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ORIGINAL ARTICLE

A common biological basis of obesity and nicotine addiction

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Smoking influences body weight such that smokers weigh less than non-smokers and smoking cessation often leads to weight increase. The relationship between body weight and smoking is partly explained by the effect of nicotine on appetite and metabolism. However, the brain reward system is involved in the control of the intake of both food and tobacco. We evaluated the effect of single-nucleotide polymorphisms (SNPs) affecting body mass index (BMI) on smoking behavior, and tested the 32 SNPs identified in a meta-analysis for association with two smoking phenotypes, smoking initiation (SI) and the number of cigarettes smoked per day (CPD) in an Icelandic sample ($N = 34\,216$ smokers). Combined according to their effect on BMI, the SNPs correlate with both SI ($r = 0.019$, $P = 0.00054$) and CPD ($r = 0.032$, $P = 8.0 \times 10^{-7}$). These findings replicate in a second large data set ($N = 127\,274$, thereof 76 242 smokers) for both SI ($P = 1.2 \times 10^{-5}$) and CPD ($P = 9.3 \times 10^{-5}$). Notably, the variant most strongly associated with BMI (rs1558902-A in *FTO*) did not associate with smoking behavior. The association with smoking behavior is not due to the effect of the SNPs on BMI. Our results strongly point to a common biological basis of the regulation of our appetite for tobacco and food, and thus the vulnerability to nicotine addiction and obesity.

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INTRODUCTION

Smoking and obesity are major risk factors for many serious diseases.[1,2] Eating and smoking are behavioral traits that are at least in part controlled by the same reward mechanisms.[3] Genome-wide association studies (GWAS) have yielded 32 single-nucleotide polymorphisms (SNPs) associated with body mass index (BMI).[4] Smoking and SNPs associated with increased smoking quantity have been shown to correlate with lower BMI.[5,6]

According to the World Health Organization (WHO), more than one billion people smoke and over 400 million people are obese (BMI $> 30\,kg\,m^{-2}$), with both prevalences rising (see url section). Eating can become compulsive, and the neurobiological processes relating to overindulgence in food overlap with those involved in substance abuse and addiction.[3] All drugs of abuse have been shown to increase dopamine in the mesolimbic reward system, and studies of both human brain images[3] and animal brains[7] have revealed that similar neurocircuits are involved in the regulation of rewarding and reinforcement in drug addiction and compulsive eating. Based on the many similarities between hyperphagia and excessive drug use in addiction, it has even been suggested that some forms of obesity should be included as a diagnosis in future editions of the Diagnostic and Statistical Manual of Mental Disorders.[8,9]

Smoking influences body weight, such that smokers weigh less than non-smokers, and smoking cessation is often accompanied by an increase in weight.[5] These effects have been largely attributed to nicotine that increases the metabolic rate and suppresses appetite. Although increased food intake upon smoking cessation is partly explained by a reward substitution mechanism, as food intake is increased to make up for the lack of nicotine, the absence of nicotine has also been shown to increase the reward value of certain foods.[10] At the molecular level, these effects are most likely achieved through activation of the nicotinic acetylcholine receptors. The melanocortin (MC) system has a key role in regulating body weight,[11] and nicotine was recently shown to interact directly with the MC system in the brain through activation of $\alpha_3\beta_4$ nicotinic acetylcholine receptors on pro-opiomelanocortin (POMC) neurons[12] in the arcuate nucleus of the hypothalamus. The POMC neurons project to secondary neurons influencing appetite, and nicotine activation leads to the release of melanocortin-4 agonists activating MC4 receptors in the paraventricular nucleus producing appetite suppression, an effect that is absent from POMC KO mice.[12]

However, the relationship between smoking phenotypes and obesity is more complicated than can be accounted for by the known effects of nicotine on appetite and metabolism. This is evident from the fact that the number of cigarettes smoked per day (CPD) correlates with elevated BMI.[13,14] Thus, although smokers weigh less than non-smokers, heavy smokers indeed weigh more than light smokers.

BMI and smoking data are widely available from various studies and large sample sizes have been obtained for GWAS of BMI[4] and some smoking phenotypes,[15–17] and these studies have uncovered a number of variants associating with obesity (BMI) and with smoking behavior. The variant most strongly correlating with CPD,[15–17] rs1051730-A/rs16969968-A, correlates with reduced BMI both in current and former smokers, but does not have an impact on the BMI of never smokers.[6] This observation is

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consistent with the notion that smoking influences body weight through nicotine's effects on body and brain, the increase of metabolic rate and suppression of appetite. Here we report how variants correlating with BMI influence smoking behavior.

MATERIALS AND METHODS

Study subjects

Written informed consent was obtained from all subjects. Inclusion in the study required the availability of genotypes from ongoing SNP array typing in Iceland or previous GWAS,[15–17] and the study populations have all been described previously.[15–17] The GWAS of smoking initiation (SI) involved comparison of ever smokers and never smokers, and the studies of smoking quantity probed CPD as a quantitative trait among smokers only. The definitions of smokers and never smokers varied somewhat between studies,[15–17] as questions addressing smoking behavior varied with most studies probing for regular smoking over a certain period of time. Questions probing for smoking quantity also varied between studies, and for analysis of smoking quantity we used CPD data for smokers in categories with each category representing 10 CPD (effect size of 0.1 = 1 CPD).[15–17] CPD at the time of smoking was used for past smokers, and never smokers were excluded from analysis of CPD. All subjects were of European descent. The total sample sizes were $N = 100\,860$ and $N = 161\,490$ for CPD and SI, respectively.

Icelandic study design

A generalized form of linear regression was used to test the correlation between quantitative traits (BMI and height) and smoking phenotypes (CPD and SI) in Iceland. The generalized form assumes that the smoking behavior of related individuals is correlated proportional to the kinship between them rather than assuming that the smoking phenotypes of all individuals are independent. Let y be the vector of smoking behavior measurements, and let x be the vector of BMI or height measurements. We assume that the expectation of the smoking behavior depends linearly on BMI or height, $Ey = \alpha + \beta x$, and that the variance–covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, $Var(y) = 2\sigma^2\Phi$, where

$$\Phi_{ij} = \begin{cases} \frac{1}{2}, i = j \\ 2\rho k_{ij}, i \neq j \end{cases}.$$

is based on the kinship between individuals as estimated from the Icelandic genealogical database (k_{ij}) and an estimate of the heritability of the trait (ρ). Assuming normally distributed errors, the maximum likelihood method gives estimates for β, which will asymptotically follow a normal distribution and can be used to estimate the correlation between height and BMI on the one side and CPD and SI on the other.

In order to test the correlation between the set of 32 BMI SNPs or the set of 180 height SNPs and smoking behavior, the same type of analysis was performed replacing the observed BMI and height with the BMI and height predicted based on the sets of 32 and 180 SNPs. We shall describe how this was achieved for BMI, the analysis for height being conceptually identical. For each of the 32 SNPs reported to associate with BMI, let f_i be its minor allele frequency and γ_i be its published effect on BMI. For an individual with g_i minor alleles at SNP i, the set of 32 BMI SNPs predict a BMI of

$$\sum_{i=1}^{32}(g_i - 2f_i)\gamma_i$$

Conditional independence

We observe a correlation between the 32 BMI SNPs and smoking behavior. The 32 BMI SNPs associate with BMI and BMI associates with CPD. The question then arises of whether the correlation between the 32 BMI SNPs and CPD is all going through BMI. In other words, are the 32 BMI SNPs and CPD correlated conditional on BMI? Assuming that the 32 BMI SNPs and CPD are independent conditional on BMI, then the correlation between the 32 BMI SNPs and CPD will be the product of the correlation between the 32 BMI SNPs and BMI and the correlation between BMI and CPD. Denoting the estimator for the correlation between the 32 BMI SNPs and BMI with $c_{BMISNPs,BMI}$, and the variance of the estimator with $\mathrm{Var}(c_{BMISNPs,BMI})$, and similarly for the correlation between BMI and CPD. Then, $c_{BMISNPs,BMI}c_{BMI,CPD}$ is an estimator of the correlation between the 32 BMI SNPs and CPD, assuming conditional independence, and $\mathrm{Var}(c_{BMISNPs,BMI})\mathrm{Var}(c_{BMI,CPD}) + Var(c_{BMISNPs,BMI})c^2_{BMI,CPD} + c^2_{BMISNPS,BMI}\mathrm{Var}(c_{BMI,CPD})$ gives an estimate of the variance of the estimator. A standard test for the mean of two samples can now be applied to test the difference between the observed correlation between the 32 BMI SNPs and CPD and the correlation predicted based on the 32 BMI SNPs and CPD being independent conditional on BMI.

Replication outside of Iceland

The non-Icelandic studies shared only summary results from the genome-wide smoking behavior association scans in the form of effect sizes, *P*-values and allele frequencies. The ~2.5 million SNPs from the HapMap dataset were imputed and tested for association within each study population.[15–17] The significance levels of each study population were adjusted individually using the method of genomic control.[18] We used standard fixed-effects additive meta-analysis to combine the results for each SNP. After combining the results from all the populations, we again applied the method of genomic control and adjusted both smoking phenotypes accordingly ($\lambda_{GC} = 1.10$ and $\lambda_{GC} = 1.06$ for SI and CPD, respectively).

As data were not available on the individual level, we could not predict SI and CPD on the individual level as was done in Iceland. In order to test for the association of the 32 SNPs associating with BMI and the 180 SNPs associating with height with smoking behavior, we weighted the combined significance over all the populations of each SNP by the expected z-score associated with the SNP, assuming that the effect on smoking behavior was proportional to the effect on BMI or height as follows. Again let us take BMI as an example. For each of the 32 SNPs reported to associate with BMI, let f_i be its minor allele frequency and γ_i be its published effect on BMI. We denote the unknown effect of each SNP on smoking behavior with β_i and our assumption about the SNP's effect on smoking behavior being proportional to the SNP's effect on BMI can be stated as $\beta_i = k\gamma_i$ for some constant k. Quantifying the signifiance of the association of each SNP with smoking behavior by its z-score z_i, maximal power is achieved by weighing the SNPs according to the expected z-score. The expected z-score for the ith SNP is proportional to $\beta_i\sqrt{f_i(1-f_i)}$, which we assume is proportional to $\gamma_i\sqrt{2f_i(1-f_i)}$, which we will refer to as w_i and use to weigh the smoking behavior z-scores of the 32 BMI SNPs together: $z = \frac{\sum_{i=1}^{32} w_i z_i}{\sqrt{\sum_{i=1}^{32} w_i^2}}$.

RESULTS AND DISCUSSION

To study the correlation between obesity variants and smoking phenotypes, we focused on the 32 SNPs associating with BMI

Table 1. Association of BMI, height and SNPs associating with BMI and height with smoking phenotypes in Iceland

	CPD			*Smoking*		
From	N	*Correlation (95% CI)*	P	N	*Correlation (95% CI)*	P
BMI	33 620	0.095 (0.085, 0.106)	2.5×10^{-68}	49 565	−0.005 (−0.014, 0.004)	0.29
32 BMI SNPs	24 618	0.032 (0.019, 0.045)	8.0×10^{-7}	34 216	0.019 (0.008, 0.030)	0.00054
Height	33 875	−0.004 (−0.015, 0.007)	0.46	49 931	−0.012 (−0.021, −0.002)	0.013
180 Height SNPs	24 630	0.001 (−0.011, 0.014)	0.84	34 231	0.004 (−0.007, 0.015)	0.44

Abbreviations: BMI, body mass index; CI, confidence interval; SNP, single-nucleotide polymorphism.

described in a recent report of a study of 249 796 subjects.[4] We weighted the 32 SNPs together based on their published effect on BMI and tested the correlation with both CPD and SI in 49 565 chip-typed Icelanders (Table 1). We also tested the correlation between the actual measured BMI and the smoking phenotypes in a slightly larger set of Icelanders. For comparison, we performed a corresponding study using Icelandic data on human height and 180 SNPs reported to influence human height in a recent study of 183 731 individuals[19] (Table 1).

BMI associated with CPD ($r=0.095$, $P=2.5\times10^{-68}$) but not SI ($r=-0.005$, $P=0.29$), whereas height did not associate with CPD ($r=-0.004$, $P=0.46$) and showed only weak association with SI ($r=-0.012$, $P=0.013$). The set of 32 BMI SNPs associated with both CPD ($r=0.032$, $P=8.0\times10^{-7}$) and SI ($r=0.019$, $P=0.00054$), whereas the set of 180 height SNPs associated with neither smoking behavior ($P=0.84$ and 0.44 for CPD and SI, respectively).

The correlation between the set of 32 BMI SNPs and BMI and the correlation between BMI and CPD predict a correlation between the 32 BMI SNPs and CPD of 0.013, which is significantly lower than the observed correlation of 0.032 between the set of 32 BMI SNPs and CPD ($P=0.0033$). The correlation between BMI and SI is negative so that the predicted correlation between the 32 BMI SNPs and SI is also negative and even more significantly different from the observed correlation of 0.019 than from 0. Hence, the observed associations between the BMI variants and the smoking phenotypes are not explained by the direct phenotypic correlations between BMI and smoking behavior.

To investigate the contributions of individual SNPs and to replicate our observations in other populations, we looked up the correlations of each of the 32 SNPs with CPD and SI, using data from our previous studies outside of Iceland[15–17] ($N=76\,242$ for CPD, and $N=127\,274$ for SI). For these studies, we utilized the fixed-effect additive meta-analysis results for ~2 500 000 SNPs obtained using the inverse-variance method for each of the two smoking phenotypes. Before conducting the meta-analysis, we performed a genomic control correction of each study.[18] The combined χ^2-test statistics were still somewhat inflated by a factor of $\lambda_{GC}=1.10$ (SI) and $\lambda_{GC}=1.06$ (CPD). The correlations between the set of 32 BMI SNPs and the two smoking variables were significant in this replication sample with $P=1.2\times10^{-5}$ and 9.3×10^{-5}, for SI and CPD, respectively. Combined with Iceland, the association between the 32 BMI SNPs and SI and CPD reached a significance of $P=1.2\times10^{-7}$ and $P=1.6\times10^{-9}$, respectively.

As expected, based on the correlations observed between the combined set of the 32 BMI SNPs (Table 1), we observe congruence in the effects that these SNPs have on BMI and smoking behavior. For most of the SNPs, the allele that associates with increased BMI also associates with both increased probability of SI and higher CPD (Figure 1). We note that the effect sizes are small and although the markers as a group clearly associate with the smoking behaviors, further studies are required to determine unequivocally which of the markers have an impact on smoking behavior. The SNP by far most strongly associated with BMI (rs1558902-A in *FTO*) represents a notable exception from the trend observed and shows no evidence for association with either CPD or SI.

Considering the 11 BMI SNPs most strongly associated with smoking ($P<0.05$), 9 SNPs associate with smoking initiation and 4 with CPD (Supplementary Table 1 and Figure 1). For smoking initiation the most significant associations were to rs10767664-A (effect = 0.050495, $P=1.14\times10^{-6}$) in the Brain Neurotrophin Factor gene (*BDNF*) and rs2867125-C (effect = 0.0397, $P=0.000021$) 45 kb upstream of the Transmembrane protein 18 gene (*TMEM18*), and for CPD the most significant associations were with rs2867125-C (effect = 0.286, $P=0.000346$) (*TMEM18*) and rs4771122-G (effect = 0.0193, $P=0.00048$) in the mitochondrial translational initiation factor 3 gene (*MTIF3*). In addition to rs286125-C (*TMEM18*), rs2815752-A (*NEGR1*) is among the top markers ($P<0.05$) for both SI (effect = 0.186, $P=0.0244$) and CPD (effect = 0.0097, $P=0.0305$). A SNP within the *BDNF* gene has previously been shown to associate with smoking initiation (rs6265-C).[16] This SNP is in linkage disequilibrium with the BMI-associated rs10767664 ($r^2=0.85$ in Iceland). The association with SI remains significant after removing rs10767664 ($P=1.3\times10^{-5}$).

In summary, we have demonstrated that as a group, the 32 common variants identified in GWAS of BMI[4] also have an impact on the smoking behavior. A variant within the *nAChR* gene cluster

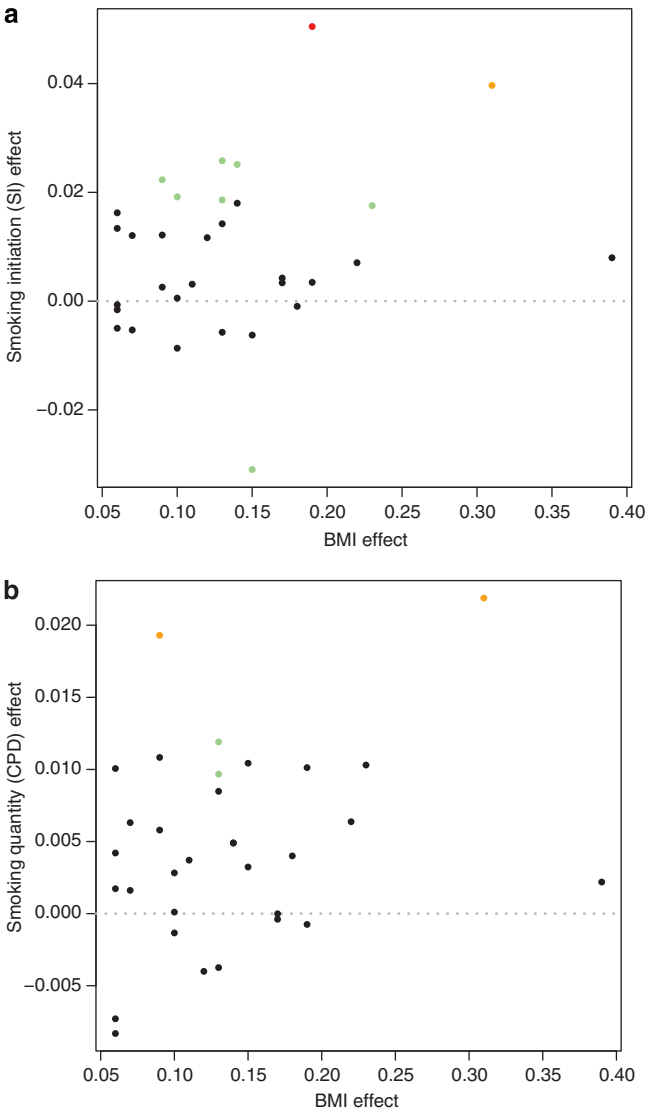

Figure 1. Association of obesity variants with smoking initiation (SI) and CPD. The effects on smoking behaviors are depicted vs the effects on BMI from a large meta-analysis.[4] (**a**) The effect on smoking initiation vs the effect on BMI. (**b**) The effect on CPD vs the effect on BMI. The BMI effect is in standard units, and the effects on SI and CPD were obtained using a standard fixed-effects additive meta-analysis to combine the results for each SNP from Iceland with additional data from three large GWAS.[15–17] The effects on SI are the β-values from logistic regression treating ever smoking as the response and the allele counts as covariates, and the GWAS of CPD used smoking quantity in categories with each category representing 10 CPD (effect size of 0.1 = 1 CPD). The dots representing each data point are color coded to indicate the *p*-value obtained as red ($P<0.0001$), yellow ($P<0.001$), green ($P<0.05$) and black ($P\geq0.05$) and the input data are provided in (Supplementary Table 1).

at chrs 15q25 (rs1051730-A) was discovered in GWAS of smoking behavior[20,21] and subsequently shown to correlate with reduced BMI in smokers without an effect on the BMI of never smokers,[6] thus most likely influencing BMI mainly through its effect on smoking behavior. The variants studied here represent a different class of SNPs affecting both BMI and smoking: They were found in GWAS of BMI and influence BMI in both smokers and never smokers, and the alleles correlating with elevated BMI tend to increase the propensity to smoke and/or associate with increased cigarette intake. We note that, in Iceland, the correlation between the predicted BMI and observed BMI is similar for smokers (0.15, $P = 3.0 \times 10^{-97}$, $N = 20\,462$) and never smokers (0.13, $P = 7.2 \times 10^{-33}$, $N = 7910$). The direction of this trend is opposite to what would be expected based on the known effects of nicotine on BMI, and inconsistent with an effect rooted in nicotine-mediated increase of metabolic rate and suppression of appetite. That the majority of variants known to associate with elevation of BMI correlate with smoking behaviors in this manner points to a common biological basis to regulation of the intake of food and tobacco.

CONFLICT OF INTEREST

Authors whose affiliations are listed as Decode genetics/AMGEN are employees of Decode genetics/AMGEN.

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AUTHOR CONTRIBUTIONS

TET, DFG, and KS wrote the manuscript. The study was designed by and the results interpreted by TET, DFG, PS, SB, UT and KS. The meta-analyses of smoking GWAS data were performed by DFG. TET, DFG, PS, SB,US, GT, BW and VS worked on data management and analysis. Smoking GWAS consortia were coordinated by HF (TAG), PFS(TAG) JM (OX-GSK) and MIM (ENGAGE). All authors contributed to the final version of the paper.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)

CONSORTIA

The data utilized came from three large GWAS done by the ENGAGE, TAG, and OX-GSK consortia (references 15–17). The additional collaborators from these three consortia are listed below.

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