Current Epidemiology Reports (2019) 6:486–490
https://doi.org/10.1007/s40471-019-00220-6

GENETIC EPIDEMIOLOGY (C AMOS, SECTION EDITOR)

Using Genomic Profiling for Understanding and Improving Response to Smoking Cessation Treatment

Laura J. Bierut[1]

Published online: 17 October 2019

Abstract

Purpose of Review This review focuses on the implementation of genomic discoveries associated with smoking behaviors and smoking-related illnesses to improve prevention efforts and smoking cessation.

Recent Findings Large-scale studies have discovered genomic variation that contributes to smoking heaviness and smoking cessation. Variation in the $\alpha 5$ nicotinic acetylcholine receptor subunit (*CHRNA5*) and the primary nicotine metabolizing gene (*CYP2A6*) strongly contribute to smoking behaviors, lung cancer, and chronic obstructive pulmonary disease. The analytic and clinical validity of these genes is clearly established, and evidence of clinical utility for risk stratification is growing. Equity will be a critical issue facing the translation of genomic findings into improved health because the majority of genomic studies have been conducted in European ancestry populations.

Summary Now is the time to increase the state of readiness for implementation of genomic profiling and we must address issues of increasing healthcare disparities that may arise with this new genomic technology.

Keywords Smoking cessation · *CHRNA5* · *CYP2A6* · Polygenic risk score · Genomic profiling

Introduction

The widespread implementation of genomic profiling will soon enter clinical medicine in the prevention and treatment of common, complex diseases [1••]. Most common diseases, including behavioral disorders such as tobacco use disorder, have underlying genetic contributions that are polygenic, meaning that hundreds, and likely thousands, of genetic variants of small effect play a role in the development of the disorder. With the large-scale genetic studies that include hundreds of thousands to millions of people, these small genetic effects can now be detected [2, 3••].

The application of state-of-the-art genomic approaches to smoking behaviors is an appealing area for genomic implementation. Even though the use of combustible cigarettes is decreasing, smoking continues to be one of the world's leading causes of preventable death. In the USA, more than 34 million people currently smoke cigarettes [4], and worldwide more than 1.1 billion people use tobacco products [5]. Smoking contributes to the development of lung cancer, chronic obstructive pulmonary disease, myocardial infarction, and many other cancers and medical illnesses [6]. Every year, more than 480,000 people perish from smoking-related illnesses in the USA [6], and worldwide more than 7 million people die because of their tobacco use [5]. These adverse health effects from smoking represent a public health crisis of immense proportion. Though preventive strategies to reduce smoking initiation have the strongest effect to improve public health, we must also aggressively facilitate smoking cessation for the large number of the people who currently smoke.

A range of behaviors is seen among smokers, from episodic, low-level smoking to heavy, daily smoking. Those individuals who smoke heavily often have the most difficulty quitting, and despite the strong adverse consequences of smoking, cessation is a difficult goal. Among current cigarette smokers, 60% to 70% report attempting to quit in the past 12 months, yet only a minority of smokers are able to quit each year [7, 8]. The difficulty with smoking cessation is most starkly seen in severely ill individuals who cannot stop smoking because of the addictive nature of nicotine. Although environmental

This article is part of the Topical Collection on *Genetic Epidemiology*

✉ Laura J. Bierut
laura@wustl.edu

[1] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

factors are critical to the establishment and persistence of smoking behaviors, genetic factors play a large role as well. This review focuses on the genetic discoveries associated with smoking behaviors and smoking-related illnesses and describes the potential for using genomic profiling to improve smoking cessation.

Genomic Contributions to Heaviness of Smoking and Smoking-Related Illnesses

Large-scale genomic studies of over 1 million people have been undertaken to discover the underlying genetic variants that contribute to smoking initiation, heaviness of smoking measured by cigarettes smoked per day, and smoking cessation [2, 3••]. The genetic contributions to the development of these smoking behaviors are polygenic, with at least hundreds of variants of small effect contributing to the initiation of smoking, number of cigarettes smoked per day, and successful smoking cessation. Yet, two genomic regions—variation in the genes encoding a nicotinic acetylcholine receptor subunit and a nicotine metabolism enzyme—stand out because of their particularly strong contributions to smoking heaviness as well as smoking-related illnesses, lung cancer, and chronic obstructive pulmonary disease (COPD) [2, 9•, 10–14, 15•, 16]. These genes can be used as a proof of principle of the opportunities and challenges of genomic profiling.

Genetic variation in the gene encoding the α5 nicotinic acetylcholine receptor subunit (*CHRNA5*) is unequivocally associated with an increased risk of heaviness of smoking, defined by smoking more cigarettes per day [2, 12]. The α5 nicotinic acetylcholine receptor subunit is one of five subunits that combines to form a pentameric receptor that binds nicotine [17]. A large-scale meta-analysis that pooled genomic data from over 300,000 European ancestry individuals who smoked associated a variant in *CHRNA5*, rs16969968, with number of cigarettes smoked per day ($p = 1.2 \times 10^{-278}$) [3••], and this finding has been confirmed across populations of African and Asian ancestry [18]. The polymorphism rs16969968 results in an amino acid change from aspartic acid to asparagine in the α5 subunit, and this specific region in the α5 protein is highly conserved across species [19]. Experiments have shown that the genomic variation marked by this single nucleotide polymorphism, rs16969968, alters the nicotinic receptor function, and thus the response to nicotine [19–21]. This variation in the function of the nicotinic receptor results in a differential response to the nicotine consumed by smoking cigarettes and alters a person's potential to become addicted.

Because combustible cigarette smoking is one of the strongest risk factors for the development of lung cancer and COPD, it is not surprising that there is a convergence of genetic findings for heaviness of smoking and these medical conditions. Large-scale studies demonstrate that this same genetic variant, rs16969968, in the gene that encodes the α5 nicotinic acetylcholine receptor subunit and which is associated with heaviness of smoking, is also one of the strongest genetic risk factors for lung cancer and COPD [9•, 10, 11, 13, 14, 15•, 16].

A parallel series of results are seen with the associations of variation in the gene that encodes the primary enzyme cytochrome P450 2A6 (*CYP2A6*) that metabolizes nicotine. Nicotine, the key addictive component in cigarettes, is metabolically inactivated by *CYP2A6*. The gene encoding this enzyme (*CYP2A6*) occurs in multiple different forms, which in turn causes marked variation in the enzymatic function and nicotine metabolism—from slow to very fast [22]. This individual variation in rates of nicotine metabolism contributes to the differential addictive risk associated with cigarette smoking as well as varying risk of developing smoking-related illnesses including lung cancer and COPD [2, 9•]. On average, fast metabolizers of nicotine smoke more cigarettes per day, and are at greater risk of developing lung cancer and COPD [9•, 15•].

Moving Genomic Evidence Into Clinical Care

Though incontrovertible evidence supports these strong associations of genetic variation in *CHRNA5* and *CYP2A6* with smoking behaviors and smoking-related illnesses, in order to translate this genomic knowledge into clinical medicine, genomic profiling must pass rigorous thresholds of analytic validity, clinical validity, clinical utility and ethical, legal, and social implications. Genomic technologies now produce highly reproducible results, so genomic testing for variation in *CHRNA5* and *CYP2A6* has strong analytic validity [2, 3••, 23, 24]. The clinical validity of these findings is robust, with convincing associations between genomic variation in *CHRNA5* and *CYP2A6* and an increased risk of smoking more cigarettes per day as well as developing smoking-related diseases, which has been independently confirmed in many studies [2, 3••, 9•, 15•]. Though analytic and clinical validity are clearly established, evidence of clinical utility of genomic profiling using these two genes remains ambiguous. Genomic variation in *CHRNA5* and *CYP2A6* is robustly associated with heaviness of smoking, lung cancer, and COPD, but what is the clinical utility of these results?

Risk stratification is the most advanced potential clinical utilization of genomic profiling with *CHRNA5* and *CYP2A6*. Clinicians currently use self-reported number of cigarettes smoked per day integrated over the duration of a person's smoking history to estimate the potential health risks of smoking-related illnesses. However, the number of cigarettes

smoked per day does not fully capture a person's cigarette smoking behavior. For the same number of cigarettes smoked per day, individuals differ in the number of puffs inhaled per cigarette, and variation in the depth of inhalation of each puff of a cigarette can be marked. These subtle inter-individual differences in smoking behaviors result in varying risk for developing lung cancer and COPD.

The addition of genomic profiling to the current standard of clinical measures of smoking behavior may offer a more precise identification of those with an elevated risk for the adverse consequences of smoking. More intensive interventions for smoking cessation, as well as more targeted lung cancer screening, may be aimed at individuals who are at highest risk. In addition, knowledge about one's own genomic profile has value in its own right. Providing personalized genomic health information directly to individuals may empower health and wellness decisions and aligns with the values of individual-centered decision-making.

Another area of potential clinical utility for genomic profiling lies in the use of genomic variation in *CHRNA5* and *CYP2A6* to guide pharmacologic interventions for smoking cessation. Heaviness of smoking is one of the strongest predictors of unsuccessful smoking cessation [25]. Given that genetic variation in *CHRNA5* and *CYP2A6* is associated with heaviness of smoking, it is not surprising that these genetic variants are also associated with a later age of quitting smoking and failed smoking cessation [2, 26, 27]. Those at highest risk for failed smoking cessation can be provided more intensive smoking cessation efforts.

Currently, there are three Food and Drug Administration–approved medication classes for smoking cessation—nicotine replacement therapy, varenicline, and bupropion. There is modest evidence that variation in *CHRNA5* and *CYP2A6* may be used for pharmacogenetics where a person's genetic makeup is used to tailor decisions regarding the most effective and safest medication to assist in smoking cessation [28–30]. This area of research is nascent, and whether knowledge of genetic variation in these genes can predict differential response to the pharmacologic treatments for smoking cessation is yet to be clearly reproduced in large, independent studies.

Perhaps the most complex issue in bringing genomic profiling to clinical care will be the issue of equity. The ethical, legal, and social implications of providing genomic profiling for smoking behaviors are in a state of flux and the potential benefits and costs are uncertain. Concerns regarding stigmatization, discrimination, and confidentiality are often raised. However, at this junction, equity is one of the most critical issues facing the translation of genomic findings into improved clinical care and health [31]. To date, polygenic risk scores have been developed and tested primarily in populations of European ancestry, the group in which the greatest number of genetic studies has been performed [2, 3••, 12]. Because allele frequencies and correlational patterns across the genome differ by ancestry, polygenic risk scores generated in European populations do not have the same predictive power in other world populations, which has important ethical and social implications. As these polygenic risk scores are developed and implemented for clinical testing and clinical care, understudied groups will not equally benefit from these scientific genomic discoveries. With continuing scientific development of genomic profiles in European ancestry populations, the unintended consequences of deploying these discoveries across individuals from diverse backgrounds may be to increase health disparities. This growth in disparities may be even more pronounced with genomic profiling of smoking behaviors because of the concentration of smoking in populations with lower educational attainment and income [32]. We must be aware of these potential adverse consequences as our science moves forward with genomic profiling for smoking-related behaviors as well as other diseases, and we must purposefully design our scientific experiments to decrease disparities. Efforts to accelerate genomic discovery in other world populations is necessary to ensure that all benefit from the potential of genomic medicine.

Moving From Two Genes to Polygenic Risk Scores

Using genomic variation in *CHRNA5* and *CYP2A6*, to illustrate the potential use of genomic profiling to predict those at risk for heavy smoking, failed smoking cessation, and smoking-related illnesses, points to the many steps that must be undertaken to move from discovery science into applications to improve clinical care. We are now well beyond the initial discovery of associations with these two genes and smoking-related behaviors, and large-scale research consortia have already identified hundreds of independent genomic loci associated with smoking behaviors. Many more regions will be discovered in the near future. In addition, parallel studies are underway establishing more and more genomic variation associated with lung cancer and COPD.

In addition to discovery, we must further research into the translational aspects of genomic implementation, including defining methods for the communication of genomic profiles to individuals and healthcare providers. One approach will be through direct-to-consumer genetic companies, such as 23andMe, which has tested millions of people. Through a web-based portal, 23andMe provides individuals access to their genetic health profiles, and now polygenic risk profiles for diabetes mellitus (www.23andMe.com). Importantly, the

utilization of web-based profiles is scalable and can be disseminated into areas with low access to medical care, which may reduce disparities related to healthcare access.

Conclusions

Polygenic risk scores that predict the risk of developing diseases as well as behaviors such as heaviness of smoking and failed smoking cessation will offer new opportunities, insights, and knowledge about individuals. Genomic variation causes differences in smoking behaviors and smoking-related illnesses across world populations, and genomic profiles are nearing entry into clinical medicine for smoking-related behaviors as well as other behaviors and diseases. Genomic profiles related to smoking behaviors can be accurately and reliably measured in European ancestry populations and have the potential to identify individuals at high and low genetic risk for heaviness of smoking, failed smoking cessation, and smoking-related illnesses such as lung cancer and COPD. Genomic profiles combined with clinical assessments of heaviness of smoking and duration of smoking history may improve the precision of predicting smoking cessation difficulty and potential response to smoking cessation pharmacotherapy. These genomic profiles may also more clearly define subgroups of heavy smokers who would most benefit from lung cancer screening. However, the implementation of genomic profiles poses challenges. The economic costs remain unclear, and communication of risk using polygenic risk scores will need the development and utilization of new paradigms in the healthcare system. The utility of knowledge of genomic profiles and the potential harms are unknown. Even with these many unknowns, polygenic genomic profiles are emerging through companies that provide direct-to-consumer testing. Now is the time to increase the state of readiness for the implementation of genomic profiling and address issues of equity in clinical medicine that may arise with this new genomic technology.

Funding Information This research was supported by the National Institutes of Health grants UL1TR002345 and U19CA203654.

Compliance with Ethical Standards

Conflict of Interest Laura J. Bierut is listed as an inventor on issued US patent 8,080,371, "Markers for Addiction" covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. Cell. 2019;177(3):587–96 e9. https://doi.org/10.1016/j.cell.2019.03.028. **This paper demonstrates the value of polygenic risk scores defined by genetic associations with body mass index and how they can predict weight and obesity from infancy to adulthood**.

2. Erzurumluoglu AM, Liu M, Jackson VE, Barnes DR, Datta G, Melbourne CA, et al. Meta-analysis of up to 622,409 individuals identifies 40 novel smoking behaviour associated genetic loci. Mol Psychiatry. 2019. https://doi.org/10.1038/s41380-018-0313-0.

3.•• Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet. 2019;51(2):237–44. https://doi.org/10.1038/s41588-018-0307-5. **This paper is the largest meta-analysis of smoking-related papers to date and defines hundreds of new loci which can be used to develop smoking-related polygenic risk scores**.

4. Wang TW, Asman K, Gentzke AS, Cullen KA, Holder-Hayes E, Reyes-Guzman C, et al. Tobacco product use among adults - United States, 2017. MMWR. 2018;67(44):1225–32. https://doi.org/10.15585/mmwr.mm6744a2.

5. World Health Organization. Tobacco key facts. 2019. https://www.who.int/news-room/fact-sheets/detail/tobacco. Accessed 09/13/19.

6. U.S. Department of Health and Human Services. The health consequences of smoking-50 years of progress: a report of the Surgeon General. Atlanta, GA, 2014.

7. Walton K, Wang TW, Schauer GL, Hu S, McGruder HF, Jamal A, et al. State-specific prevalence of quit attempts among adult cigarette smokers - United States, 2011–2017. MMWR. 2019;68(28):621–6. https://doi.org/10.15585/mmwr.mm6828a1.

8. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults - United States, 2000–2015. MMWR. 2017;65(52):1457–64. https://doi.org/10.15585/mmwr.mm6552a1.

9.• McKay JD, Hung RJ, Han Y, Zong X, Carreras-Torres R, Christiani DC, et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. Nat Genet. 2017;49(7):1126–32. https://doi.org/10.1038/ng.3892. **This study is the largest consortium of lung cancer genetic studies.**

10. Pillai SG, Ge D, Zhu G, Kong X, Shianna KV, Need AC, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. PLoS Genet. 2009;5(3):e1000421. https://doi.org/10.1371/journal.pgen.1000421.

11. Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet. 2008;40(5):616–22. https://doi.org/10.1038/ng.109.

12. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008;452(7187):638–42. https://doi.org/10.1038/nature06846.

13. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008;452(7187):633–7. https://doi.org/10.1038/nature06885.

14. Liu P, Vikis HG, Wang D, Lu Y, Wang Y, Schwartz AG, et al. Familial aggregation of common sequence variants on 15q24-25.1 in lung cancer. J Natl Cancer Inst. 2008;100(18):1326–30. https://doi.org/10.1093/jnci/djn268.
15.• Sakornsakolpat P, Prokopenko D, Lamontagne M, Reeve NF, Guyatt AL, Jackson VE, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. Nat Genet. 2019;51(3):494–505. https://doi.org/10.1038/s41588-018-0342-2. **This consortium is the largest group of researchers studying chronic obstructive pulmonary disease.**
16. Hobbs BD, de Jong K, Lamontagne M, Bosse Y, Shrine N, Artigas MS, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. Nat Genet. 2017;49(3):426–32. https://doi.org/10.1038/ng.3752.
17. Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia AS, McNamara JO, et al., editors. Neuroscience. 5th ed. Sunderland: Sinauer Associates; 2011.
18. Chen LS, Saccone NL, Culverhouse RC, Bracci PM, Chen CH, Dueker N, et al. Smoking and genetic risk variation across populations of European, Asian, and African American ancestry–a meta-analysis of chromosome 15q25. Genet Epidemiol. 2012;36(4):340–51. https://doi.org/10.1002/gepi.21627.
19. Bierut LJ, Stitzel JA, Wang JC, Hinrichs AL, Grucza RA, Xuei X, et al. Variants in nicotinic receptors and risk for nicotine dependence. Am J Psychiatry. 2008;165(9):1163–71. https://doi.org/10.1176/appi.ajp.2008.07111711.
20. Kuryatov A, Berrettini W, Lindstrom J. Acetylcholine receptor (AChR) alpha5 subunit variant associated with risk for nicotine dependence and lung cancer reduces (alpha4beta2)alpha5 AChR function. Mol Pharmacol. 2011;79(1):119–25. https://doi.org/10.1124/mol.110.066357.
21. Wang JC, Cruchaga C, Saccone NL, Bertelsen S, Liu P, Budde JP, et al. Risk for nicotine dependence and lung cancer is conferred by mRNA expression levels and amino acid change in CHRNA5. Hum Mol Genet. 2009;18(16):3125–35. https://doi.org/10.1093/hmg/ddp231.
22. Chenoweth MJ, Novalen M, Hawk LW Jr, Schnoll RA, George TP, Cinciripini PM, et al. Known and novel sources of variability in the nicotine metabolite ratio in a large sample of treatment-seeking smokers. Cancer Epidemiol Biomark Prev. 2014;23(9):1773–82. https://doi.org/10.1158/1055-9965.EPI-14-0427.
23. Chenoweth MJ, Ware JJ, Zhu AZX, Cole CB, Cox LS, Nollen N, et al. Genome-wide association study of a nicotine metabolism biomarker in African American smokers: impact of chromosome 19 genetic influences. Addiction. 2018;113(3):509–23. https://doi.org/10.1111/add.14032.
24. Loukola A, Buchwald J, Gupta R, Palviainen T, Hallfors J, Tikkanen E, et al. A genome-wide association study of a biomarker of nicotine metabolism. PLoS Genet. 2015;11(9):e1005498. https://doi.org/10.1371/journal.pgen.1005498.
25. Fagerstrom KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav. 1978;3(3–4):235–41.
26. Chen LS, Hung RJ, Baker T, Horton A, Culverhouse R, Saccone N, et al. CHRNA5 risk variant predicts delayed smoking cessation and earlier lung cancer diagnosis–a meta-analysis. J Natl Cancer Inst. 2015;107(5):djv100. https://doi.org/10.1093/jnci/djv100.
27. Freathy RM, Ring SM, Shields B, Galobardes B, Knight B, Weedon MN, et al. A common genetic variant in the 15q24 nicotinic acetylcholine receptor gene cluster (CHRNA5-CHRNA3-CHRNB4) is associated with a reduced ability of women to quit smoking in pregnancy. Hum Mol Genet. 2009;18(15):2922–7. https://doi.org/10.1093/hmg/ddp216.
28. Chen LS, Baker TB, Piper ME, Breslau N, Cannon DS, Doheny KF, et al. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRNB4) and cessation treatments in smoking cessation success. Am J Psychiatry. 2012;169(7):735–42. https://doi.org/10.1176/appi.ajp.2012.11101545.
29. Lerman C, Schnoll RA, Hawk LW Jr, Cinciripini P, George TP, Wileyto EP, et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med. 2015;3(2):131–8. https://doi.org/10.1016/S2213-2600(14)70294-2.
30. Sarginson JE, Killen JD, Lazzeroni LC, Fortmann SP, Ryan HS, Ameli N, et al. Response to transdermal selegiline smoking cessation therapy and markers in the 15q24 chromosomal region. Nicotine Tob Res. 2015;17(9):1126–33. https://doi.org/10.1093/ntr/ntu273.
31. Siontis KC, Patsopoulos NA, Ioannidis JP. Replication of past candidate loci for common diseases and phenotypes in 100 genome-wide association studies. Eur J Hum Genet. 2010;18(7):832–7. https://doi.org/10.1038/ejhg.2010.26.
32. Jamal A, Phillips E, Gentzke AS, Homa DM, Babb SD, King BA, et al. Current cigarette smoking among adults - United States, 2016. MMWR. 2018;67(2):53–9. https://doi.org/10.15585/mmwr.mm6702a1.