A common biological basis of obesity and nicotine addiction

Thorgeirsson, T. E.

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ORIGINAL ARTICLE

A common biological basis of obesity and nicotine addiction


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 x 10^{-7}). These findings replicate in a second large data set (N = 127 274, thereof 76 242 smokers) for both SI (P = 1.2 x 10^{-5}) and CPD (P = 9.3 x 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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Keywords: addiction; body mass index; nicotine dependence; obesity; smoking

INTRODUCTION

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

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. All drugs of abuse have been shown to increase dopamine in the mesolimbic reward system, and studies of both human brain images and animal brains 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.

Smoking influences body weight, such that smokers weigh less than non-smokers, and smoking cessation is often accompanied by an increase in weight. 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. 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, and nicotine was recently shown to interact directly with the MC system in the brain through activation of a_{3}b_{4} nicotinic acetylcholine receptors on pro-opiomelanocortin (POMC) neurons 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.

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. 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 and some smoking phenotypes, and these studies have uncovered a number of variants associating with obesity (BMI) and with smoking behavior. The variant most strongly correlating with CPD, 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. This observation is
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, $E[y] = \beta x + \delta$, and that the variance–covariance matrix of the smoking behavior depends only on the pairwise kinship between the study participants, $Var(y) = 2\sigma^2\delta$, where

$$\Phi = \left\{ \frac{1}{2} \delta k, i \neq j \right\}$$

is based on the kinship between individuals as estimated from the Icelandic genealogical database (kij) and an estimate of the heritability of the trait (δ). Assuming normally distributed errors, the maximum likelihood method gives estimates for δ, 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 be its minor allele frequency and γi be its published effect on BMI. For an individual with gi minor alleles at SNP i, the set of 32 BMI SNPs predict a BMI of

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

**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 $\tilde{\rho}_{BMISNP-BMI}$, and the variance of the estimator with $Var(\tilde{\rho}_{BMISNP-BMI})$, and similarly for the correlation between BMI and CPD. Then, $\tilde{\rho}_{BMISNP-BMI-BMI}$ is an estimator of the correlation between the 32 BMI SNPs and CPD, assuming conditional independence, and $Var(\tilde{\rho}_{BMISNP-BMI-BMI})$ 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 be its minor allele frequency and $\gamma_i$ be its published effect on BMI. We denote the unknown effect of each SNP on smoking behavior with $\beta_i$ 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 significance 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 weighted by $\gamma_i$. 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 $\gamma_i \sqrt{f_i(1 - f_i)}$, which we will refer to as $w_i$ and use to weight 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**

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>N</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>0.030 (0.013, 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.\textsuperscript{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\textsuperscript{15–17} (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 CPD and SI, using data from our previous studies outside of Iceland\textsuperscript{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 $\sim 2.500\,000$ 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.\textsuperscript{18} The combined $\chi^2$-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 $P = 1.2 \times 10^{-5}$ and $9.3 \times 10^{-5}$, for SI and CPD, respectively. Combined with Iceland, the association between the 32 BMI SNPs and SI and CPD reached a significance of $P = 1.2 \times 10^{-7}$ and $P = 1.6 \times 10^{-9}$, 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 ($P<0.05$, 5 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 $= 0.0397$, $P = 0.00021$) 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

\begin{figure}[ht]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{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.\textsuperscript{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.\textsuperscript{15–17} The effects on SI are the $\beta$-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 ($P\geq 0.05$) and the input data are provided in (Supplementary Table 1).}
\end{figure}

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 $= 0.0397$, $P = 0.00021$) 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).\textsuperscript{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 ($P = 1.3 \times 10^{-5}$).

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 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.

REFERENCES


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 by.


1 Decode genetics/AMGEN, Sturlugata 8, Reykjavik, Iceland.
2 National Institute for Health and Welfare, Helsinki, Finland.
3 Department of Biological
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Research Institute, Evanston, Illinois, USA. 34Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA. 35Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA. 36International Agency for Research on Cancer (IARC), Lyon, France. 37Institut Catalá d’Oncologia, Barcelona, Spain. 38General Hospital, Pordenone, Italy. 39Institute of Hygiene and Epidemiology, First Faculty of Medicine, Charles University, Prague, Czech Republic. 40Institut National de la Santé et de la Recherche Médicale (INSERM) U794, Paris, France. 41Institut Gustave Roussy, Villejuif, France. 42Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy. 43University of Glasgow Medical Faculty Dental School, Glasgow, UK. 44Specialized Institute of Hygiene and Epidemiology, Banska Bystrica, Slovakia. 45Department of Cancer Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic. 46Palacky University, Olomouc, Czech Republic. 47Trinity College School of Dental Science, Dublin, Ireland. 48Cancer Registry of Cambridge, Massachusetts, USA. 49Department of Molecular Medicine and Genetics, Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. 50Department of Cancer Epidemiology and Prevention, Maria Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland. 51University of Newcastle Dental School, Newcastle, UK. 52University of Amsterdam, Amsterdam, The Netherlands. 53University of Public Health, Bucharest, Romania. 54Center for Experimental Research and Medical Studies, University of Turin, Turin, Italy. 55National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, Maryland, USA. 56Department of Occupational Medicine, Lodz, Poland. 57Institute of Carcinogenesis, Cancer Research Centre, Moscow, Russia. 58Croatian National Cancer Registry, Zagreb, Croatia. 59Center National de Genotypage, Inserm, Paris, France. 60Fondation Jean Dausset-Centre d’Etude du Polymorphisme Humain (CEPH), Paris, France. 61Geriatric Unit, Azienda Sanitaria di Firenze, Florence, Italy. 62Genetics of Complex Traits, Peninsula Medical School, The University of Exeter, Exeter, UK. 63Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland, USA. 64Tuscany Health Regional Agency, Florence, Italy. 65Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. 66Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts, USA. 67Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. 68Center for Human Genetics Research, Massachusetts General Hospital, Boston, Massachusetts, USA. 69Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA. 70Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. 71Cardiovascular Epidemiology and Genetics, Institut Municipal d’Investigacio Medica, Barcelona, Spain. 72Harvard Medical School, Boston, Massachusetts, USA. 73Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, University Hospital Malmö, Lund University, Malmö, Sweden. 74National Heart, Lung, and Blood Institute’s Framingham Heart Study, Framingham, Massachusetts, USA. 75National Institute for Health and Welfare (THL), Helsinki, Finland. 76Department of Medical Genetics, Karolinska Institute, Stockholm, Sweden. 77EMGO Institute, Vrije Universiteit (VU) Medical Center, Amsterdam, The Netherlands. 78Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. 79Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands. 80Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA. 81Program in Molecular and Genetic Epidemiology, Department of Epidemiology, Harvard University, Boston, Massachusetts, USA. 82Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA. 83Department of Epidemiology, Erasmus Medical Center, Member of the Netherlands Consortium on Healthy Aging, Rotterdam, The Netherlands. 84Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands. 85Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. 86Centre for Medical Systems Biology, Erasmus Medical Center, Rotterdam, The Netherlands. 87Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands. 88Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA. 89Department of Cardiovascular Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA. 90Department of Psychiatry and Neurobehavioural Sciences, University of Virginia, Charlottesville, Virginia, USA. 91Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. 92Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, USA. 93Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 94Department of Functional Genomics, VU Amsterdam, Amsterdam, The Netherlands. 95Department of Medical Genomics, VU University Medical Center Amsterdam, Amsterdam, The Netherlands. 96Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, USA. 97Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 98Institute for Molecular Medicine, University of Helsinki, Helsinki, Finland. 99Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA. 100Depal Genetics, Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. 101Tufts Clinical and Translational Science Institute, Tufts University School of Medicine, Boston, Massachusetts, USA. 102Center for Genetic Epidemiology and Modeling, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA. 103Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, USA. 104Oxford-GSK Consortium—Jason S Liu1, Federica Tozzizz2, Dawn M Waterworth3, Sreekumar G Pillai4, Pierandrea Muglia5, Lefkos Middleton6, Wade Berrettini7, Christopher W Knouff8, Xin Yuan9, Gérard Waelder10,11, Peter Vollenweider12, Nicholas J Wareham13, Jing Hua Zhao13, Ruth JF Loos14, Inês Barroso14, W-Tee Khaw15, Scott Grundy16, Philip Barter17, Robert Mahley18,19, Antero Kesaniemi20, Ruth McPherson21,22, John Vincent23, John Strauss23, James Kennedy23, Anne Farmer24, Peter McGuffin24, Richard Dav25, Keith Matthews26, Per Bakke27, Amund Gulsvik28, Susanne Luce29, Marcus Ising27, Tanja Brueckel27, Sonja Horstmann27, Joachim Heinrich28,29,30, Rajesh Rawal28, Norbert Dahmen31, Claudia Lamina32,33, Ozren Polasek34, Lina Zgaga34, Jennifer Huffman35, Susan Campbell35, Jaspal Kooner36, John C Chambers37, Mary Susan Burnett37, Joe Devaney38, Augusto D Pichard39, Kenneth M Kent38, Lowell Satther38, Joseph M Lindsay38, Ron Waksman38, Stephen Epstein38, Jim F Wilson39, Sarah H Wild39, Harry Campbell39, Veronique Vitart40, Muredach P Reilly40,41, Mingya Li42, Li Ming42, Robert Wilensky43, William Mathait44, Hakon H Hakonarson45, Daniel J Rader45, Andre Franke46, Michael Spitz47, Arne Schäfer48, Manuela Udé49, Antonio Terracciano46, Xianguang Xiao46, Fabio Busonero46, Paul Scheet47, David Schlessinger48, David St Clair49, Dan Rujescu49, Gonçalo R Abecasis50, Hans Jörgen Grabe51, Alexander Teumer52, Henry Völke53, Astrid Petersmann54, Ulrich John55, Igor Rudan56, Jane Worthington57, Wendy Thomson58, Steve Eyer56,67, Anne Barton56,68, Vincent Mooser68, Clyde Franks69. 1Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK. 2Clinical Sciences-Apupt Medicines
Reasearch Center, Verona, Italy. 3Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA. 4Genetics Division, GlaxoSmithKline, Upper Merion, Pennsylvania, USA. 5Roche Pharmaceuticals, Nutley, New Jersey, USA. 6Neurosearch Denmark and Department of Psychiatry, University of Toronto, Toronto, Canada. 7Division of Neurosciences and Mental Health, Imperial College London, UK. 8Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. 9Genetics Division, GlaxoSmithKline, Research Triangle Park, North Carolina, USA. 10University Hospital Center, University of Lausanne, Lausanne, Switzerland. 11Department of Internal Medicine, University of Lausanne, Lausanne, Switzerland. 12Department of Psychiatry, University of Lausanne, Lausanne, Switzerland. 13MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge, UK. 14Wellcome Trust Sanger Institute, Hinxton, UK. 15Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK. 16Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA. 17The Heart Research Institute, Sydney, New South Wales, Australia. 18Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA. 19American Hospital, Istanbul, Turkey. 20Department of Internal Medicine, University of Oulu, Oulu, Finland. 21Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. 22Biocenter Oulu, University of Oulu, Oulu, Finland. 23Centre for Addiction and Mental Health, University of Toronto, ON, Canada. 24Medical Research Council Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, UK. 25Center for Neuroscience, Division of Medical Sciences, University of Dundee, Dundee, UK. 26Institute of Medicine, University of Bergen, Bergen, Norway. 27Max-Planck Institute of Psychiatry, Munich, Germany. 28Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 29Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany. 30Klinikum Grosshadern, Munich, Germany. 31Psychiatrische Klinik und Poliklinik University of Mainz, Germany. 32Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria. 33Medical School, University of Split, Split, Croatia. 34Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK. 35Institute of Genetics and Molecular Medicine, MRC Human Genetics Unit, Edinburgh, UK. 36National Heart and Lung Institute, Imperial College London, UK. 37Division of Epidemiology, Imperial College London, UK. 38Cardiovascular Research Institute, MedStar Health Research Institute, Washington Hospital Center, Washington, District of Columbia, USA. 39Centre for Population Health Sciences, University of Edinburgh, UK. 40The Cardiovascular Institute, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 41The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 42Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 43The Center for Applied Genomics, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. 44Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany. 45Istituto di Neurogenetica e Neurofarmacologia, CNR, Monserrato, Cagliari, Italy. 46National Institute on Aging, Baltimore, Maryland, USA. 47Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA. 48Department of Mental Health, University of Aberdeen, Aberdeen, UK. 49Department of Psychiatry, University of Halle, Halle, Germany. 50Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA. 51Department of Psychiatry and Psychotherapy, University of Greifswald, Greifswald, Germany. 52Interfaculty Institute for Genetics and Functional Genomics, University of Greifswald, Greifswald, Germany. 53Institute for Community Medicine, University of Greifswald, Greifswald, Germany. 54Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Greifswald, Germany. 55Department of Social Medicine and Epidemiology, University of Greifswald, Greifswald, Germany. 56Department of Health Sciences, University of Leicester, Leicester, UK. 57Multidisciplinary Cardiovascular Research Centre (MCRC), Leeds Institute of Genetics, Health and Therapeutics (LiGHT), University of Leeds, Leeds, UK. 58Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK. 59Peninsula College of Medicine and Dentistry, Exeter, UK. 60Department of Medical and Molecular Genetics, King’s College London School of Medicine, Guy’s Hospital, London, London, UK. 61Gastroenterology Research Unit, Addenbrooke’s Hospital, Cambridge, UK. 62Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK. 63Clinical Pharmacology and Barts and the London Genome Centre, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK. 64Department of Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Oxford, UK. 65BHF Glasgow Cardiovascular Research Centre, Division of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK. 66Arthritis Research UK Epidemiology Unit, Manchester Academic Health Sciences Centre, Manchester, UK. 67NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester, UK. 68Department of Pathology and Laboratory Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. 69Max Planck Institute for Psycholinguistics.

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