. It is like the instructions that tell cells what to do.

What are genes and alleles?
Genes are segments of DNA that tell a cell how to make certain proteins. These proteins can act alone or with other proteins to perform cell functions. Alleles are versions of each gene. There can be one or more versions of each gene. The version that you have will determine certain things about you – like your hair color, eye color, or even how you respond to some drugs.

What is pharmacogenomics?
Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that person. This new field combines the science of how drugs work, called pharmacology, with the science of the human genome, called genomics.

What does this mean for you?
Until recently, it was thought that drugs work pretty much the same in everybody. But we now know that this "one size fits all" approach may not be true.

Depending on your genetic makeup, some drugs may work better or worse for you than they do in other people.

Some drugs may also produce more or less side effects in you than in someone else.

By using information about your genetic makeup, doctors are beginning to be able to choose drugs which are thought to work best for you.

The BEACON Trial is using this approach. The stop-smoking medication prescribed for you was chosen based on your genes. It is believed that this drug will work better than the other medication being offered in this trial. We do not know how you might respond to drugs not offered in this study.

Overall Feasibility

• **Recruitment:**
  – **Number needed to recruit** previously genotyped (7.4) vs. previously not genotyped patients (68.5) patients.
  – Far more previously non-genotyped (70/137, 51%) vs. genotyped (45/237, 19%) patients declined participation. **Fisher exact test, p = 0.0003.**

• **No statistically significant differences in depressive symptoms, fatalism, self-efficacy, patient satisfaction, clinician communication, trust, treatment interest or adherence.**

• **Patient feedback:** globally positive regarding acceptability of treatment. Suggestions for improvement were to add additional support calls. Study staff did not identify any barriers to treatment using the telephone-based counseling.

• Personal Treatment Profiles & medication delivered effectively.
• Saliva samples delivered by mail for genotyping & genotype data was transferred securely to study staff to guide treatment.

Qualitative Results (In-Depth Interviews)

- **Confidence**: Most participants interviewed in the GF group who had relapsed expressed a high degree of confidence their treatment effectiveness.

- **Perceived control**: All GF group participants who had relapsed attributed the likelihood of success to the medication, genetics or to chance (external locus of control); whereas, participants in both groups who remained abstinent generally focused on will power (internal locus of control).

- **Response efficacy**: Both groups expressed apprehension because of failed quit attempts on one of the study medications.

- **Understanding of test results**: GF participants who relapsed, most stated some indifference to the information or interpreted in concrete terms rather than the probabilistic language used in the pharmacogenetic Personal Treatment Profile.

A 38 year old woman with asthma, hyperlipidemia and a family history of early onset heart disease comes to see you because of increased wheezing and dyspnea.

How can we help Sally to stop smoking?

• Personalize treatment

• On her tobacco history: CPD, withdrawal, previous quit attempts.

• On her medical history & concurrent medications.

• Emphasize benefits of reducing risk of heart disease, LDL cholesterol & reducing asthma symptoms now.

• Pharmacogenetic treatment may be feasible.
Translational Gaps and Future Directions

- Better evidence (analytical validation & prospective trials).
- Non-European populations 1-4.
- Cost effectiveness 5-7.
- International health impact.
- Triple threat (nicotine dependence, lung cancer, smoking cessation) susceptibility loci.

What about Sam or Harry?

Three Main Points

1. Smoking cessation treatments have major room for improvement.

2. Pharmacogenomics has potential to improve effectiveness of smoking cessation, identify high-risk smokers & inform drug discovery.

3. Must first address translational gaps from cell to society.
Chinese cigarette increase 40 years after US increase

Delayed hazard: observed (1950, 1990) and predicted (2030) proportions of all deaths at ages 35-69 due to tobacco

<table>
<thead>
<tr>
<th></th>
<th>US (all adults)</th>
<th>China (men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>1990</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>2030</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Important Points Highlighted by Individual Speakers

- Genomic information has great potential to identify new pathways involved in complex diseases, suggest new therapeutic targets, evaluate adverse drug effects, and identify populations for which a drug is most effective or has the least deleterious effects.

- Pharmaceutical and biotechnology companies have integrated genomics-based strategies for drug discovery, but this has largely not been translated into late-stage development.

- The cost of therapeutic development has increased significantly over the past few decades while the success rate has remained unchanged, and many drug failures often occur after large investments have been made.

- While targeted therapeutics may decrease market size, overall market share may increase, leading to a significant potential advantage for developing stratified medicines.

- Commercial and marketing organization may need to be aligned with research and development in order to develop a successful commercial model for targeted therapeutics.
Civic and Scientific Role for Family Doctors in Global Tobacco Control

- Worldwide, HIV, tobacco, alcohol, war & obesity are the only big causes of death that have increased substantially since 1990.
- Only tobacco will claim 1 billion deaths in the 21st century.
- Physicians have a **civic and scientific** obligation to lead the end game of the tobacco epidemic through knowledge generation, treatment, prevention and policy.