Title: The genetics of nicotine addiction liability: Ethical and social policy implications

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Family and twin studies indicate that there is a substantial genetic contribution to the risk of developing nicotine dependence. Heritability estimates for nicotine and other types of drug dependence range from 39% to 80% [1-3], indicating that susceptibility to these conditions is influenced by individual genetic makeup as well as environmental factors. There also appear to be both unique and overlapping genetic factors for initiation of drug use and progression to regular use and dependence [4]. Genes that affect drug metabolism and dopaminergic neurotransmission are plausible candidates for genes that underlie the heritability of nicotine (and other types of drug dependence) [5-7].

In 1999, Francis Collins, Director of the US Human Genome Institute, outlined an optimistic vision of the future contribution of "genomic medicine": the use of genetic information to improve human health [8,9]. Collins foresaw genomic screening being used preventively to identify healthy individuals who carry susceptibility alleles for diseases, such as cancers and heart disease, and intervening with those at higher genetic risk to either change their behaviour (e.g. exercise, eat a healthier diet) or to use drugs (e.g. antihypertensives) that reduced their chance of developing these diseases. Collins imagined, for example, screening smokers for genetic susceptibility to lung cancer and counselling those at high risk to stop smoking. Similarly, optimistic projections have been expressed by some addiction genetics researchers [10].

In this paper we consider the promise and the potential harms emerging from research on genetic liability to develop nicotine dependence. We use nicotine dependence as a case study for two reasons. First, tobacco smoking is the leading avoidable cause of premature death globally and in developed countries [11]. Second, the genetics of nicotine initiation and dependence is a very active research field and explicit attention has been paid to its clinical and public health applications (e.g. [12-14]).

We begin by considering briefly what the available evidence suggests about the genetics of nicotine dependence. We then consider the ethical and policy implications that may arise from empirically plausible uses that may be made of genetic information on susceptibility to nicotine dependence and response to different pharmacotherapies for smoking cessation.

Challenges in Identifying Addiction Susceptibility Alleles

Single, autosomal dominant genes of high penetrance have been identified for some human cancers (e.g. BRCA1 and BRCA2 in breast cancer and FAP in colorectal cancer) but these mutations account for very few cases of these diseases. It has proven more challenging to identify alleles that predict susceptibility to common human diseases and disorders [15,16]. Meta-analyses of association studies in common disease have shown that most positive findings have not been replicated and the minority of associations that have been replicated are very modestly predictive of increased disease risk [17,18]. Typically persons who have these susceptibility alleles are only 1.2 to 1.5 times more likely to develop these diseases than are persons who do not [19].

These findings in general medicine have been replicated in addiction genetics [20]. Although adoption and twin studies provide good evidence of a genetic contribution to addiction liability [20,21], specific alleles and chromosomal regions are only

weakly correlated with addiction liability [20]. The exception has been the allele that controls the enzyme, alcohol dehydrogenase: persons who have one form of this allele are *less* likely to use alcohol and develop alcohol dependence [20].

In the case of smoking, genome-wide scans have identified associations between nicotine dependence and loci near genes of biological relevance, such as the mu_1-opiod receptor (OPRM1), serotonin receptor 5A, $alpha_2$-nicotinic acetylcholine receptor (CHRNA2), $alpha_{1A}$-adrenergic receptor (ADRA1A) and dopamine receptor (D_1) genes [22]. Few of these associations, however, have been replicated between studies. This may reflect in part publication bias: journals are more likely to publish early positive associations that are not subsequently replicated [17,18,23].

Studies of candidate genes have been similarly disappointing. Meta-analyses of the most replicated genetic association (Taq1 A1 allele of the ANKK1 gene) demonstrate that persons with this allele are only 1.3 to 1.5 times more likely to be regular smokers [24,25]. Other associations (e.g. Cytochome P450 2A6 polymorphisms, a variable number tandem repeat polymorphism in the dopamine transporter gene, and the 5-HTTLPR polymorphism in the serotonin transporter gene) have not been confirmed [24-26].

Optimists argue that predictive alleles will be identified by improved study designs, attributing the failure to date to studies using small samples and poor designs [23]. More sceptical researchers argue that the lack of replication of genetic associations reflects the complexity of the genetics of human behaviour [27,28]. While some authors have suggested that addictive disorders may be influenced by a small number of alleles that vary between individuals [5], the more popular view is that these disorders are polygenic [10,20].

If addictive disorders are polygenic then we should only expect modest associations between alleles and addiction. This is because there will be multiple susceptibility alleles involved, each of which only marginally increases the risk of developing the disorder because their effects depend upon interactions with other genes and with environmental exposures [10,15,29]. Plausible estimates of the number of susceptibility alleles for major disorders range between the tens, at the most optimistic for autism [30], to the hundreds for common cancers [31,32]. In the remainder of this paper we assume that nicotine dependence is a polygenic disorder.

The Prospects for Genomic Medicine in Nicotine Dependence

Genomic Prediction of Addiction Liability

Sceptics argue that it will not be feasible to screen populations for genes that predict polygenic disorders like addiction [33]. Single alleles are poor predictors of disease risk unless the lifetime risk of the disease is 5% or more, and the genotype is either rare or it increases addiction risk 20 or more times [33-35]. And it will be very costly to screen whole populations for alleles with either a low prevalence and high penetrance or a high prevalence and low penetrance because there will be only a very small number of people at high risk of developing these disorders [36].

Testing for multiple genetic variants can potentially improve the prediction of addiction risk [29,37]. Simulations suggest that the prediction of risk will be substantially improved if multiple susceptibility alleles are tested and the results are combined to produce a risk score [34,38]. Nonetheless, even on the most optimistic variants of this scenario, large populations still need to be screened to identify the small number of persons who will be at high risk because they carry multiple susceptibility alleles [39].

The efficiency of genomic screening could be improved if screening was confined to persons at high risk of the disease on the basis of a history of early onset disease among first degree relatives, i.e. around 10% of the population [29,37,40]. Appropriate preventive interventions could then be provided to this group [40]. Triaging genetic screening on the basis of family history is nonetheless a substantial retreat from the whole population screening envisaged by Collins. A critical policy question will be: Will the addition of genetic information improve upon family history? Epidemiological modelling of breast cancer genetics suggests that it may [38] but evaluations are needed in the addictions field.

Effects of Genetic Information on Quitting and Initiation

Screening is only ethically justifiable if there is an effective intervention to prevent the disorder in those who are identified as being at risk [15,40,41]. Since smoking is a necessary condition for nicotine dependence, everyone should be advised not to smoke regardless of their genotype [15,42,43].

Francis Collins assumed that people will be more likely to comply with advice not to smoke if they have been given personalised feedback on their genetic susceptibility to tobacco-related diseases. Randomised trials of personalised feedback about genetic susceptibility to tobacco-related disease have failed to demonstrate improvements in long-term smoking cessation rates [44-47]. Smokers who were advised they had a positive test result for genetic susceptibility to lung cancer (CYP2D6 status) were no more likely to attempt to quit, nor were they more likely to succeed in quitting, than smokers who were not advised of their genetic risk [45,48]. In one study, smokers who were told they had a greater genetic susceptibility to COPD (chronic obstructive pulmonary disease) were more likely to attempt to quit and to use cessation aids than those who tested negative [47]. Smokers who tested positive were more likely to be abstinent at 3 months than those who tested negative, however the difference was not substantial (12% versus 4%). Another study, which provided NRT (nicotine replacement therapy) and telephone counselling for all participants, did not observe any difference in cessation rates between smokers advised of a positive or negative test result [46].

A further concern is that smokers who are told that they are at lower genetic risk of tobacco-related diseases may be less motivated to quit [49,50]. Studies of smokers presented with hypothetical genetic feedback have found less motivation to quit among those presented with a ‘low risk’ result [51]. Similarly, randomised trials have found that smokers who were told that they were at low risk of tobacco-related diseases had *lower* smoking cessation rates than those not provided with any genetic risk information [44].

Genetic testing of children and adolescents to discourage smoking initiation has also been proposed. Such testing poses additional ethical concerns. The potential impact of 'labeling' a child or adolescent as being at 'high risk' of addiction is unknown, but could be damaging to self-image and future behaviour [50]. These issues require careful consideration as some providers of adolescent medicine have already expressed an interest in genetic testing of their patients for nicotine addiction susceptibility [52], as have adolescents themselves [53,54].

Nicotine Pharmacogenetics

Genetic information could be used to select treatment for persons who are nicotine dependent. For example, genetic information about nicotine metabolism or dopamine response to nicotine could be used to match smokers to the treatment that was most likely to produce abstinence [55]. This presupposes (1) that there are alleles that predict different responses to smoking cessation treatments, and (2) that matching in this way is more cost-effective than giving everyone the treatment that is the most effective regardless of genotype [39]. For nicotine pharmacogenetics to be cost-effective, the genotypes identified must reliably predict a differential response to treatment that is of sufficient size to justify the additional costs of genetic testing [56].

To date, pharmacogenetic studies of smoking cessation have examined polymorphisms in the DRD2 [57-62], OPRM1 [63,64], CYP2B6 [65], SLC6A3 [66], SLC6A4 [67,68], DBH [69], FREQ [70] and COMT genes [71]. Some trials report a differential response to treatment (typically NRT or bupropion compared to placebo), but the differences are small, they weaken over time, and most of these findings have not been replicated. Attempts to replicate one such finding, for example, produced a null effect in two studies [67,68] and contradictory findings in the others [63,64].

The positive results are also of questionable utility because of the low prevalence in the population of the polymorphisms tested [14]. For example, a polymorphism that Berrettini *et al.* [71] found predicted a poor response to bupropion was found in only 11% of Caucasian smokers.

Because of the poor results with individual alleles, many pharmacogenetic studies now examine combinations of multiple alleles in more than one polymorphism (e.g. [57,70,71]). The studies to date have also found a low prevalence of predictive allele combinations and also failed to replicate each others' results.

Evaluations of pharmacogenetic tests will also need to evaluate the psychological effects of giving smokers genetic information on their likelihood of quitting. Will smokers interpret genetic risk information as meaning that smoking is an immutable behaviour that can only be changed with great difficulty, if at all, by biological interventions [49,72,73]? Two studies of smokers' understanding of the implications of information about genetic risk for cessation [74,75] have suggested that they may. In these studies, smokers who accepted that genetic factors contributed to cigarette smoking were less confident about their self-efficacy in quitting and were more likely to believe that a biological intervention was required to help them become abstinent.

Research will also need to examine the effects of providing genetic information on future quit attempts. Smokers who fail to achieve abstinence despite having treatment tailored to their genotype may be discouraged from trying again. This would be an undesirable outcome because most smokers need to make a number of failed quit attempts before achieving long-term abstinence [76-78]

It is also unclear whether pharmacogenetic strategies will reduce population smoking prevalence. Despite their efficacy in clinical trials, bupropion and NRT have not had a measurable population impact because of low uptake in the community [79]. It is difficult to believe that pharmacogenetic tests will increase uptake rates given the additional costs of genetic testing that are commonly cited as barriers to use of existing treatments [79,80]. Disadvantaged groups, who typically have the highest smoking prevalence, may find genetic tests particularly unappealing because of their cost, and possibly, fears of discrimination [81].

Finally, pharmacogenetic research on smoking may distract researchers from developing therapies that are more effective for *all* smokers. Nicotine vaccines and varenicline are two new therapies that have shown promising early results [82,83]. The cannabinoid antagonist, rimonabant, whilst possibly no more effective than bupropion and denied approval by the FDA as a smoking cessation aid, may be more attractive to smokers because it may prevent weight gain [83,84]. New faster-acting and stronger-dose preparations of NRT may also be more effective at relieving withdrawal symptoms and more attractive to smokers [85].

Competing Public Health Strategies

Population-based tobacco control strategies such as taxing cigarettes and reducing the opportunities to smoke have halved cigarette smoking rates in Australia [86] and the USA [87] over the past three decades. These strategies contrast with the strategy of using genetic information to identify and intervene with those at “highest risk” [41] entailed by genomic medicine [34]. Population-based strategies are likely to be more efficient than high risk strategies when smoking prevalence is high [41]. In this situation it makes more sense to reduce cigarette smoking by increasing taxes on tobacco products, banning cigarette advertising, and restricting opportunities to smoke than it does to spend resources on identifying those at higher genetic risk of becoming nicotine dependent, *if they smoke tobacco* [34,42]. A major challenge for advocates of using genomic medicine to reduce nicotine dependence will be in obtaining any health benefits from genetic screening without undermining effective public health policies [13,34].

Tobacco Harm Reduction

A more controversial population health strategy is to encourage current smokers to adopt less harmful ways of using nicotine [88,89]. Snus, or oral snuff, appears to have substantially lower health risks compared to cigarettes. Because snus is a smokeless product, it does not produce any of the combustion products of smoked tobacco and it has low levels of tobacco-specific nitrosamines, the main carcinogens in tobacco. Research in Sweden, where men have used snus for several decades, have so far failed

to detect any increase in the risks of oral cancers or cardiovascular disease among snus users [90-92].

The evidence of a substantially reduced risk with snus use compared to smoking is convincing, but the potentially detrimental effect on other tobacco control policies from its promotion also needs to be considered. Critics argue that the promotion of snus may reduce tobacco-related mortality and morbidity in current smokers at the cost of increasing tobacco use in the population by recruiting new tobacco users and discouraging smokers from quitting. Epidemiological modelling indicates that for net harm to result from snus use, many more non-smokers would need to take up snus for each smoker who switched to snus [93]. If snus use is confined to current smokers, switching from smoking tobacco to using snus would produce a net population health benefit, as it appears to have done in Sweden [94].

Ethical and Policy Concerns

Medicalisation of Addictive Behaviour

A major concern expressed by critics of genetic studies of human behaviour is that it will "medicalise" human behaviour [95-98], that is, it will lead to an overemphasis on the biological, and particularly genetic, origins of behaviour, at the expense of social and psychological explanations, in ways that will adversely affect people who engage in stigmatised forms of behaviour like smoking [13]. If addictions are seen as genetic disorders, critics argue that it could lead to a focus on medical interventions to the detriment of social measures such as higher taxes, prohibition of access to under 18's and so on [13,43,99].

Medicalisation could also potentially affect the types of cessation treatments that are made available. Pharmacological treatments and genetic tests could be marketed to smokers for commercial rather than health gains, as some argue has happened with NicoTest (www.nicotest.com), a commercially available pharmacogenetic test marketed as a way of choosing either NRT or bupropion for smoking cessation [100,101]. This is particularly relevant for the treatment of nicotine addiction, where the consumer may be desperate to quit because of the social, health and financial burden of smoking.

Critics argue that behaviour genetics may also change the way in which we think about nicotine dependence, and the ability of smokers to quit [13,102]. Such a view could lead to the further stigmatisation of those who possess particular genetic alleles or mutations, or genetic markers associated with smoking [13]. On this view, behaviour genetics could lead to both institutionalised discrimination, particularly by courts, educators and employers, and health and life insurers, as well as intensifying more informal stigmatisation [103-108]. These possibilities deserve to be investigated [13,50,55,109,110].

Third Party Uses of Genetic Information

Genetic information on addiction risk may potentially be used by third parties such as insurance companies, employers and educators, and the courts. Given the nature of

genetic transmission, the implications of this information not only affect the individual being tested, but also their close relatives. This raises ethical issues about who should be able to access this information. What measures should be taken to protect privacy? Under what circumstances should this information be shared and with whom [103,111,112]?

Bioethicists' concerns about the ethical and policy implications of genetic testing have been strongly influenced by experiences with genetic testing for Mendelian disorders, the paradigm case being Huntington's disease [113]. Because the mutations that cause this serious neurological disorder are strongly predictive of disease risk, and there is no effective treatment, genetic testing creates serious ethical dilemmas for affected individuals and family members [113]. Such testing also raises real concerns about the discriminatory use of genetic risk information by health and life insurers and employers [55,104,114].

But Huntington's disease is a poor model of the situation that we face with the addictive disorders. As argued above, since addictive disorders are most likely to be polygenic disorders, genetic testing will probably only modestly improve upon the prognostic value of family history. Any discussion of the ethical implications of the predictive genomics of addiction has to take account of the most likely ways in which genomics information will be used.

If the pessimists are right, the ethical and policy issues identified by bioethicists will not arise because we will not identify predictively useful alleles for addiction. Even on the most optimistic scenario, the predictive genomics of addition is unlikely to lead to genetic screening of whole populations for the reasons outlined above. Rather, predictive genetic testing is more likely to be offered to the minority of persons with a family history of early onset addictive disorders, perhaps 10% of the population.

Fear of genetic discrimination may nonetheless deter people with family histories of addictive disorders from having genetic tests that may benefit them. Similar fears may also deter individuals from participating in genetic research on addictive disorders, thereby impairing the acquisition of scientific knowledge about the genetics of these disorders. It remains to be seen whether community concerns about third party use of genetic information prove to be a major impediment to addiction genomic research and future medical applications.

We can, of course, eliminate the risks of third party use of genetic information by banning all genetic tests. But this policy could prevent us from realising any benefits that genetic testing may bring; it would also be an overly paternalistic policy. A better approach would be to look for safeguards to prevent individuals' privacy and confidentiality being unfairly compromised. The challenge will be to develop policies that allow for the use of genetic information to reduce the incidence of disease and improve the health and welfare of individuals and society, while minimising stigmatisation and discrimination.

Preventive Uses of Addiction Genetics

If we were able to predict genetic liability to nicotine dependence, we would need to decide if we should use potentially coercive means to prevent adolescents from

smoking [42]. For example, vaccines that are being developed against nicotine, primarily for smoking cessation [115-118], could potentially be used in childhood to prevent 'high risk' adolescents from smoking [116,119]. Children are unable to consent to such interventions but parents may be able to consent on their behalf, as they do for other childhood vaccinations and health care interventions.

In order to be ethical, the preventive use of a nicotine vaccine would need to demonstrate (1) the long term benefits of the vaccine [116,117,119] and (2) that genetic tests accurately predict the risk of nicotine addiction. Given the limited predictive power of genes studied to date, and doubts about the long term efficacy of preventive vaccination [39], it is unlikely that preventive vaccination would be an effective or an ethical intervention [115].

Challenges for Public Education

Popular understandings of the role of genetics, at least as expressed in the media, are often deterministic, suggesting that if you have "the gene for X" you are very likely to develop that disorder, and conversely that you will be at low risk of doing so if you do not have the "gene" for that disorder [120]. For example, popular media reporting of NicoTest describes it as a test for "the smoker's gene" or the "addiction gene" [121,122].

These views probably reflect the media focus on Mendelian disorders like Huntington's disease, cystic fibrosis and Tay-Sachs disease, where modes of genetic transmission are easier to understand [120]. If these views of genetics are indeed widely held, the challenge for public education will be explaining the personal and public health implications of polygenic disorders in which individual alleles weakly predict risk, and interact with each other and with the person's environment. If done well, this type of public education may allay anxieties about the third party uses of genetic information.

Public education will also need to avoid any unintended message that public health tobacco strategies can be replaced by high risk genomic medicine strategies [43,99,123]. The surest way for many individuals in developed societies to reduce their disease risks remains to stop smoking, reduce caloric intake and increase exercise [31,36,41,43]. In order to avoid blaming individuals for their risk status we also need to modify physical and social environments in ways that facilitate desirable changes in risk behaviour.

Conclusions

Despite good evidence from twin studies that genes contribute to addiction susceptibility, substantial challenges remain before Francis Collin's vision of genomic medicine can be realised in nicotine addiction. A major challenge has been the failure to date to identify commonly occurring, susceptibility alleles that are strongly predictive for nicotine addiction. The susceptibility alleles that have been identified to date only weakly predict addiction risk. Multiple alleles may better predict individual risk but the costs of screening and counselling large numbers of individuals in order to identify the small number at high risk may be difficult to justify, especially in the

absence of any effective preventive strategies. Population health strategies such as increased taxation and reduced opportunities to smoke are also more efficient in reducing cigarette smoking. Tobacco harm reduction policies applied to populations may also have an important role to play in reducing tobacco-related harm, although this remains controversial.

Any future predictive use of genomic information on addiction risk will need to address ethical and policy issues such as community concerns about privacy and the third party use of genetic information (e.g. by insurers or employers). Public education will be needed about the implications of the genetics of nicotine dependence and research is needed on how best to present genetic information to motivate desired behavioural change and avoid undermining successful public health strategies for reducing disease risk.

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