INTRODUCTION

Smoking and obesity are major risk factors for many serious diseases. 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 ($r = 0.032, P = 8.0 \times 10^{-5}$). 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.

Keywords: addiction; body mass index; nicotine dependence; obesity; smoking

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 ($r = 0.032, P = 8.0 \times 10^{-5}$). 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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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, \( E(y) = \beta x \), and that the variance–covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, \( \text{Var}(y) = 2\sigma^2 G \), where

\[
\Phi_y = \left\{ \begin{array}{cc} \frac{1}{2} & i = j \\ \frac{1}{2k_{ij}} & i \neq j \end{array} \right. 
\]

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 (\( \sigma^2 \)). Assuming normally distributed errors, the maximum likelihood method gives estimates for \( \beta \), 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 \( g_i \) 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

\[
\sum_{i=1}^{32} (g_i - \bar{g}_i) f_i 
\]

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

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From</strong></td>
<td><strong>N</strong></td>
<td>Correlation (95% CI)</td>
</tr>
<tr>
<td>BMI</td>
<td>33 620</td>
<td>0.095 (0.085, 0.106)</td>
</tr>
<tr>
<td>32 BMI SNPs</td>
<td>24 618</td>
<td>0.032 (0.019, 0.045)</td>
</tr>
<tr>
<td>Height</td>
<td>33 875</td>
<td>-0.004 (−0.015, 0.007)</td>
</tr>
<tr>
<td>180 Height SNPs</td>
<td>24 630</td>
<td>0.001 (−0.011, 0.014)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; SNP, single-nucleotide polymorphism.
described in a recent report of a study of 249,796 subjects. 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 ($r = 0.095$, $P = 2.5 \times 10^{-68}$) 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 ($r = 0.032$, $P = 8.0 \times 10^{-7}$) 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 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 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 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 ($r = 0.032$, $P = 8.0 \times 10^{-7}$) 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).

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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 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, $P = 1.14 \times 10^{-9}$) 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, $P = 0.000486$) 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). 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 ($P = 1.3 \times 10^{-5}$).

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

Authors whose affiliations are listed are 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, SBUS, 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 (references 15–17). The ENGAGE Consortium—Ida Surakka 8,9, Jacqueline M Vink 10, Najaf Amin 11, Frank Geller 12, Thorunn Rafnar 13, Tónu Esko 13,14, Stefan Walter 15, Christian Gieger 15, Rajesh Rawal 15, Massimo Mangino 16, Inga Prokopenko 5,6, Reedik Mägi 5,6,13, Kaisu Keskitalo 19, Iris H. Gudjonsdottir 1, Solveig Grettardottir 1, Heintrih Stefansson 1, Yurii S Aulchenko 1, Mari Nellis 13,14, Katja K Aben 21,22, Martin den Heijer 21,22, Nicole Soranzo 16,24, Ana M Valdes 16, Claire Steves 16, André G Uitterlinden 11,12,15, Albert Hofman 15, Anke Tönjes 26,27, Peter Kovacs 18, Jouke Jan Hottenga 19, Gonneke Willemsen 19, Nicole Vogelzangs 16, Angela Döring 15, Norbert Dahmen 15, Barbara Nitz 15, Samuli Ripatti 23, Markus Perola 11,13, Johannes Kettunen 24, Anna-Liisa Hartikainen 10, Anneli Pouta 3,1, Jaana Laitinen 2, Matti Isohanni 10, Shen Hui-v6,8, Maxine Allen 15, Maria Krestyaninova 13, Alastair S Hall 18,19, John R Thompson 20, HOGNI Ooskarsson 20, Thorarinn Tyrfingsson 20, Lambertus A Kiemeneij 11,12,38, Marjo-Riitta Järvelin 11,19,40,41, Veikko Salomaa 8,9, Michael Stumvoll 26, Tim D Spector 16, H-Erich Wichmann 15,42,43, Andres Metspalu 13,14, Niles J Samani 24, Brenda W Penninx 25, Ben A Oostra 26,40, Dorret I Boomsma 27, Henning Tiemeier 11, Cornelis M van Duijn 11, Jaakko Kaprio 6,19,46, Jeffrey R Gulcher 1

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