Identification of Pleiotropic Genetic Effects on Obesity and Brain Anatomy

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Key Words

Body mass index · Obesity · Imaging · Brain · Pleiotropy

Abstract

Background/Aims: Obesity is a major contributor to the global burden of chronic disease and disability, though current knowledge of causal biologic underpinnings is lacking. Through the regulation of energy homeostasis and interactions with adiposity and gut signals, the brain is thought to play a significant role in the development of this disorder. While neuroanatomical variation has been associated with obesity, it is unclear if this relationship is influenced by common genetic mechanisms. In this study, we sought genetic components that influence both brain anatomy and body mass index (BMI) to provide further insight into the role of the brain in energy homeostasis and obesity. **Methods:** MRI images of brain anatomy were acquired in 839 Mexican American individuals from large extended pedigrees. Bivariate linkage and quantitative analyses were performed in SOLAR. **Results:** Genetic factors associated with an increased BMI were also associated with a reduced cortical surface area

and subcortical volume. We identified two genome-wide quantitative trait loci that influenced BMI and the ventral diencephalon volume, and BMI and the supramarginal gyrus surface area, respectively. **Conclusions:** This study represents the first genetic analysis seeking evidence of pleiotropic effects acting on both brain anatomy and BMI. Our results suggest that a region on chromosome 17 contributes to the development of obesity, potentially through leptin-induced signaling in the hypothalamus, and that a region on chromosome 3 appears to jointly influence the food-related reward circuitry and the supramarginal gyrus.

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Introduction

Obesity is a major contributor to chronic disease and disability worldwide. In the US alone, one third of the adult population is obese and more than two thirds are overweight or obese. The prevalence of obesity among youth has tripled in the past 10 years, with 17% of children and adolescents now considered obese [1, 2]. In

2009, only two US states had an obesity prevalence rate of less than 20%, and a staggering 33 states had prevalence rates greater than 25% [1]. Of major importance for providing insight into this epidemic is the characterization of a poorly understood genetic component to disease susceptibility. Obesity-related phenotypes are 40–70% heritable [2–4], yet risk genes remain elusive. The latest update of the Obesity Gene Map reports 127 candidate genes identified for common human obesity. However, only 22 of these genes (or more accurately, gene regions) are supported by multiple studies. Furthermore, the established body mass index (BMI) loci detected from large-scale genome-wide association analyses jointly account for <2% of the interindividual variation in BMI [5, 6].

Several of the most strongly associated and replicated gene regions for obesity including *FTO*, *BDNF*, *SH2B1* and *NEGR1* have also been shown to influence aspects of neuronal function, particularly in the hypothalamus, reinforcing the view that obesity is in part a brain-related disorder [6]. Further supporting a role for a significant link between the brain and obesity is the increased risk of brain atrophy, cognitive dysfunction and dementia later in the life of obese individuals. In an imaging study of 94 elderly subjects, Raji et al. [7] showed that a higher BMI was significantly correlated with reduced gray matter and white matter volumes throughout the brain, and that atrophy (indicating an increased risk for dementia) was evident in people with greater percentages of body fat tissue. Similar results were observed for individuals with high fasting insulin levels and type 2 diabetes. A third imaging study of 50 adults demonstrated that an increased BMI is associated with axonal and/or myelin abnormalities in the frontal white matter and neuronal injury in the frontal gray matter [8]. In a fourth study by Ho et al. [9], subjects with a higher BMI had significantly lower regional brain volumes, and structural brain atrophy was observed in carriers of at least one copy of a risk allele correlated with a marker in the *FTO* gene, although it still remains to be established whether *FTO* is the underlying causal gene. Additionally, individuals carrying this risk allele showed brain tissue deficits in the frontal and occipital lobe regions, which are the same areas associated with brain volume reductions in subjects with a high BMI. These results suggest an underlying common susceptibility variant for obesity that is independently associated with brain atrophy [9]. Together, these neuroanatomical studies demonstrate a consistent link between increasing obesity and brain atrophy and suggest that this relationship may be mediated by genetic factors. However,

formal genetic experiments to implicate pleiotropy between obesity and neuroanatomical phenotypes have not been reported.

The current study represents an attempt to examine the potential pleiotropic basis of obesity and brain structural variation in a human population. Using an extended pedigree design, we examine the evidence for such shared genetic influence and attempt to exploit it to identify likely genomic locations harboring causal loci.

Research Design and Methods

Human Subject Selection

All subjects included in this analysis were Mexican-American individuals from the Genetics of Brain Structure and Function Study (GOBS) who were originally recruited to participate in the San Antonio Family Heart Study (SAFHS) [10] or the San Antonio Family Gallbladder Study (SAFGS) [11]. At baseline, the SAFHS included 1,431 individuals from 42 extended families. Ascertainment occurred by way of a single adult Mexican-American proband selected at random, regardless of the presence or absence of disease and almost exclusively from Mexican-American census tracts in San Antonio. To ensure large multigenerational pedigrees, the probands had to have at least 6 age-eligible offspring and/or siblings living in San Antonio. All first-, second- and third-degree relatives of the proband and of the proband's spouse, aged 16 years or above, were eligible to participate in the study. The SAFGS cohort currently includes 907 individuals from 39 large Mexican-American families. Recruitment was similar to that of the SAFHS, with probands recruited from a random sample of Mexican-American individuals, but in the SAFGS probands were selected for type 2 diabetes [12]. All first-, second- and third-degree relatives of the proband, aged 18 years or above, were invited to participate. The near-identity of the ascertainment designs for the SAFHS and SAFGS trials has been confirmed via comparisons of all diabetes- and obesity-related phenotypes.

For the analyses herein, we utilized 839 GOBS subjects [13], from whom we had acquired MRI-based anatomical brain measures and BMI as a measure of obesity. Our sample consisted of 514 females with an average age of 43.0 ± 14.2 years and 325 males with an average age of 43.7 ± 15.1 years from 57 extended families. Of these families, 19 represented large extended pedigrees, each with 18 or more participants (max. pedigree size = 125).

All participants gave written informed consent, and the Institutional Review Boards of the University of Texas Health Science Center at San Antonio and Yale University approved all protocols.

MRI Acquisition and Processing

MR images were acquired on a Siemens 3T TIM Trio scanner with an 8-channel head coil in the Research Imaging Institute, University of Texas Health Science Center at San Antonio. The anatomical imaging protocol included seven T1-weighted 3D turbo-flash scans with an adiabatic inversion contrast pulse and the following parameters: TE/TR/TI = 3.04/2100/785 ms, flip angle = 13°, and 800 μ m isotropic voxel resolution. These images underwent a retrospective motion correction [14] and were averaged to achieve optimal gray/white matter contrast for each subject.

Anatomical (gray matter) image processing was based on surface representations of the cortex using FreeSurfer [15, 16] as previously implemented by our group [17]. First, images underwent inhomogeneity corrections and intensity normalization, linear alignment to a common atlas space, and were skull-stripped. Next, white matter voxels were identified, and the borders between the gray and white matter were defined. Hemispheres were separated, and a tessellated mesh was built around white matter voxels. This mesh was smoothed, and topological defects were corrected to accurately model the white matter surface. The gray matter (pial) surface was generated by expanding the white matter surface to the gray matter/CSF boundary while constraining the smoothness of the surface, resulting in continuous polygonal tessellations spanning the cortex. Surfaces were visually inspected and manually edited if necessary. The pial surface was inflated into a sphere, registered to an atlas and parceled into regions of interest defined by the Desikan atlas [18]. The cortical surface area was calculated as the sum of the areas of each tessellation falling within a given region in the subject's native space. Subcortical regions were parceled using analogous procedures, and volumetric measures were calculated accordingly, also in the subject's native space. FreeSurfer measurements have been validated against histological [19] and manual measurements [20, 21].

High-Density SNP Typing

More than 1 million SNPs, using the Illumina HumanHap550 BeadChip (in tandem with the supplemental HumanHap450S BeadChip) or the 1M BeadChip, were analyzed. These SNPs capture approximately 90% of the common variation in humans. Raw genotype data were processed using standard quality control procedures, and variants were checked for consistency of Mendelian transmission, an advantage of family-based designs. Missing genotypes were imputed using the pedigree-exploiting procedure developed by Burdick et al. [22] as implemented in MERLIN [23].

Quantitative Genetic Analysis

Heritability of each trait was estimated using SOLAR [24]. SOLAR employs variance component methods to analyze family-based quantitative data by partitioning the observed covariance into genetic and environmental components. The demographic covariates sex, age, age² and their interactions were included in all genetic analyses. Prior to analysis, each phenotype was transformed to approximate normality using a direct inverse Gaussian transformation.

Genetic correlation represents the common genetic covariance between two traits, referred to as pleiotropy [25]. Bivariate quantitative genetic analysis was used to estimate the genetic (ρ_g) and environmental (ρ_e) correlations between each potential obesity-related and brain-related phenotype. The phenotypic correlation (ρ_p), which quantifies the overall relationship between the two traits, can be derived from the genetic and environmental correlations as $\rho_p = \rho_g \sqrt{(h_1^2 h_2^2)} + \rho_e \sqrt{[(1 - h_1^2)(1 - h_2^2)]}$. These parameters were estimated by jointly utilizing all available familial relationships with a multivariate normal threshold model for combined dichotomous and continuous traits [25, 26].

Results from bivariate quantitative analyses of obesity and brain measures were used to assess the overall potential for identifying overlapping influences of causal genetic variants across these two major phenotypic domains. Specifically, we assessed the endophenotypic value of quantitative brain measures vis-à-vis

obesity using the endophenotype ranking value (ERV), which represents the standardized genetic covariance between trait and illness [27]. Mathematically, the ERV is defined as the absolute value of the product of the square-root of illness heritability (h_1^2), the square-root of the endophenotypic heritability (h_2^2) and their genetic correlation (ρ_g): $ERV_{ie} = |\sqrt{h_1^2} \sqrt{h_2^2} \rho_g|$, where heritability is the portion of phenotypic variance accounted for by additive genetic variance ($h^2 = \sigma_g^2 / \sigma_p^2$). In this context, a brain-based endophenotype is both heritable and genetically correlated with obesity. Therefore, ranking endophenotypes served as an a priori theoretical mechanism for placing focus on the action of gene sets that affect both brain and susceptibility to obesity.

The ERV varies between 0 and 1, where higher values indicate that the endophenotype and illness are more strongly influenced by common genetic factors. All brain imaging traits were ranked for relevance to obesity using this approach to identify those pairs of traits that showed the most significant evidence for being jointly influenced by common gene sets. Only these pairs of traits underwent quantitative trait locus (QTL) localization and identification analyses.

Bivariate QTL Localization Analysis of Brain-Related Endophenotypes and Obesity

Quantitative trait linkage analysis was used to identify specific chromosomal regions harboring QTLs that influence both brain and obesity phenotypic domains simultaneously. Bivariate linkage analysis exploits the genetic covariance between two traits to improve the power to localize QTLs and to detect QTL-specific pleiotropic effects [26]. In the current experiment, we performed bivariate linkage analyses (again using the SOLAR package) between the cortical surface area or subcortical volume measures selected via the ERV analysis and BMI to search for chromosomal regions that influence both neuroanatomical variability and body composition. More specifically, after addressing (by blanking, recalling or retyping) mistyping errors identified using Simwalk II [28], genotype data were used to compute maximum likelihood estimates of allele frequencies. Matrices of empirical estimates of identity-by-descent (IBD) allele sharing at points throughout the genome for every relative pair were computed using the Loki package [29] based on a selection of approximately 15,000 common SNPs that were in linkage equilibrium (defined as $r^2 < 0.2$) with one another. SNPs were only used for their combined information on IBD status; we did not test individual SNPs. We used high-resolution chromosomal maps provided by deCODE genetics [30] to project physical genomic distances onto recombination-relevant genetic distances. For the localization of QTLs, we performed both univariate and bivariate variance component linkage analyses. All QTL analyses included covariates for age, age², sex and their interactions. Bivariate LOD scores were adjusted for additional degrees of freedom incurred, making them directly comparable to traditional univariate LOD scores. Once a genome-wide significant localization was made, formal single degree of freedom likelihood ratio tests for pleiotropy were performed to test the specific hypothesis that a QTL at that location influenced a given brain measure and BMI risk jointly.

We employed the theoretical method of Feingold et al. [31] to calculate genome-wide significance levels for our linkage analyses. For our pedigree structure (which determines the average non-independence between IBD vectors involving approximately 388 effective tests), genome-wide significance requires a LOD score of

Fig. 1. Genetic correlations between BMI and cortical surface area.

2.9 (nominal p value = 1.3×10^{-4}), while suggestive evidence (i.e., expected to occur only once by chance in a genome scan) requires a LOD of 1.68 (nominal $p = 0.0027$). We did not additionally correct for the testing of multiple phenotypes since each bivariate analysis also included BMI and represented a separate hypothesis with prior support from our *ERV* analyses.

Results

Heritability of BMI and Brain Phenotypes

Using the complete extended pedigree information, the heritability of BMI in our Mexican-American sample was estimated to be 0.565 ± 0.057 ($p = 1.8 \times 10^{-30}$), indicating a substantial genetic component and suggesting it is reasonable to search for genes responsible for the observed variance. As we have previously shown, all of our cortical surface areas and subcortical volumes are significantly heritable (tables 1, 2) [17].

Bivariate Correlations between BMI and Cortical Surface Area

We performed bivariate quantitative genetic analyses examining the phenotypic, genetic and environmental correlations between BMI and brain traits for the 839 GOBS participants with available neuroanatomical images (table 1). Genetic correlations were typically negative (fig. 1), suggesting the same genetic factors that increase BMI act to reduce cortical surface area. The strongest genetic correlations were observed in mesial and lateral temporal, frontal, occipital and parietal lobes as well as the insular cortex, including the following gyri: fusiform ($\rho_g = -0.385$), middle temporal ($\rho_g = -0.321$), inferior parietal ($\rho_g = -0.376$), lateral orbitofrontal ($\rho_g = -0.293$) and supramarginal ($\rho_g = -0.293$). In contrast to genetic correlations, environmental correlations were typically posi-

tive, suggesting a potential dynamic feedback mechanism between the genetic component and an environmental stressor.

A very similar pattern of results was observed for subcortical volumes (table 2). The strongest genetic correlations between BMI and subcortical regions included the ventral diencephalon ($\rho_g = -0.274$) and accumbens area ($\rho_g = -0.255$), with each region showing positive environmental correlations ($\rho_e = 0.191$ and $\rho_e = 0.109$, respectively). The ventral diencephalon is primarily composed of the hypothalamus, which regulates food intake and is strongly associated with obesity [6].

Endophenotype Ranking

To select a subset of brain traits for linkage analyses, we utilized the *ERV* approach to select neuroanatomical traits that likely share causal mechanisms with BMI [27]. The top 10-ranked *ERV* statistics for brain traits and BMI are presented in table 3. After this objective prioritization, bivariate linkage analysis was run on each trait combination to search for specific genome locations that harbor pleiotropic QTLs influencing brain and obesity.

Bivariate Linkage Analysis

Two significant QTLs and a number of suggestive regions were observed after performing bivariate linkage on the top 10-ranked *ERV* brain traits and BMI. We identified a QTL with an LOD of 3.27 for BMI and the ventral diencephalon on chromosome 17p13.1. This chromosomal region was previously implicated in obesity and related disorders [32, 33], and the ventral diencephalon directly supports the regulation of food intake. Another QTL, with a genome-wide significant LOD of 3.26 on chromosome 3q22.1, was identified for BMI and the surface area of the supramarginal gyrus. Both the genomic

Table 1. Bivariate analyses between BMI and cortical surface area

Lobe	Region of interest	Heritability	Environmental correlation (ρ_e)	Genetic correlation (ρ_g)	Phenotypic correlation (ρ_p)
Cingulate	Caudal anterior	0.529	-0.022	-0.034	-0.028
	Isthmus	0.707	0.250	-0.013	0.088
	Posterior	0.684	0.241	-0.133	0.017
	Rostral anterior	0.512	0.086	-0.071	0.006
Frontal	Middle frontal gyrus, caudal	0.673	0.081	0.005	0.035
	Frontal pole	0.152	0.009	-0.022	0.000
	Orbitofrontal cortex, lateral	0.670	0.484	-0.293	0.020
	Orbitofrontal cortex, medial	0.568	0.250	-0.187	0.015
	Paracentral gyrus	0.644	0.203	-0.036	0.065
	Inferior frontal gyrus, pars opercularis	0.565	-0.321	-0.155	-0.066
	Inferior frontal gyrus, pars orbitalis	0.491	-0.219	-0.300	-0.042
	Inferior frontal gyrus, pars triangularis	0.648	-0.336	-0.183	-0.037
	Precentral gyrus	0.717	0.131	0.047	0.078
	Middle frontal gyrus, rostral	0.719	0.296	-0.247	-0.039
	Superior frontal gyrus	0.755	0.265	-0.058	0.056
Insula	Insular cortex	0.712	0.449	-0.242	0.021
Occipital	Cuneus cortex	0.612	0.268	-0.296	-0.047
	Lateral occipital cortex	0.731	0.361	-0.231	-0.010
	Lingual gyrus	0.728	0.227	-0.191	-0.032
	Pericalcarine cortex	0.684	0.052	-0.135	-0.058
Parietal	Inferior parietal cortex	0.590	0.367	-0.321	-0.015
	Postcentral gyrus	0.648	0.252	-0.207	-0.014
	Precuneus cortex	0.749	0.430	-0.116	0.080
	Superior parietal cortex	0.677	0.268	-0.065	0.070
	Supramarginal gyrus	0.645	0.359	-0.274	-0.006
Temporal, lateral	Banks of the superior temporal sulcus	0.497	-0.099	-0.157	-0.029
	Inferior temporal gyrus	0.621	0.104	-0.208	-0.072
	Middle temporal gyrus	0.640	0.319	-0.315	-0.048
	Superior temporal gyrus	0.738	0.566	-0.228	0.060
	Transverse temporal cortex	0.670	0.375	-0.200	0.034
Temporal, medial	Entorhinal cortex	0.612	0.030	-0.140	-0.065
	Fusiform gyrus	0.623	0.411	-0.385	-0.040
	Parahippocampal gyrus	0.637	0.267	-0.166	0.019
	Temporal pole	0.477	0.003	-0.145	-0.070

region [34] and brain region [35] have been independently associated with obesity in previous reports. Thus, our joint analyses of brain structure and obesity build on these findings and provide unequivocal evidence for two location-specific pleiotropic QTLs. In addition, we observed a number of genome-wide suggestive scores ($\text{LOD} > 1.68$; table 3), such as a locus on chromosome 6q13–16 that included the surface area of the fusiform gyrus ($\text{LOD} = 2.2$, 6q13), the lateral orbitofrontal gyrus ($\text{LOD} = 1.9$, 6q16) and the rostral middle frontal gyrus ($\text{LOD} = 2.0$, 6q14).

Discussion

This is the first report to quantify shared genetic factors of brain anatomy and obesity and localize significant pleiotropic influence. Specifically, we performed bivariate linkage analyses with a subset of brain traits and BMI to localize two genome-wide significant QTLs on chromosomal regions 3q22.1 and 17p13.1, respectively. Region 17p13.1 harbors genes that pleiotropically influence the ventral diencephalon volume and BMI. Meyre et al. [36] reported suggestive evidence for linkage in this re-

Table 2. Bivariate analyses between BMI and subcortical volumes

Region of interest	Heritability	Environmental correlation (ρ_e)	Genetic correlation (ρ_g)	Phenotypic correlation (ρ_p)
Accumbens area	0.495	0.109	-0.255	-0.075
Amygdala	0.793	0.365	-0.116	0.041
Caudate	0.761	0.139	-0.178	-0.064
Hippocampus	0.740	0.401	-0.197	0.020
Pallidum	0.727	0.137	-0.136	-0.032
Putamen	0.758	0.208	-0.085	0.019
Thalamus	0.777	0.144	-0.185	-0.069
Ventral diencephalon	0.726	0.191	-0.274	-0.098

Table 3. ERV and bivariate linkage results

Brain trait	ERV	ERV p value	Maximal LOD score	QTL nominal p value	Chromosomal region
Fusiform	0.217	0.002	2.248	6.5×10^{-4}	6q13
Inferior parietal	0.184	0.009	2.200	7.3×10^{-4}	2q34
Middle temporal	0.178	0.009	1.817	0.0019	17p11
Lateral orbitofrontal	0.173	0.014	1.890	0.0016	6q16
Cuneus	0.166	0.019	2.292	5.8×10^{-4}	5p15
Supramarginal	0.164	0.024	3.257	5.4×10^{-5}	3q22
Pars orbitalis	0.152	0.031	2.505	3.4×10^{-4}	15q14
Rostral middle frontal	0.152	0.033	1.966	0.0013	6q14
Insula	0.152	0.035	2.037	0.0011	10p13
Ventral diencephalon	0.168	0.051	3.271	5.2×10^{-5}	17p13

gion for childhood obesity. Additionally, strong evidence for a QTL influencing plasma leptin levels (LOD = 5) [33] and marginal evidence for linkage with both hip and waist circumference (LOD = 1.1) were also reported in this region [32]. The second QTL we identified was 3q22.1, which significantly influences the surface area of the supramarginal gyrus and BMI. This genomic region has been previously associated with obesity by Wu et al. [34], who found significant evidence for linkage with BMI (LOD = 3.45) in a sample of African-Americans. Our results identify regions of the genome that are directly related to both brain structure and obesity. Therefore, the same causal biological pathway likely influences the underlying function of these brain regions and the outcome measure of obesity.

The ventral diencephalon houses the hypothalamus, which is involved in the regulation of eating tendencies. Although feeding behavior is complex, the lateral hypothalamus is commonly referred to as the 'feeding center' of the brain because animal models show that stimulation

increases food intake yet a lesion inhibits motivation to feed [37]. This suggests functional plausibility for our finding on chromosome 17. Furthermore, leptin, which is secreted by fat cells, triggers signaling from neurons of the arcuate nucleus to the paraventricular nucleus, lateral hypothalamus and lateral horn of the spinal cord. Depending on the particular type of peptide carried by these neurons, metabolism is increased (or decreased), along with sympathetic tone, while feeding is decreased (or increased, respectively). Additionally, neurons containing these peptides project to widespread areas of the cortex and may be involved in other components of feeding strategies [37]. Therefore, our findings and those of Kissebah et al. [33] provide strong circumstantial evidence that the region identified on chromosome 17 contributes to the development of obesity through leptin-induced signaling in the hypothalamus.

The supramarginal gyrus has been linked to brain function differences in overweight and healthy-weight individuals. Frankort et al. [35] reported that both left

($p = 0.00025$) and right ($p = 0.00083$) gyri, amongst other regions, showed significant activation differences in response to passively viewing versus imagining the taste of high-calorie food pictures. This paradigm was designed to depict reward-related brain activity. Similarly, Rothe-mund et al. [37] reported that, in obese compared to normal-weight women, viewing high-calorie food stimuli differentially activated the dorsal striatum, insula, hippocampus and an area just deep to the left supramarginal gyrus ($T = 3.0$). This result was interpreted as a habit-forming system associated with lowered dopamine receptor availability in obese subjects. While the role of the supramarginal gyrus is poorly understood in this context, our findings in conjunction with these reports implicate its involvement in the pathogenesis of obesity due to shared influence of a region on chromosome 3.

The initial results from this study suggest that genetic factors associated with increasing BMI are also associated with a reduced cortical surface area, with the strongest correlations observed in mesial and lateral temporal, frontal, occipital and parietal lobes and the insular cortex. We also observed the same pattern of negative genetic correlations between BMI and subcortical volumes, indicating that genes associated with increased BMI are also associated with reduced subcortical volumes. This observation is conceptually similar to that of Ho et al. [9], who reported significantly lower regional brain volumes with increasing BMI ($p = 0.02$). Specifically, with every 1-unit increase in BMI there was an associated 1–1.5% average brain tissue reduction in several brain regions including the frontal, occipital and parietal lobe regions. However, this work was based exclusively on phenotypic correlations and did not contain a genetic component. Together, these results provide substantial evidence for an underlying biological mechanism, and our pedigree-based design enabled us to go beyond the inferential limits of traditional epidemiological studies that enlist only unrelated individuals.

It should be noted that the neuroanatomical data used here do not directly index neuronal activity specifically or neurophysiological function more generally. Rather, measures of the cortical surface area or subcortical volume are highly heritable traits that have been previously related to obesity (e.g. [9]). Unlike previous investigations of neuroanatomical variation and BMI, our strategy involved prioritizing brain traits by only selecting those with common genetic effects related to obesity (via the *ERV* analysis [27]). Indeed, the *ERV* analysis significantly reduced the number of brain traits tested and ensured that linkage was only performed on traits with high levels

of genetic covariance with BMI. However, this prioritization strategy, combined with the fact that BMI was always one of the two traits used in the bivariate analyses, makes it very difficult to correct for the number of linkage analyses performed. Yet, given that both of the identified genome-wide significant QTLs have been previously linked to BMI, it is unlikely that these results are spurious.

The final results from this study localized two chromosomal regions whose genes pleiotropically influence BMI and brain structure. Future use of whole-genome sequence data in these regions provides a powerful approach to find causal variants and inform potential obesity treatments. Indeed, by discovering genes that predispose obesity risk, it is our eventual goal to speed the development of drug targets to slow the epidemic advancement of obesity and its sequelae.

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