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## A genome-wide investigation of food addiction

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### Abstract

**Objective**—Evidence of parallels between drug addiction and eating behavior continues to accumulate. Genetic studies of addictive substances have yielded a number of susceptibility loci that point to common higher-order genetic pathways underlying addiction. We hypothesized that a genome-wide association study (GWAS) of food addiction would yield significant enrichment in genes and pathways linked to addiction.

**Methods**—We conducted a GWAS of food addiction, determined by the modified Yale Food Addiction Scale (mYFAS), among 9,314 women of European ancestry and examined results for enrichment of single-nucleotide polymorphisms (SNPs)(n=44), genes (n=238) and pathways (n=11) implicated in drug addiction.

**Results**—Two loci met GW-significance ( $P < 2.5 \times 10^{-8}$ ) mapping to 17q21.31 and 11q13.4 that harbor genes with no obvious roles in eating behavior. GW results were significantly enriched for gene members of the MAPK signaling pathway ( $P = 0.02$ ). No candidate SNP or gene for drug addiction was significantly associated with food addiction after correction for multiple-testing.

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**Conclusions**—In the first GWAS of mYFAS, we identified suggestive loci worthy of further follow-up, but provide limited support for shared genetic underpinnings of food addiction and drug addiction. The latter might be due to limited study power and knowledge of the genetics of drug addiction.

### Keywords

food addiction; genetics; population; eating behavior

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## Introduction

Evidence of parallels between addiction and feeding behavior continues to accumulate in neurobiological and behavioral research(1). The novel view of obesity as a neurobehavioral disorder caused by an interaction between a vulnerable brain and an obesogenic environment is reminiscent of models of drug addiction(2). Indeed, genome-wide association studies (GWAS) of adiposity and follow-up studies of confirmed loci yield evidence supporting a behavioral component to obesity(3–5). Early candidate and more recent GWAS of addictive behaviors have yielded a number of susceptibility loci that point to common higher-order genetic pathways underlying addiction(6–8) and thus, provide an opportunity to elucidate whether specific genetic influences on drug addiction generalize to addictive eating behaviors.

The Yale Food Addiction Scale (YFAS) is a psychometric tool based on the Diagnostic and Statistical Manual for Mental Disorders (DSM)-IV codes for substance dependence criteria to assess food addiction in individuals(9). The YFAS has previously been associated with binge-eating episodes, hedonic eating, emotional eating, impulsivity, food and snack craving as well as patterns of neural response implicated in other addictive disorders (10). Food addiction was recently assessed in women participating in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS2) using a modified version of the YFAS, which has similar psychometric properties relative to the original YFAS(11). Among the subset of these women who have GW scan data our aim was to conduct the first comprehensive genetic analysis of food addiction in a population. If food addiction, as captured by mYFAS, shares a molecular pathophysiology to classical addictions, we hypothesized that a GWAS of food addiction would yield significant enrichment in genes and pathways linked to addiction.

## Methods

### Study populations

The NHS was established in 1976 with 121,700 female registered nurses aged 30–55 years and residing in 11 U.S. states(12). The NHS2 cohort was established in 1989 with enrollment of 116,609 female nurses aged 25–44 years and residing in 14 U.S. states(13). Every two years, women in both cohorts have been followed-up with mailed questionnaires on medical history and lifestyle characteristics (12, 13). Study protocols were approved by the institutional review board of Brigham and Women's Hospital.

## Measures

**Assessment of food addiction and covariates**—The YFAS is composed of 25 questionnaire items that are used to assess diagnostic criteria for food addiction and provides both a count of food addiction symptoms and a diagnosis of food addiction as scoring options(9, 14). We recently developed and validated a modified YFAS (mYFAS) for use in large epidemiologic cohorts by adapting the original YFAS to a core of 9 questionnaire items with 1 question from each of the symptom groups that compose the 7 diagnostic criteria plus 2 individual items that assess the presence of clinically significant impairment and distress, respectively (Table S1). For each of the diagnostic criteria, the frequency threshold from the original YFAS was used, and all questions were summed for a total score from 0 to 7 (mYscore). Reliability, convergent, discriminant, and incremental validity of the mYFAS have been reported in detail elsewhere(11). Briefly, in a study sample whose data were previously reported in the validation of the YFAS, the internal consistency of mYscore was adequate and identical to that of the full version of YFAS (Kuder-Richardson  $\alpha = 0.75$ ). Convergent and discriminant validity of mYscore and the original YFAS were also similar. The mYFAS diagnostic version and mYscore were also significantly associated with binge-eating scores above and beyond other measures of eating pathology compared with for the original YFAS diagnostic version and YFAS symptom count(11).

The mYFAS questionnaire was administered in NHS in 2008, at which time the participants were aged 62 to 87 years. In NHS2, mYFAS questionnaires were administered in 2009, when participants were aged 45 to 64 years. Response rates exceeded 80% for both cohorts and those who responded to the food addiction questions were not substantially different from those who did not, with respect to age, BMI, or smoking status(11). A subset of NHS2 responders were invited to complete the full YFAS in 2012 and a strong correlation in scores (Pearson's  $r=0.98$ ) and internal consistency (Cronbach's coefficient  $\alpha =0.84$ ) was observed (11).

For the current GW analysis, we examined two food addiction traits: i) food addiction symptoms (mYscore) modeled as a continuous or dichotomous (mYscore  $\geq 3$ ) trait and ii) the presence/absence of clinically significant impairment and distress (Yclinical). mYscore and Yclinical are derived from a different set of questions as detailed in Table S1. The *combined* presence of  $\geq 3$  food addiction symptoms (mYscore) *and* significant impairment or distress (Yclinical) are proposed diagnostic criteria for food addiction (mYdiag)(9, 11).

All covariates were collected via self-administered questionnaire and concurrently with food addiction measures. BMI ( $\text{kg}/\text{m}^2$ ) was derived from self-reported weight and height, which were reported with high accuracy in our cohorts(15).

**Genotyping, quality control and imputation**—Blood was collected from 32,826 NHS members between 1989 and 1990 and from 29,611 NHS2 members between 1996 and 1999. DNA was extracted from white blood cells. Women contributing to the current genetic analysis were those previously selected for independent GWAS in nested case-control studies initially designed for a variety of chronic diseases (Table S2). To allow for maximum efficiency and power we pooled samples genotyped on the same platforms, which resulted in three datasets herein referred to as Affy (NHS), Illumina (NHS, NHS2) and Omni (NHS).

Detailed methods and quality assurance pertaining to these genetic datasets have been reported elsewhere(16) and relevant descriptive and quality control (QC) data are provided in Table S2. Any samples that had substantial genetic similarity to non-European reference samples were excluded. For each of the three datasets we used MACH (v.1.0.18.c) and Minimac (v.2012-08-15) to impute ~31 million SNPs based on the 1000G v3 ALL reference panel.

### Statistical analysis

**Genome-wide analysis of mYFAS**—Each genetic dataset was examined separately for each cohort of women and the results were combined by meta-analysis. Within the Illumina dataset there are data from NHS *and* NHS2. Thus, four datasets were examined: Affy-NHS (N=3298), Illumina-NHS (N=2690), Omni-NHS (N=2520) and Illumina-NHS2 (N=806). For each dataset we performed GWA-testing for each trait across ~31 million SNPs (expressed as allele dosage), based on linear (mYscore) or logistic (mYscore<sub>3</sub>, Yclinical) regression under an additive genetic model and adjusting for age, BMI, initial case-control dataset, and four principal components of population substructure. SNPs with minor allele frequency (MAF) <0.01 or with low imputation quality scores (MACH's Rsq<0.3) were removed prior to meta-analysis (Table S2). In secondary analyses we removed BMI from the model or further adjusted for smoking status (current, past, never).

For both food addiction traits (mYscore, mYclinical), GW meta-analysis was conducted using a fixed effects model and inverse-variance weighting with a single genomic control (GC) correction as implemented in METAL(17). Between-dataset heterogeneity was investigated using the  $I^2$  statistic (18). Top loci associated with each trait were retained and formally presented if i) SNPs passed QC filters in all four datasets and ii) direction of effects were consistent across all datasets. GW significance was defined as  $P < 2.5 \times 10^{-8}$ ; the traditional threshold ( $P < 5 \times 10^{-8}$ )(19) corrected for the number of independent traits. Nominally significant loci were tabulated if the direction of effects was consistent across all datasets *and* food addiction traits. Top loci were examined for associations with mYdiag, BMI and smoking in the NHS (the larger of the two contributing cohorts). Our full summary level results were also investigated for associations with BMI based on a published large-scale GWAS(3).

**Candidate SNP, gene-set and pathway analysis**—We interrogated summary levels results from our GWAS of mYscore and Yclinical for evidence of overlap with SNPs, genes and pathways implicated in drug addiction. 'Addiction SNPs' included 44 independent ( $r^2 < 0.8$ ) common (MAF > 0.01) SNPs achieving at least nominal significance ( $< 1 \times 10^{-6}$ ) in GWAS for addiction traits as reported in the NHGRI catalogue (August 2014) and unrelated to drug metabolism (Table S3). 'Addiction Genes' were also unrelated to drug metabolism and included 5 genes associated with at least one drug addiction that have been verified by meta-analysis and 60 genes associated with more than one drug addiction, as reviewed by Li et al (20), and genes within 300kb (or closest gene >300 kb) of each 'Addiction SNP'. In total, 238 genes were considered 'Addiction Genes' (Table S4). Candidate gene-based analyses were performed using VEGAS (21). We applied Bonferroni-corrected thresholds of  $P < 0.001$  [ $0.05/44$  (number of SNPs tested)] and

$P < 2.1 \times 10^{-4}$  [ $0.05/238$  (number of genes tested)] for SNP-level and gene-level significance, respectively. Multi-SNP linear kernel tests were additionally used to assess the joint relation between the 44 ‘Addiction SNPs’ and food addiction(22). These linear models allow associations of multiple SNPs to be tested simultaneously with one test and require no prespecification of risk allele direction.

Meta-Analysis Gene-set Enrichment of variant Associations (MAGENTA) (23) was used to test our GW mYFAS results for addiction pathway enrichment. In preliminary pathway analyses of our ‘Addiction Genes’ (defined above) we observed consistent enrichment of genes related to the Kegg pathways: (1) ‘neuroactive ligand-receptor interaction’, (2) ‘tyrosine metabolism’, (3) ‘calcium signaling pathway’, (4) ‘amyotrophic lateral sclerosis’, (5) ‘tryptophan metabolism’, (6) ‘histidine metabolism’ and (7) ‘long-term potentiation’ (Table S5). Two of these pathways overlapped with those reported by Li et al(8); who further reported over enrichment of genes related to (8) ‘GnRH signaling pathway’, (9) ‘MAPK signaling pathway’ and (10) ‘Gap junctions’. We additionally created an (11) ‘Addiction’ gene-set that included the ‘Addiction Genes’ defined above (excluding 14 genes: hypothetical or pseudo genes or genes not annotated by MAGENTA). Taken together, 11 gene-sets or pathways were specifically tested and MAGENTA’s nominal significance threshold of 0.05 was applied. Hypothesis testing was supplemented with exploration: results were tested against 3,218 pathways from seven databases. For each pathway, enrichment of highly ranked gene scores above the 95<sup>th</sup> percentile of all gene scores in the meta-analyses was evaluated compared to 10,000 randomly sampled gene-sets(23).

## Results

### Characteristics of NHS and NHS2

General characteristics of the 9,314 women included in the current analysis are presented in Table S2. The mean (standard deviation, SD) mYscore for NHS and NHS2 was 0.60 (1.05) and 1.04 (1.6), respectively. The prevalence of Yclinical and mYdiag were 4.9% and 2.6% in NHS. Corresponding prevalences in NHS2 were 11.2% and 8.7%. mYscore was correlated with BMI in both cohorts (NHS Pearson’s  $r=0.27$ , NHS2 Pearson’s  $r=0.42$ ;  $P < 0.001$ ). These results are similar to those reported for the full NHS and NHS2 cohorts, showing a higher presence of food addiction in the younger cohort(11).

### GWAS of mYFAS

Two loci met criteria for GW-significance in GWAS of food addiction traits (Table 1, Figure S1–S3). SNPs at 17q21.31 mapping to the intronic region of *PRKCA* were significantly associated with mYscore ( $P=2.0 \times 10^{-8}$ ) and also associated with Yclinical ( $P=6.4 \times 10^{-4}$ ). In the NHS, the variant of the 17q21.31 index SNP rs74902201 linked to higher mYscore was also associated with a positive mYdiag ( $P=3.4 \times 10^{-5}$ ). SNPs at 11q13.4 mapping to the intronic region of *NTM* were significantly associated with mYscore but not with Yclinical. In the NHS, the variant of the 11q13.4 index SNP rs75038630 linked to higher mYscore was also associated with a positive mYdiag ( $P=1.7 \times 10^{-4}$ ) but with a *lower* BMI ( $P=0.02$ ). A borderline GW-significant association was observed between an intergenic 6q22.32 locus near *CENPW* and mYscore ( $P=3.1 \times 10^{-8}$ ). In the NHS, the variant of the 6q22.32 index

SNP rs139878170 linked to higher mYscore was associated with a positive mYdiag ( $P=1.4 \times 10^{-5}$ ). Removing BMI from the regression model strengthened the association between rs139878170 and mYscore ( $P=6.9 \times 10^{-9}$ , Table S6).

Loci (or proxies) reported in Table 1 were not associated with BMI according to a published large-scale GWAS of BMI(3). Of the 32 BMI loci reported in the latter, rs1558902 (*FTO*,  $P=0.04$ ), rs206936 (*NUDT3*,  $P=0.01$ ), and rs10150332 (*NRXN3*,  $P=0.05$ ) were associated with mYscore when modeled dichotomously.

### Candidate addiction SNPs

No association between candidate SNPs and food addiction traits met our pre-specified significance threshold ( $P<0.001$ ). Among the 44 SNPs previously associated with addiction traits in GWAS, only a nominally significant association between the intergenic SNP rs1868152 (previously associated with illicit drug use(24)) was observed for mYscore and Yclinical ( $P<0.004$ , Table S7). Results from multi-SNP linear kernel tests were not consistent across Affy-NHS, Omni-NHS, Illumina-NHS and Illumina-NHS2. Tests were only significant for dichotomously modeled mYscore in NHS-Affy ( $P=0.03$ ) and Yclinical in NHS2-Illumina ( $P=0.01$ ). Tests performed on the combined datasets were not significant ( $P>0.07$ ).

### Candidate addiction genes

No candidate gene-based test for associations with food addiction traits met our pre-specified significance threshold ( $P<2.1 \times 10^{-4}$ ) (Table S7). The most statistically significant gene was *LOC100130673* ( $P<5.0 \times 10^{-4}$  for mYscore), a pseudogene on chromosome 7 selected for its proximity to a smoking behavior SNP (rs215614)(25). The latter is ~135kb away from our top SNP in this pseudogene (rs61436781,  $P<9.7 \times 10^{-6}$ ) and is not in LD ( $r^2<0.2$ ). Four ‘addiction genes’ were nominally significant ( $P<0.05$ ) for both mYscore and Yclinical including *HOMER1*, *ZHX2*, *DRD2* and *SURF6*.

### Candidate addiction pathways

Yclinical results were significantly enriched for MAPK signaling pathway genes ( $P=0.02$ , Table 2) and this same gene-set reached borderline significance for mYscore ( $P=0.07$ ). Enrichment for tyrosine, histidine and tryptophan metabolism genes was observed for the continuously modeled mYscore ( $P<0.03$ ). Our mYscore and Yclinical results were not significantly enriched for gene members of our custom addiction gene-set (Table 2). An exploratory GW pathway analysis of food addiction, yielded significant enrichment for genes in GO’s interleukin-1 receptor (IL1R) binding pathway [mYscore (binary),  $FDR=0.003$ ]. Larger but similar gene sets from Ingenuity (IL-10 signaling) and Biocarta (IL1R pathway) were also among the top pathways.

## Discussion

The concept of ‘food addiction’ (or ‘eating addiction’) is an ongoing debate of growing scientific interest. The most compelling evidence supporting such a condition is the overlapping neurobiological systems reportedly activated by both drugs of abuse and highly

palatable foods in experimental and clinical models(1). In the current study, we examined whether genetic determinants of food addiction overlap with those of drug addictions. To this end, we conducted the first GWAS of mYFAS and identified suggestive loci worthy of further follow-up but provide limited support of shared genetics with drug addictions based on comprehensive candidate SNP, gene and pathway analysis.

We identified novel GW significant loci in *PRKCA* and *NTM* in two populations of U.S. women of European ancestry. Each index SNP variant conferring a higher mYscore occurs in ~6% of European populations and in 0 to 16% in non-European populations(26). *PRKCA* encodes a calcium-activated, phospholipid- and diacylglycerol-dependent serine/threonine-protein kinase that is involved in regulating numerous biological processes such as insulin signaling, inflammation and mitogen-activated protein kinase (MAPK) activity(27). MAPK signaling is highly implicated in brain function and also a candidate drug addiction pathway(28). The index SNP in *PRKCA* resides in regulatory regions for multiple tissues, notably enhancer regions for the brain(29), and alters a binding site of NRSF(30), a transcriptional repressor of neuronal genes in non-neuronal tissues. *PRKCA* has previously been associated with both BMI and asthma via linkage and follow-up SNP analysis by Murphy et al(31). SNPs examined by Murphy et al(31) were not associated with mYFAS in the current study ( $P>0.32$ ) nor with BMI in GWAS(3). *NTM* at 11q25 encodes neurotrimin and is highly expressed in human brain tissue and closely linked to opioid binding protein/cell adhesion molecule-like (*OPCML*), also on chromosome 11(32). This SNP region binds NR2C2, which serves as an important repressor of several nuclear receptor signaling pathways and is required for normal cerebellum development(33). Significant to nominal associations in the 11q25 region have also been reported for alcohol dependence (*OPCML*) (24), body fat distribution (*OPCML*)(34, 35), and various other traits(36) but none of the index SNPs in these reports were associated with food addiction in the current study. Only one (rs4937665) of the top SNPs near *NTM* previously associated with IQ in GWAS was also associated with food addiction traits(37). Food addiction has not been measured in any other large population-based study and thus we were unable to replicate our two novel and promising loci in an independent study.

Our GW analysis of food addiction provides limited support for shared pathways among food addiction and drug addiction. Literature informed SNPs and genes linked to addiction traits were not associated with mYFAS. Of the eleven addiction related pathways tested, only the MAPK signaling pathway met our threshold for significance. The same pathway was nominally significant (nominal GSEA  $P=0.02$ ) in the published gene-set enrichment analysis of BMI (3); *BDNF*, *NFKB1* and *MAP2K5* were this pathway's gene-members mapping to established BMI loci. *PRKCA* and its neighboring calcium channel genes are also members of this pathway which may have induced a degree of chance or, alternatively, lends support for our novel loci and a link between drug addiction and food addiction. Interestingly, interleukin-1 receptor binding, a significant pathway in our global pathway analysis and also recently implicated in addiction behavior(38), does not include *PRKCA* or *NTM*, suggesting additional and novel loci of sub-GW significance in the current study await discovery in future efforts.

Davis et al(39) developed a genetic risk score for dopamine signaling and among 121 overweight adults reported a higher score (conferring elevated dopamine signaling) in those with YFAS diagnosed food addiction and a positive correlation with binge eating, food cravings, and emotional eating. Their score included 6 SNPs near *DRD2*, *SLC6A3* and *COMT*. Four (rs1800497, rs6277, rs12364283, rs4680) of the 6 SNPs were genotyped/ imputed in the current study. High quality proxies for the remaining two SNPs were not available. rs1800497 was associated with Yclinical (P=0.04) and in the expected direction. rs12364283 was associated with mYscore when modeled dichotomously (P=0.03) but the direction of effect was opposite to that expected. All three genes were ‘addiction candidate genes’ that were examined in the current study but none met our significance criteria. Differences in study population might explain the discrepancies between the current study and that of Davis et al(39).

GWAS of BMI have identified several loci and some of these are implicated in hedonic rather than homeostatic pathways for obesity(3–5). BMI is not a direct measure of food addiction but purportedly has a behavioral component which forms the basis of the obesity-addiction hypothesis. Thorgeirsson et al(40) recently reported a significant positive correlation between a genetic risk score for higher BMI and smoking behaviors (smoking initiation, and dose). Less than 10% of our cohort participants were current smokers and this limited our ability to conduct a similar analysis. Nevertheless, none of our GW-significant food addiction SNPs were associated with BMI in a large GWAS(3) and only nominal associations between 4 of 32 validated obesity loci and food addiction were observed. These results together with limited evidence of overlap with addiction pathways conflict with conclusions drawn by Thorgeirsson et al(40). In the NHS, the associations between our GW-loci and mYFAS were largely independent of BMI. Nevertheless, individuals genetically predisposed to food addiction might be more susceptible to obesity in the presence of an environment that fosters availability of palatable foods; a concept analogous to that described for illicit drug addiction.

The current study marks the first comprehensive genetic analysis of food addiction in a population. We discovered novel loci associated with food addiction traits warranting independent replication. We additionally gained insight to potential genetic overlaps between food addiction and drug addiction by integrating our GW food addiction results with extant genetic knowledge of drug addiction. Although results suggested that the MAPK signaling pathway may be a shared determinant, our results taken together suggest the genetic underpinnings of food addiction and drug addiction are largely distinct. However, our study may have had modest power to detect novel loci and significant overlap with genetic variation of other addictions, given the sample size, measurement error in food addiction assessment and the narrow range and low prevalence of food addiction symptomology. The latter might be addressed in future studies by employing a case-enrichment design. The ability to identify shared genetic determinants of food and drug addiction may also be limited by incomplete knowledge of genetic determinants of drug addiction.



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## References

1. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev.* 2013; 14:2–18. [PubMed: 23016694]
2. Dagher A. The neurobiology of appetite: hunger as addiction. *Int J Obes (Lond).* 2009; 33(Suppl 2):S30–33. [PubMed: 19528977]
3. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010; 42:937–948. [PubMed: 20935630]
4. Stutzmann F, Cauchi S, Durand E, Calvacanti-Proenca C, Pigeyre M, Hartikainen AL, et al. Common genetic variation near MC4R is associated with eating behaviour patterns in European populations. *Int J Obes (Lond).* 2009; 33:373–378. [PubMed: 19153581]
5. Cornelis MC, Rimm EB, Curhan GC, Kraft P, Hunter DJ, Hu FB, et al. Obesity susceptibility loci and uncontrolled eating, emotional eating and cognitive restraint behaviors in men and women. *Obesity (Silver Spring).* 2014; 22:E135–141. [PubMed: 23929626]
6. Li CY, Zhou WZ, Zhang PW, Johnson C, Wei L, Uhl GR. Meta-analysis and genome-wide interpretation of genetic susceptibility to drug addiction. *BMC Genomics.* 2011; 12:508. [PubMed: 21999673]
7. Uhl GR, Drgon T, Johnson C, Liu QR. Addiction genetics and pleiotropic effects of common haplotypes that make polygenic contributions to vulnerability to substance dependence. *Journal of neurogenetics.* 2009; 23:272–282. [PubMed: 19152208]
8. Li CY, Mao X, Wei L. Genes and (common) pathways underlying drug addiction. *PLoS computational biology.* 2008; 4:e2. [PubMed: 18179280]
9. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite.* 2009; 52:430–436. [PubMed: 19121351]
10. Carlier N, Marshe VS, Cmorejova J, Davis C, Müller DJ. Genetic Similarities between Compulsive Overeating and Addiction Phenotypes: A Case for “Food Addiction”? *Current psychiatry reports.* 2015; 17:1–11. [PubMed: 25617038]
11. Flint AJ, Gearhardt AN, Corbin WR, Brownell KD, Field AE, Rimm EB. Food-addiction scale measurement in 2 cohorts of middle-aged and older women. *Am J Clin Nutr.* 2014; 99:578–586. [PubMed: 24452236]
12. Colditz GA, Hankinson SE. The Nurses’ Health Study: lifestyle and health among women. *Nat Rev Cancer.* 2005; 5:388–396. [PubMed: 15864280]
13. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Spiegelman D, et al. Physical activity and breast cancer risk in a cohort of young women. *J Natl Cancer Inst.* 1998; 90:1155–1160. [PubMed: 9701365]
14. Gearhardt AN, Corbin WR, Brownell KD. Food Addiction: An Examination of the Diagnostic Criteria for Dependence. *Journal of Addiction Medicine.* 2009; 3:1–7. DOI: 10.1097/ADM.1090b1013e318193c318993 [PubMed: 21768996]

15. McAdams MA, Van Dam RM, Hu FB. Comparison of self-reported and measured BMI as correlates of disease markers in US adults. *Obesity (Silver Spring)*. 2007; 15:188–196. [PubMed: 17228047]
16. Lindstrom S, Loomis S, Chen C, Huang H, Huang J, Aschard H, et al. A comprehensive survey of genetic variation in 20,691 subjects from four large cohorts. *Bioinformatics*. 2015 submitted.
17. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010; 26:2190–2191. [PubMed: 20616382]
18. Ioannidis JP, Patsopoulos NA, Evangelou E. Heterogeneity in meta-analyses of genome-wide association investigations. *PLoS One*. 2007; 2:e841. [PubMed: 17786212]
19. Pe'er I, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. *Genet Epidemiol*. 2008; 32:381–385. [PubMed: 18348202]
20. Li MD, Burmeister M. New insights into the genetics of addiction. *Nat Rev Genet*. 2009; 10:225–231. [PubMed: 19238175]
21. Liu JZ, McRae AF, Nyholt DR, Medland SE, Wray NR, Brown KM, et al. A versatile gene-based test for genome-wide association studies. *Am J Hum Genet*. 2010; 87:139–145. [PubMed: 20598278]
22. Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, et al. Powerful SNP-set analysis for case-control genome-wide association studies. *Am J Hum Genet*. 2010; 86:929–942. [PubMed: 20560208]
23. Segre AV, Groop L, Mootha VK, Daly MJ, Altshuler D. Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits. *PLoS Genet*. 2010; 6:e1001058. [PubMed: 20714348]
24. McGue M, Zhang Y, Miller MB, Basu S, Vrieze S, Hicks B, et al. A genome-wide association study of behavioral disinhibition. *Behavior genetics*. 2013; 43:363–373. [PubMed: 23942779]
25. Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F, et al. Sequence variants at CHRN3-CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet*. 2010; 42:448–453. [PubMed: 20418888]
26. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, et al. Genomes Project C. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012; 491:56–65. [PubMed: 23128226]
27. Cuadrado A, Nebreda AR. Mechanisms and functions of p38 MAPK signalling. *Biochem J*. 2010; 429:403–417. [PubMed: 20626350]
28. Chen RS, Deng TC, Garcia T, Sellers ZM, Best PM. Calcium channel gamma subunits: a functionally diverse protein family. *Cell biochemistry and biophysics*. 2007; 47:178–186. [PubMed: 17652770]
29. Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, et al. Roadmap Epigenomics C. Integrative analysis of 111 reference human epigenomes. *Nature*. 2015; 518:317–330. [PubMed: 25693563]
30. Ernst J, Kheradpour P, Mikkelsen TS, Shores N, Ward LD, Epstein CB, et al. Mapping and analysis of chromatin state dynamics in nine human cell types. *Nature*. 2011; 473:43–49. [PubMed: 21441907]
31. Murphy A, Tantisira KG, Soto-Quiros ME, Avila L, Klanderma BJ, Lake S, et al. PRKCA: a positional candidate gene for body mass index and asthma. *Am J Hum Genet*. 2009; 85:87–96. [PubMed: 19576566]
32. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. *Nat Genet*. 2013; 45:580–585. [PubMed: 23715323]
33. Hirose T, Apfel R, Pfahl M, Jetten AM. The orphan receptor TAK1 acts as a repressor of RAR-, RXR- and T3R-mediated signaling pathways. *Biochem Biophys Res Commun*. 1995; 211:83–91. [PubMed: 7779113]
34. Liu CT, Monda KL, Taylor KC, Lange L, Demerath EW, Palmas W, et al. Genome-wide association of body fat distribution in African ancestry populations suggests new loci. *PLoS Genet*. 2013; 9:e1003681. [PubMed: 23966867]

35. Fox CS, Liu Y, White CC, Feitosa M, Smith AV, Heard-Costa N, et al. Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women. *PLoS Genet.* 2012; 8:e1002695. [PubMed: 22589738]
36. Hindorf L, MacArthur J, Morales J, Junkins H, Hall P, Klemm A, et al. Catalogue of Published Genome-Wide Association Studies. [accessed January 1, 2015]
37. Pan Y, Wang KS, Aragam N. NTM and NR3C2 polymorphisms influencing intelligence: family-based association studies. *Progress in neuro-psychopharmacology & biological psychiatry.* 2011; 35:154–160. [PubMed: 21036197]
38. Bajo M, Herman MA, Varodayan FP, Oleata CS, Madamba SG, Harris RA, et al. Role of the IL-1 receptor antagonist in ethanol-induced regulation of GABAergic transmission in the central amygdala. *Brain, behavior, and immunity.* 2015; 45:189–197.
39. Davis C, Loxton NJ, Levitan RD, Kaplan AS, Carter JC, Kennedy JL. ‘Food addiction’ and its association with a dopaminergic multilocus genetic profile. *Physiol Behav.* 2013; 118:63–69. [PubMed: 23680433]
40. Thorgeirsson TE, Gudbjartsson DF, Sulem P, Besenbacher S, Styrkarsdottir U, Thorleifsson G, et al. A common biological basis of obesity and nicotine addiction. *Translational psychiatry.* 2013; 3:e308. [PubMed: 24084939]

**What is already known about this subject?**

- The concept of ‘food addiction’ is supported by the overlapping neurobiological systems reportedly activated by both drugs of abuse and highly palatable foods in experimental and clinical models
- Early candidate and more recent GWAS of addictive substances have yielded a number of susceptibility loci that point to common higher-order genetic pathways underlying addiction
- The Yale Food Addiction Scale (YFAS) is a psychometric tool used to assess food addiction and has previously been associated with disordered eating and patterns of neural response implicated in other addictions

**What does this study add?**

- The authors conducted a GWAS of food addiction, determined by a modified version of the YFAS among women and examined results for enrichment of single-nucleotide polymorphisms, genes and pathways implicated in drug addiction
- Two loci met GW-significance mapping to regions that harbor genes with no obvious roles in eating behavior. GW results were significantly enriched for gene members of the MAPK signaling pathway but no candidate SNP or gene for drug addiction was significantly associated with food addiction
- The authors identified suggestive loci worthy of further follow-up, but provide limited support for shared genetic underpinnings of food addiction and drug addiction

**Table 1**  
Top SNPs associated with the modified Yale food addiction scale in the Nurses' Health Studies

CHR:POS	Index SNP <sup>a</sup>	Rsq <sup>b</sup>	EA/NEA	EAF	Continuous		Binary		Yclinical <sup>d</sup>		Closest genes	
					$\beta$ (SD)	P	OR(95%CI)	P	OR (95% CI)	P	P	P
1:192035026	rs12126348	0.72	T/G	0.03	-0.25 (0.05)	7.76×10 <sup>-7</sup>	0.42 (0.25-0.71)	1.19×10 <sup>-3</sup>	0.37 (0.21-0.68)	1.12×10 <sup>-3</sup>		<i>RGS18, RGS21</i>
4:77953009	<b>rs1135642</b>	0.95	A/G	0.08	0.12 (0.03)	5.90×10 <sup>-6</sup>	1.66 (1.37-2.01)	2.68×10 <sup>-7</sup>	1.36 (1.09-1.69)	6.70×10 <sup>-3</sup>		<i>SEPT11</i>
5:7296723	rs147346874	0.65	A/G	0.85	-0.06 (0.03)	0.03	0.76 (0.63-0.93)	6.65×10 <sup>-3</sup>	0.60 (0.49-0.73)	9.93×10 <sup>-7</sup>		<i>ADCY2</i>
6:127020869	rs139878170	0.50	A/C	0.02	0.37 (0.07)	3.14×10 <sup>-8</sup>	2.42 (1.60-3.66)	2.59×10 <sup>-5</sup>	2.46 (1.58-3.81)	6.32×10 <sup>-5</sup>		<i>CENPW, RSPO3, RNF146</i>
11:131758328	<b>rs75038630</b>	0.55	A/C	0.06	0.19 (0.04) <sup>e</sup>	4.93×10 <sup>-6</sup>	2.27 (1.70-3.02)	<b>2.32×10<sup>-8</sup></b> <sup>g</sup>	1.34 (0.94-1.91) <sup>e</sup>	0.11		<i>NTM</i>
14:20888553	<i>indel</i>	0.70	CA/C	0.16	0.10 (0.02)	2.95×10 <sup>-5</sup>	1.57 (1.31-1.88)	7.90×10 <sup>-7</sup>	1.26 (1.03-1.55)	0.03		<i>TEP1, KLHL33, OSCEP</i>
17:64711563	<b>rs74902201</b>	0.98	A/G	0.06	0.17 (0.03)	<b>2.00×10<sup>-8</sup></b> <sup>g</sup>	1.74 (1.41-2.15)	1.92×10 <sup>-7</sup>	1.52 (1.20-1.93) <sup>f</sup>	6.36×10 <sup>-4</sup>		<i>PRKCA</i>

CHR, chromosome; EA, effect allele; EAF, effect allele frequency; indel, insertion/deletion; NEA, non-effect allele; POS, position; SNP, single-nucleotide polymorphism.

<sup>a</sup>Genic SNPs are in boldface.

<sup>b</sup>Sample-size weighted mean SNP imputation quality score.

<sup>c</sup>Effect estimates and corresponding P values from fixed-effects meta-analysis of linear (Continuous,  $\beta$ ) or logistic (Binary: mYscore -3, OR) regressions of SNP and food addiction symptoms (mYscore).

<sup>d</sup>Effect estimates and corresponding P values from fixed-effects meta-analysis of logistic regressions of SNP and presence/absence of clinically significant food-related impairment and distress.

<sup>e</sup>I<sup>2</sup> for heterogeneity >50%.

<sup>f</sup>Different trait effect directions across datasets.

<sup>g</sup>Meets criteria for GW-significance (see Methods)

Candidate addiction pathway analysis of the modified Yale food addiction scale in the Nurses' Health Studies

Table 2

Database, Pathway	Original #Genes	Effective #Genes	mYscore <sup>a</sup>		Yclinical <sup>b</sup>	
			Continuous	Binary	P	P
			P	P	P	P
Custom, Addiction	224	162 to 172	0.64	0.30	0.99	0.99
KEGG, Amyotrophic lateral sclerosis	53	51 to 53	0.48	0.26	0.46	0.46
KEGG, Calcium signaling pathway	178	162 to 172	0.86	0.63	0.87	0.87
KEGG, Gap junction	90	85 to 86	0.80	0.82	0.26	0.26
KEGG, GnRH signaling pathway	101	94 to 97	0.71	0.87	0.05	0.05
KEGG, Long term potentiation	70	65 to 69	0.67	0.68	0.45	0.45
KEGG, MAPK signaling pathway	267	241 to 254	0.07	0.29	0.02	0.02
KEGG, Neuroactive ligand receptor interaction	272	235 to 252	0.59	0.57	0.19	0.19
KEGG, Tyrosine metabolism	42	38 to 39	0.01	0.86	0.86	0.86
KEGG, Histidine metabolism	29	26 to 27	0.003	0.74	0.99	0.99
KEGG, Tryptophan metabolism	40	36 to 37	0.03	0.85	0.55	0.55

Addiction pathway-enrichment analysis (see Methods) using summary statistics from fixed-effects meta-analysis of

<sup>a</sup>linear (continuous) or logistic (binary) mYscore regressions of SNP and food addiction symptoms (mYscore) and

<sup>b</sup>logistic regressions of SNP and presence/absence of clinically significant food-related impairment and distress. Presented are nominal P-values for pathway-enrichment based on a 95% gene-level P-value threshold.