ONLINE FIRST

Association Between Common Variants Near the Melanocortin 4 Receptor Gene and Severe Antipsychotic Drug–Induced Weight Gain

Anil K. Malhotra, MD; Christoph U. Correll, MD; Nabilah I. Chowdhury, BSc; Daniel J. Müller, MD; Peter K. Gregersen, MD; Annette T. Lee, PhD; Arun K. Tiwari, PhD; John M. Kane, MD; W. Wolfgang Fleischhacker, MD; Rene S. Kahn, MD; Roel A. Ophoff, PhD; Jeffrey A. Lieberman, MD; Herbert Y. Meltzer, MD; Todd Lencz, PhD; James L. Kennedy, MD

Context: Second-generation antipsychotics (SGAs) are increasingly used in the treatment of many psychotic and nonpsychotic disorders. Unfortunately, SGAs are often associated with substantial weight gain, with no means to predict which patients are at greatest risk.

Objective: To identify single-nucleotide polymorphisms associated with antipsychotic drug–induced weight gain.

Design: Pharmacogenetic association study.

Setting: The discovery cohort was from a US general psychiatric hospital. Three additional cohorts were from psychiatric hospitals in the United States and Germany and from a European antipsychotic drug trial.

Participants: The discovery cohort consisted of 139 pediatric patients undergoing first exposure to SGAs. The 3 additional cohorts consisted of 73, 40, and 92 subjects.

Intervention: Patients in the discovery cohort were treated with SGAs for 12 weeks. Additional cohorts were treated for 6 and 12 weeks.

Main Outcome Measures: We conducted a genome-wide association study assessing weight gain associated with 12 weeks of SGA treatment in patients undergoing first exposure to antipsychotic drugs. We next genotyped 3 independent cohorts of subjects assessed for antipsychotic drug–induced weight gain.

Results: Our genome-wide association study yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of $P < 10^{-5}$. This locus, near the melanocortin 4 receptor (*MC4R*) gene, overlaps a region previously identified by large-scale genome-wide association studies of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect ($P = 5.59 \times 10^{-12}$). Moreover, we observed consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels.

Conclusions: These data implicate *MC4R* in extreme SGA-induced weight gain and related metabolic disturbances. A priori identification of high-risk subjects could lead to alternative treatment strategies in this population.

Arch Gen Psychiatry. 2012;69(9):904-912.
Published online May 7, 2012.
doi:10.1001/archgenpsychiatry.2012.191

Author Affiliations are listed at the end of this article.

ALTHOUGH SECOND-GENERATION antipsychotics (SGAs) are the cornerstone of treatment for many psychotic and nonpsychotic disorders, these medications are associated with substantial weight gain, including the development of obesity and other cardiovascular risk factors.[1] These medication effects are important mediating factors in the reduction in life expectancy, estimated to reach 20 to 30 years, in those with chronic and severe mental illnesses.[2] Moreover, SGA-induced weight gain frequently leads to medication nonadherence and decreased quality of life, and adequate treatments to prevent or ameliorate weight gain are lacking.[3]

A subgroup of patients experience severe weight gain following exposure to SGAs. In a study[4] of the weight and metabolic effects of SGAs in a unique cohort of 272 antipsychotic-naive pediatric patients beginning initial treatment with 1 of 4 SGAs, we found that approximately one-quarter of patients treated with ris-

peridone, quetiapine fumarate, or aripiprazole gained more than 14% of their baseline weight, with the top quartile gaining between 6.8 and 15.8 kg (15 and 35 lb, respectively), in just 12 weeks of treatment (**Figure 1**). Olanzapine-treated patients demonstrated a markedly different distribution, with the majority of subjects experiencing extreme weight gain. The amount of weight gain was not related to age, pubertal status, ethnicity, or sex of the subjects, and SGA dosage ranges were relatively restricted. These data are consistent with multiple clinical reports indicating that a significant proportion of patients gain extreme amounts of weight when treated with SGAs.[5-7]

The use of pharmacogenetic approaches to identify patients at risk for severe SGA-induced weight gain could lead to targeted interventions to ameliorate effects in high-risk individuals, as well as provide data on the molecular substrates of SGA-induced weight gain. To date, however, pharmacogenetic studies of weight gain have been restricted by methodological and technological limitations. In particular, prior studies have typically used samples of convenience, including patients with varying and often lengthy prior exposure to antipsychotics, considerably confounding prospectively observed weight gain. Moreover, nonadherence to treatment, a substantial problem in antipsychotic pharmacotherapy,[8] can lead to misclassification of nonadherent subjects as low-risk for weight gain. Finally, only a modest number of genetic loci have been examined, with only one study (in chronically treated adults) using genome-wide association.[9]

Therefore, to our knowledge, we conducted the first genome-wide association study (GWAS) of SGA-induced weight gain in patients carefully monitored for medication adherence who were undergoing initial treatment with SGAs. To confirm our results, we next assessed 3 independent replication cohorts: (1) a cohort of adult subjects undergoing their first treatment with a single SGA (clozapine), (2) a cohort of adult subjects treated with the same SGAs as in our discovery sample, and (3) a cohort of adult subjects in the first episode of schizophrenia and enrolled in a randomized clinical trial of antipsychotic drugs.[10]

METHODS

SUBJECTS IN DISCOVERY COHORT

Subjects assessed in the GWAS were enrolled in an observational cohort study assessing the weight and metabolic effects of SGAs on pediatric psychiatric patients. Participants aged 18 to 19 years, and caregivers of all participants aged 4 to 17 years, provided written informed consent; participants aged 9 to 17 years signed informed assent to a protocol approved by the institutional review board of the North Shore–Long Island Jewish Health System. Detailed methods have been previously reported elsewhere.[4]

In brief, subjects undergoing initial treatment with an SGA were included if (1) they were 19 years of age or younger and (2) their prior lifetime exposure to all antipsychotics as a class was 1 week or less. Exclusion criteria included an active or past diagnosis of an eating disorder, biochemical evidence of thyroid dysfunction, pregnancy or breastfeeding, and any acute nonpsychiatric medical disorder. The specific choice of antipsychotic drug, the drug dosage, and the titration schedule were based on clinical indications. To ensure adherence to SGA treatment, antipsychotic plasma levels were measured; individuals with undetectable antipsychotic plasma levels were excluded.

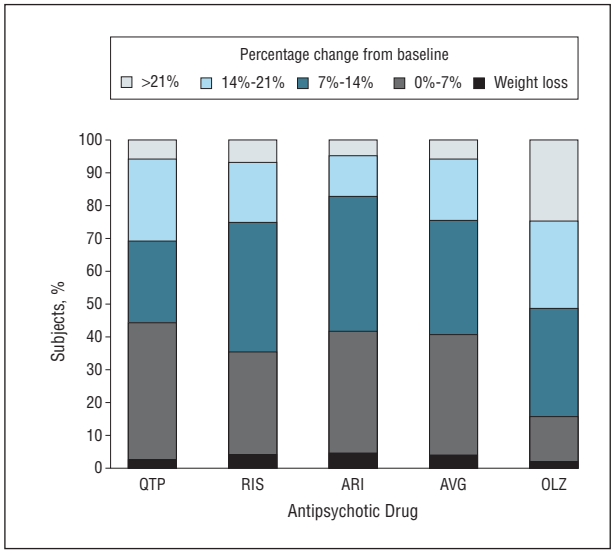

Figure 1. Distribution of antipsychotic drug–induced weight gain in antipsychotic-naive subjects following 12 weeks of treatment with second-generation antipsychotic drugs. The y-axis represents the percentage of subjects in each of the 5 weight gain categories; for example, subjects gaining more than 21% of their baseline weight are indicated in light gray, and subjects gaining more than 14% of their baseline weight are indicated in light blue. ARI indicates aripiprazole; AVG, the average of quetiapine (QTP), risperidone (RIS), and ARI; OLZ, olanzapine.

PHENOTYPIC ASSESSMENTS OF DISCOVERY COHORT

Subjects were assessed after 8 hours or more of overnight fasting at baseline and weeks 4, 8, and 12 of treatment. Height was measured using the stadiometer Seca 214. Weight, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and fat mass were assessed by use of impedantiometry with the Tanita Body Composition Analyzer TBF-310. As shown in Figure 1, weight gain profiles after 12 weeks of treatment for 3 SGAs (quetiapine [n=36], risperidone [n=135], and aripiprazole [n=41]) were indistinguishable from each other but significantly differed from weight gain profiles after 12 weeks of treatment for olanzapine (n=45). An omnibus χ^2 test of the distributions displayed in Figure 1 (merging the lowest 2 categories) demonstrated a significant effect of medication (χ^2_9=24.68, P=.003). When olanzapine was removed, there was no significant difference across the 3 remaining drugs (χ^2_6=4.42, P=.62), and pairwise comparisons demonstrated each of these medications differed in weight gain distributions compared with olanzapine (all $P<.05$) but did not differ from each other (all $P>.40$). Consequently, subjects taking olanzapine were excluded from the planned GWAS analysis to maintain homogeneity of phenotype.[11]

Fasting blood samples were obtained between 7 and 11 AM, prior to taking morning medications. Plasma levels were measured at each postbaseline visit (weeks 4, 8, and 12). Glucose and lipid levels were analyzed with the Roche Hitachi 747 chemistry analyzer, and insulin levels were analyzed via the Roche Elecsys 2010 immunochemistry analyzer. Plasma levels were measured by use of liquid chromatography at the Cooper Laboratory (Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York).

DNA COLLECTION, GENOTYPING, AND QUALITY CONTROL OF DISCOVERY COHORT

Of 272 individuals reported in Correll et al,[4] 245 (90.1%) provided blood samples for DNA extraction. DNA samples were genotyped on approximately 1 million single-nucleotide polymorphisms (SNPs) using the Illumina Omni-1Quad platform. All quality-control procedures were performed in SVS version 7.3.1 (GoldenHelix Inc), except for cryptic identity and cryptic relatedness, which were performed in PLINK version 1.07.[12] Of 245 available samples, 16 (6.5%) were eliminated during quality control owing to low call rates (<97%), sex mismatch, cryptic identity, or cryptic relatedness. Elimination of SNPs with a low call rate (<95%), a low minor allele frequency (<2%), or out of Hardy-Weinberg equilibrium ($P < 10^{-6}$) resulted in 803 582 high-quality autosomal SNPs available for analysis. The mean call rate per sample was 99.7%. Of 229 samples passing quality control, 38 were from individuals who were prescribed olanzapine, and, therefore, these samples were excluded from the GWAS, and 10 other samples were excluded because of demonstrated SGA nonadherence on the part of the 10 individuals. A total of 139 subjects completed the full study, with 12-week BMI change data and high-quality genotype data available for GWAS analysis (eTables 1 and 2, http://www.archgenpsychiatry.com).

STATISTICAL ANALYSIS OF DISCOVERY COHORT

Principal components analysis was performed using the eigenstrat method[13] implemented in SVS version 7.3.1 using default settings, and the 10 top principal components were entered into subsequent GWAS analyses. Principal components analysis–corrected correlation and trend tests were performed to test dominant, recessive, and additive models, using 12-week change in BMI as the quantitative dependent measure.

ADDITIONAL COHORTS

To validate the GWAS results from the discovery cohort, we identified an additional cohort of subjects undergoing their first exposure to an SGA with ensured adherence to medication. The details of this cohort have been published previously.[14] In brief, this cohort consists of 73 patients without prior exposure to SGAs who began treatment with the prototypic SGA, clozapine. Patients were 18 to 60 years of age, diagnosed with schizophrenia according to *DSM-III-R* criteria, and were either refractory or intolerant to treatment with typical antipsychotics. Subjects were excluded from our study if they were pregnant and/or breastfeeding, had an organic brain disorder or severe head injuries, had previous medical conditions that required treatment and were not stable, were dependent on a substance, had mental retardation, or had a severe personality disorder. Prior to initiating treatment with clozapine, subjects underwent a medication washout period of 7 to 14 days. The dosage of clozapine was titrated based on clinical indication, and treatment was continued for at least 6 weeks. Clozapine plasma levels were monitored to ascertain compliance. Patients underwent weight assessment at baseline and at 6 weeks of treatment.

In addition, a second replication cohort of 40 subjects from the Charite University of Medicine, Berlin, Germany, were enrolled in our study.[14] Subjects 18 to 62 years old were diagnosed with schizophrenia or schizoaffective disorder according to *DSM-IV* criteria. Hospital admission was either due to the first manifestation or a relapse of psychosis with significant deterioration. Exclusion criteria were the same as already described. Patients were not excluded if they had undergone previous antipsychotic treatment. Patients underwent 6 weeks of treatment with risperidone, quetiapine, or aripiprazole. The choice of antipsychotic drug, the drug dosage, and the titration schedule were based on clinical indications (eTable 1). A subject's weight was assessed at baseline and following 6 weeks of treatment.

Finally, a third replication cohort of patients treated for their first episode of schizophrenia was enrolled as part of the European Union First Episode Schizophrenia Trial. (Note that only a subset of patients enrolled in the larger trial provided DNA samples.)[10] Because there was an insufficient number of nonwhite subjects available to conduct meaningful covariate analyses, only white subjects were included for this report. Patients were excluded if more than 2 years had passed since the onset of positive symptoms or if any antipsychotic drug had been used for more than 2 weeks in the previous year or for 6 weeks at any time. Patients were randomly assigned to 1 of 4 antipsychotics: haloperidol, amisulpride, quetiapine, or ziprasidone hydrochloride (as in the discovery cohort, subjects assigned to olanzapine were excluded from the present study). Patients were excluded from pharmacogenetic analyses if nonadherence to medication was reported. Weight was assessed at baseline and after 12 weeks of treatment as part of a longer trial; results are reported for a total of 92 subjects meeting the inclusion criteria (eTable 1).

GENOTYPING OF ADDITIONAL COHORTS

Genotyping of the second 2 cohorts was completed subsequent to analysis of the GWAS results from the discovery cohort and consisted of the 5 SNPs highlighted in Table 1. As shown in **Table 1**, **Table 2**, and eFigure 1, the SNPs identified by the GWAS of the discovery cohort were in strong linkage disequilibrium, with $D' = 1$ in most instances. Thus, there was considerable redundancy, which obviated the need to test more SNPs in the replication cohorts. However, there was some difference in minor allele frequencies across the SNPs in Tables 1 and 2, with 3 modes (~21%, ~34%, and ~44%) as depicted in Table 2. The 5 SNPs chosen for replication in the first 2 replication cohorts were selected based on their providing a comprehensive assessment across this frequency distribution. The SNPs rs1942786 and rs996022, as well as other SNPs in the region, were not selected because they were in near complete linkage disequilibrium with other selected SNPs, were at very low allele frequencies, or failed in assay development. No other SNPs from Tables 1 and 2 were successfully genotyped in the replication cohorts.

All genotyping was performed using TaqMan SNP genotyping assays (Applied Biosystems). Two independent researchers confirmed the calling of genotypes, and 10% of the sample was regenotyped to ensure concordance. The concordance rate was 99.5%, and discordant genotypes were treated as missing data in the statistical analysis. Samples with more than 2 missing genotype calls were excluded and are not included in Table 2.

Finally, genotyping of the European Union First Episode Schizophrenia Trial cohort was performed after all prior analyses had been completed as part of an ongoing study of antipsychotic drug efficacy. Genotyping was performed on the Illumina Omni-1Quad platform using the already-described quality-control parameters. For purposes of the present study, only rs469893 was examined. The SNP rs469893 was selected after analysis of the replication cohorts revealed that it was significant in both replication cohorts ($P = .00014$ and $P = .007$, respectively). No other SNPs yielded a P value of less than .05 in all 3 prior cohorts, and, therefore, none of them were selected for follow-up.

Table 1. Association of Top Chromosome 18 SNPs With Antipsychotic Drug–Induced Weight Gain in Discovery Cohort

Reference SNP ID	Position	MAF, %	*P* Value	ΔBMI		
				Minor Allele Homozygotes	Heterozygotes	Major Allele Homozygotes
rs8092668	55934091	22.66	1.30×10^{-6}	3.939	1.856	1.568
rs1942879	55939970	33.81	4.63×10^{-6}	3.201	1.696	1.519
rs952044	55949090	33.33	5.57×10^{-6}	3.201	1.687	1.548
rs66723169	55959958	19.15	5.45×10^{-6}	3.827	1.846	1.613
rs12967878[a]	55977550	19.15	3.60×10^{-7}	4.153	1.787	1.613
rs6567160[a]	55980115	22.34	8.16×10^{-7}	4.277	1.952	1.512
rs476828[b]	56003567	28.01	3.29×10^{-3}	2.674	1.865	1.574
rs619825	56010046	45.74	4.62×10^{-6}	2.625	1.663	1.430
rs1942876	56022246	42.20	1.20×10^{-7}	2.886	1.662	1.454
rs996022	56023341	41.84	1.32×10^{-7}	2.925	1.667	1.454
rs12955983	56023969	21.58	4.09×10^{-6}	3.760	1.900	1.560
rs11663816	56027207	21.99	3.17×10^{-6}	3.760	1.864	1.567
rs17175602	56033697	21.63	3.17×10^{-6}	3.760	1.898	1.554
rs489693[a]	56033767	34.40	2.80×10^{-7}	3.333	1.797	1.382
rs646749[a]	56034105	44.33	3.09×10^{-7}	2.884	1.624	1.417
rs694780	56034525	44.33	3.09×10^{-7}	2.884	1.624	1.417
rs12957325	56035596	21.28	3.17×10^{-6}	3.760	1.938	1.538
rs12970134[a]	56035730	21.43	3.26×10^{-6}	3.760	1.927	1.554
rs11660069	56036393	21.63	3.17×10^{-6}	3.760	1.898	1.554
rs603940	56036763	44.33	3.28×10^{-6}	2.806	1.657	1.428
rs581401	56036944	44.33	3.28×10^{-6}	2.806	1.657	1.428

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ID, identification; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

[a] Genotyped in additional cohorts. The SNPs rs12967878 and rs6567160 produced an insufficient number of minor allele homozygotes to test recessive effects in the additional cohorts.

[b] Proxy SNP for rs17782313.

Table 2. Association of Top SNPs With Antipsychotic Drug–Induced Weight Gain in 3 Cohorts

Reference SNP ID	Position	MAF, %	*P* Value			
			Discovery Cohort	Replication 1 Cohort	Replication 2 Cohort	Replication 3 Cohort
rs489693	56033767	34.40	2.80×10^{-7}	.00014	.007	.042
rs646749	56034105	44.33	3.09×10^{-7}	.00026	.092	
rs12970134	56035730	21.43	3.26×10^{-6}	.143	.007	

Abbreviations: ID, identification; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

STATISTICAL ANALYSIS OF ADDITIONAL COHORTS

Based on the results from the GWAS of the discovery cohort, we tested for recessive effects for each SNP by comparing minor allele homozygotes with all others using *t* tests, with change in weight across the 6- or 12-week trial as the dependent measure. Effects of potential confounding variables, including sex, race, and baseline weight, were tested using analysis of covariance. Meta-analysis of *P* values derived from *t* tests was conducted using the Stouffer *z* trend test, an extension of the Fisher method that permits weighting for sample sizes and effect directions, as implemented in MetaP (http://compute1.lsrc.duke.edu/softwares/MetaP/metap.php).

RESULTS

DISCOVERY COHORT

The GWAS of the BMI-change phenotype revealed a striking genotypic effect under the recessive model (**Figure 2**A). Twenty SNPs at a single locus exceeded a statistical threshold of $P<10^{-5}$ (Table 1), with no evidence of inflation of test statistics due to population effects ($\lambda_{\text{genomic control}}=1$; Figure 2B). This locus, extending from coordinate 55934091 to coordinate 56036944 on chromosome 18, is approximately 190 kilobases (kb) downstream from the *MC4R* gene and overlaps the region previously identified by large-scale GWAS studies of obesity and BMI in the general population.[15,16] For each of these SNPs, the minor allele homozygotes gained significantly more weight during the 12-week trial than either heterozygotes or common allele homozygotes, both of which groups did not differ from each other. Results did not substantially change when drug assignment, sex, or race were entered into a regression model. Importantly, distribution of drug assignment across the minor allele homozygotes did not differ from the proportions in the group as a whole ($\chi^2_2=0.86$, $P=.65$). There was also no significant correlation between baseline BMI and ΔBMI

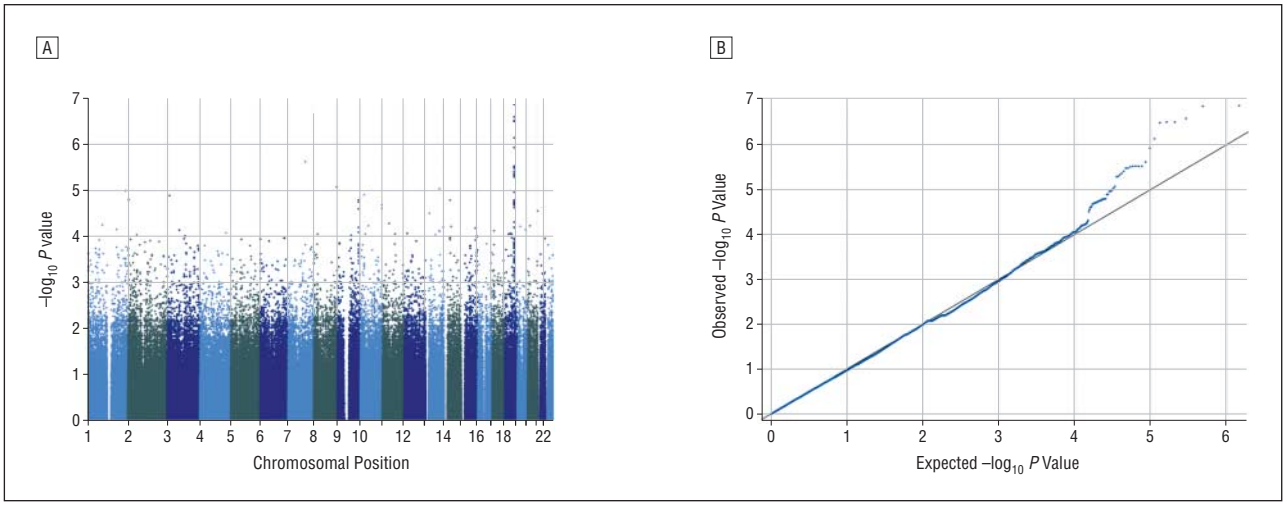

Figure 2. Genome-wide association study results. A, Manhattan plot displays statistical significance levels ($-\log_{10}$ *P* values) of correlation and trend tests for change in body mass index (BMI) in the discovery cohort, plotted by chromosomal position for all autosomal single-nucleotide polymorphisms (SNPs). Peak values are observed on chromosome 18, between positions 55.934 and 56.037 megabases (Mb), as detailed in Table 1. B, Quantile-quantile plot displays statistical significance levels ($-\log_{10}$ *P* values) of correlation and trend tests for change in BMI in the discovery cohort, plotted against expected values under the null hypothesis. With the exception of the most strongly associated SNPs on chromosome 18, there is no deviation from the diagonal ($\lambda_{\text{genomic control}}=1.00$).

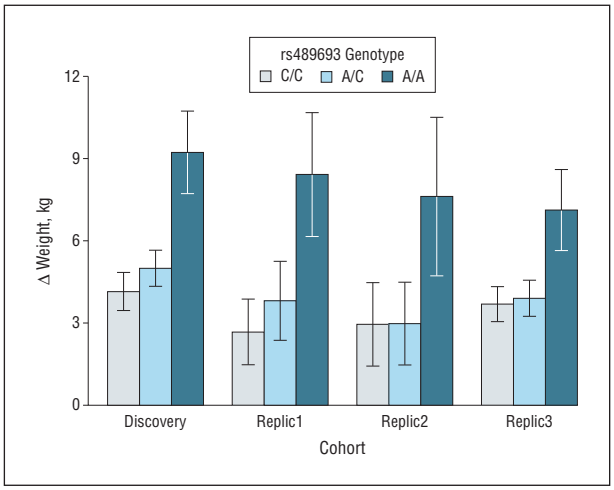

Figure 3. Single-nucleotide polymorphism rs489693 genotype and antipsychotic drug–induced weight gain in 4 cohorts of subjects. Replic1 indicates the first replication cohort; Replic2, the second replication cohort; Recplic3, the third replication cohort.

($r=-0.032$, $P=.71$). Moreover, results did not substantially change when baseline BMI was added to a regression, and there was no significant association between genotype at any of the top GWAS SNPs and baseline BMI (eg, $P=.32$ for rs489693).

ADDITIONAL COHORTS

The SNPs emerging from the GWAS are in strong linkage disequilibrium ($D'=1$ for most SNPs; eFigure 1, upper panel) but vary in minor allele frequency (Table 1), resulting in variable degrees of r^2 (eFigure 1, lower panel). We genotyped 5 SNPs, representing the various levels of minor allele frequency evident at this locus (Table 1, highlighted SNPs) in the first 2 replication cohorts. However, 2 SNPs (rs6567160 and rs12967878) produced an insufficient number of minor allele homozygotes ($n<5$) in either cohort to test recessive effects. Results for the remaining 3 SNPs are displayed in Table 2; the r^2 values for these 3 SNPs in the discovery cohort were of moderate strength (rs489693/rs646749, $r^2=0.66$; rs489693/rs12970134, $r^2=0.52$; rs646749/rs12770134, $r^2=0.34$). Of these 3 SNPs, rs489693 yielded consistent and statistically significant recessive effects across each cohort. Results did not change substantially when race, sex, or baseline weight were added to an analysis of covariance model. We next examined rs489693 in a third replication cohort and, again, obtained statistically significant recessive effects that remained significant when sex, baseline weight, and study drug were added using analysis of covariance. Meta-analysis across all 4 cohorts yielded a strong, genome-wide significant effect (Stouffer *z* trend, $P=5.59\times10^{-12}$). To graphically demonstrate the effects, in **Figure 3**, we plot the mean change in weight in each cohort as a function of genotype at rs489693 (percentage weight change displayed in eFigure 2). Baseline weight and BMI did not significantly differ among rs489693 genotype groups in any of the cohorts.

METABOLIC INDICES

Finally, we examined the relationship between rs489693 genotype and SGA-induced changes in metabolic indices in our discovery cohort (**Table 3**). Minor allele homozygotes had significantly greater increases in levels of triglycerides, leptin, and insulin, in the homeostasis model assessment insulin resistance index, and in total fat mass compared with the group of heterozygotes and common allele homozygotes. Other measures approached significance ($P>.05$ and $P<.10$), including changes in total cholesterol and high-density lipoprotein cholesterol.

COMMENT

To our knowledge, we conducted the first GWAS of SGA-induced weight gain in an antipsychotic-naive cohort of pediatric subjects, and we have identified evidence of re-

cessive effects at multiple SNPs located at chromosome 18q21.32. This peak directly overlaps a region that has been repeatedly identified as a predictor of weight and BMI in healthy individuals (eFigure 1), and has been implicated in obesity, type 2 diabetes mellitus, and related phenotypes.[15,16] The SNP rs489693 demonstrated statistically significant recessive effects in 3 additional independent cohorts, with minor allele homozygotes in all cohorts at risk for extreme weight gain following a short duration of treatment, and consistent effects on related metabolic indices in our discovery cohort. This locus is approximately 190 kb downstream from *MC4R*, the melanocortin 4 receptor gene, which has previously been identified as a candidate for weight-related phenotypes because mutations in this gene have been linked to extreme obesity in children and adolescents and *Mc4r* knockout mice develop obesity.[17]

A major strength of our approach was the assessment of subjects undergoing their first exposure to antipsychotic drug treatment, unlike prior GWASs of weight change induced by antipsychotics.[9] Baseline weight variability due to prior treatment with agents known to induce substantial weight gain was therefore minimized, and this provided us with substantially enhanced power to detect the effects of genetic variation on a complex weight regulation phenotype. Moreover, the use of antipsychotic plasma levels to ensure medication compliance reduced phenotypic variation due to the nuisance (nongenetic) effects of medication nonadherence, thereby enhancing the strength of the genotype-phenotype relationships. This effect may be particularly important in psychotic disorders, in which noncompliance with treatment is estimated to occur in 40% or more of patients.

Although sample size in the discovery cohort was small in comparison with GWASs of complex disease entities and quantitative traits in the general population, the GWASs of pharmacogenetic phenotypes have, in some instances, demonstrated extremely robust effects in small samples.[18,19] Although our initial GWAS result did not meet conventional thresholds for genome-wide significance, the possibility that our result is a false positive is substantially reduced by 3 factors: (1) the convergence of results across 4 independent cohorts, resulting in a meta-analytic *P* value several orders of magnitude beyond genome-wide thresholds; (2) the inherent biological plausibility of *MC4R* for weight gain; and (3) the high prior probability for association with this genomic region based on numerous previous GWASs of obesity and related phenotypes in the general population.[15,16,20-26] Similarly, although our discovery sample included subjects from multiple ethnic groups, the likelihood that the results are artifacts of population stratification is greatly reduced by several factors: (1) the principal components analysis correction of the GWAS analysis resulted in no evidence of population stratification ($\lambda_{\text{genomic control}} = 1.00$), (2) the results were replicated in an ethnically homogeneous German sample, and (3) the overlapping obesity locus from general population GWASs has been replicated in African-ancestry populations.[27,28]

It should be noted, however, that the GWAS signal for antipsychotic-induced weight gain is not precisely the same as that identified in general population studies. First, our genotypic effects followed a recessive pattern (Figure 3); heterozygotes did not substantially differ from common allele homozygotes. Moreover, no SNPs on any chromosome exceeded a statistical threshold of $P < 10^{-6}$ for analyses testing the dominant or additive models in our cohort. By contrast, GWAS effects reported in the general population are additive, with heterozygotes intermediate to the 2 homozygous groups. Second, although this genomic region is marked by considerable linkage disequilibrium, with multiple SNPs achieving nominal associations in both our GWAS and general population studies of obesity, specific SNP effects differ. For example, a proxy for the strongest additive correlate of general population obesity was not among the top 20 recessive SNPs in our cohort, although it was nominally significant (Table 1). Similarly, the SNP in our study (rs489693) has not emerged as the most strongly associated SNP in general population studies, except for a single study of waist circumference.[20] Further research with larger samples will be needed to test for multiple, independent allelic effects at this locus, as has been reported in a recent study of obesity.[29]

Our results may inform the design of GWASs seeking to identify risk alleles for complex phenotypes, such as obesity, that are mediated by a plethora of genetic and environmental factors. In GWASs of weight, sample sizes

Table 3. SNP rs489693 Genotype and Metabolic Changes in Antipsychotic-Naive Subjects Following 12 Weeks of Treatment With Second-Generation Antipsychotics

Metabolic Index, rs489693 Genotype	Mean (SEM)	2-Tailed *P* Value
Fat mass, kg		
AC/CC	4.87 (0.46)	<.001
AA	10.03 (1.63)	
Triglycerides, mg/dL		
AC/CC	7.29 (5.60)	.011
AA	51.67 (17.5)	
Total cholesterol, mg/dL		
AC/CC	3.18 (2.25)	.066
AA	15.73 (5.73)	
HDL cholesterol, mg/dL		
AC/CC	0.03 (0.81)	.052
AA	–2.87 (1.18)	
LDL cholesterol, mg/dL		
AC/CC	1.78 (1.75)	.292
AA	7.50 (4.70)	
Glucose, mg/dL		
AC/CC	1.56 (0.86)	.566
AA	3.07 (2.74)	
Insulin, μIU/mL		
AC/CC	0.35 (0.75)	.043
AA	4.91 (1.88)	
HOMA-IR index		
AC/CC	0.12 (0.17)	.033
AA	1.23 (0.49)	
Leptin, ng/mL		
AC/CC	3.40 (0.68)	.028
AA	8.27 (3.10)	

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance; LDL, low-density lipoprotein; SNP, single-nucleotide polymorphism.

SI conversion factors: To convert triglycerides to millimoles per liter, multiply by 0.0113; to convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert insulin to picomoles per liter, multiply by 6.945.

in the thousands were necessary to achieve statistically significant results, presumably because of the vast numbers of unmeasured (and uncontrolled) environmental factors working over variable amounts of time to influence the ultimate weight phenotype. In the present study, the critical environmental factor predisposing individuals to weight gain was antipsychotic drug administration over a short period of time. The experimental control of this one factor provided us with sufficient environmental homogeneity to detect genome-wide significant results in a study of slightly more than 100, rather than thousands, of subjects. Future studies of complex phenotypes may benefit from consideration of pharmacological or other environmental "challenge" paradigms for the detection of susceptibility alleles.

These data have potential clinical implications. For example, a priori identification of those subjects at increased risk of severe weight gain could lead to alternative treatments (ie, other than SGAs), particularly in patients without an Axis I psychotic disorder. Of note, recent data from the 2007 National Ambulatory Medical Care survey[30] indicate that antipsychotic drugs (most commonly quetiapine and risperidone) were prescribed in 21.3% of patient visits for anxiety disorders, with the largest increase in new patient visits, despite the fact that there is little evidence for these drugs' efficacy in anxiety. Therefore, it might be plausible to consider pharmacotherapeutic strategies that would not include antipsychotic drugs for those nonpsychotic individuals who carry the high-risk genotype for weight gain, as well as increased behavioral and psychosocial interventions focused on dietary and exercise habits. Finally, research on the coadministration of MC4R agonists, of which several are being developed,[31] in this subset of patients could be informative for the development of ameliorative strategies.

Submitted for Publication: November 8, 2011; final revision received January 13, 2012; accepted January 16, 2012.
Published Online: May 7, 2012. doi:10.1001/archgenpsychiatry.2012.191
Author Affiliations: Feinstein Institute for Medical Research, Manhasset (Drs Malhotra, Correll, Gregersen, Lee, Kane, and Lencz), Zucker Hillside Hospital, Glen Oaks (Drs Malhotra, Correll, Kane, and Lencz), and New York State Psychiatric Institute/Columbia University, New York (Dr Lieberman), New York; Centre for Addiction and Mental Health, Toronto, Ontario (Ms Chowdhury and Drs Müller, Tiwari, and Kennedy); Medical University Innsbruck, Austria (Dr Fleischhacker); University Medical Center Utrecht, the Netherlands (Drs Kahn and Ophoff); and Vanderbilt University Medical Center, Nashville, Tennessee (Dr Meltzer).
Correspondence: Anil K. Malhotra, MD, Psychiatry Research, Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (malhotra@lij.edu).
Author Contributions: Dr Malhotra had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Correll and Chowdhury contributed equally to this work, and Drs Lencz and Kennedy also contributed equally.

Financial Disclosure: Dr Malhotra is a consultant to Eli Lilly, Shire, and Genomind. He has grant support from Abbott. Dr Correll has received grants from Bristol-Myers Squibb (BMS), Janssen and Janssen, Otsuka, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the American Academy of Child and Adolescent Psychiatry, the Feinstein Institute for Medical Research, and the National Institute of Mental Health (NIMH). He has received consultant fees or honoraria from Actelion, Alexza, AstraZeneca, Boehringer Ingelheim, Biotis, BMS, Cephalon, Desitin, Eli Lilly, IntraCellular Therapies, MedAvante, Ortho-McNeil/Janssen/Johnson & Johnson, GlaxoSmithKline, Hoffmann–La Roche, Lunbeck, Medicure, Merck, Novartis, Otsuka, Pfizer, Schering-Plough, Sunovion, Takeda, and Vanda. He has been a consultant to AstraZeneca, BMS, Cephalon, Lundbeck, Medicure, Otsuka, Supernus, Medscape, Asante, Physicians Postgraduate Press, the Network for Continuing Medical Education, OptumHealth, PeerView, Veritasime, the Albert Einstein College of Medicine Center for Continuous Medical Education, the UCLA (University of California, Los Angeles) Center for Continuous Medical Education, and CME LLC. He has been an advisory board member for Actelion, Alexza, AstraZeneca, BMS, IntraCellular Therapies, Lundbeck, MedAvante, Merck, Novartis, Otsuka, Pfizer, Schering-Plough, Sunovion, Takeda, and Vanda. He also has served on the speaker's bureau for AstraZeneca, BMS, Eli Lilly, Merck, Otsuka, and Pfizer. He also received payment for manuscript preparation and development of educational presentations from PeerView, Physicians Postgraduate Press, the UCLA Center for Continuous Medical Education, Veritasime, the Albert Einstein College of Medicine Center for Continuous Medical Education, Asante, CME LLC, Medscape, the Network for Continuing Medical Education, and OptumHealth. Dr Müller has grants from the Canadian Institutes of Health Research (CIHR) and NARSAD. Dr Kane receives honoraria or consulting fees from AstraZeneca, Boehringer-Ingelheim, BMS, Sunovion, Eli Lilly, Lundbeck, Intracellular Therapeutics, Janssen, Johnson & Johnson, Merck, Novartis, Otsuka, Pfizer, Takeda, Wyeth, Vanda, and Roche. He has received travel support from BMS, Eli Lilly, Lundbeck, Janssen, Merck, Otsuka, Pfizer, and Roche. He also receives fees for participation in review activities from Otsuka. Dr Fleischhacker receives research support from Otsuka, Pfizer, Janssen, Alkermes, and Eli Lilly. He receives honoraria for consulting with Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, United BioSource, MedAvante, Sunovion, Merck, Neurosearch, Amgen, and Endo Pharmaceuticals. He receives speaker honoraria from Lundbeck, Sunovion, Janssen, Eli Lilly, Otsuka, Astra Zeneca, Roche, and Sunovion. He also holds stock in MedAvante. Dr Kahn is a consultant for the data and safety monitoring board and receives grants or honoraria from Astra-Zeneca, BMS, Envivo, Lilly, Janssen-Cilag, Otsuka, Gedeon Richter, Roche, and Sunovion. Dr Lieberman is a consultant to AstraZeneca, Bioline, Cephalon, GlaxoSmithKline, Intracellular Therapies, Eli Lilly, Forest Laboratories, Janssen, Otsuka, Pfizer, Pierre Fabre, Psychogenics, and Wyeth. He has active or pending grants from Allon, AstraZeneca, BMS, GlaxoSmithKline, For-

est Laboratories, Janssen, Merck, Novartis, Pfizer, Sunovion, Targacept, Wyeth, Eli Lilly, and Roche. He also has patents from Repligen and royalties from Oxford Publishing, Wiley Publishing, and American Psychiatric Publishing. Dr Lencz is a consultant to Eli Lilly. Dr Kennedy has grant support from CIHR, NIMH, and Eli Lilly. He is a consultant to sanofi-aventis and Dainippon Sumitomo. He is also on the speaker's bureau for Eli Lilly and has a patent from Theragenetics.

Funding/Support: This work was supported by National Institutes of Health grants P50MH080173 (to Dr Malhotra), P30MH090590 (to Dr Kane), an NARSAD Independent Investigator Award (to Dr Malhotra), and an NARSAD Young Investigator Award (to Dr Müller).

Online-Only Material: The eTables and eFigures are available at http://www.archgenpsychiatry.com.

REFERENCES

1. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry*. 2009;24(6):412-424.
2. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620-627.
3. Maayan L, Correll CU. Management of antipsychotic-related weight gain. *Expert Rev Neurother*. 2010;10(7):1175-1200.
4. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.
5. Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, Ambler D, Puglia M, Maloney AE, Michael E, De Jong S, Slifka K, Noyes N, Hlastala S, Pierson L, McNamara NK, Delporto-Bedoya D, Anderson R, Hamer RM, Lieberman JA. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry*. 2008;165(11):1420-1431.
6. Martin A, Scahill L, Anderson GM, Aman M, Arnold LE, McCracken J, McDougle CJ, Tierney E, Chuang S, Vitiello B. Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. *Am J Psychiatry*. 2004; 161(6):1125-1127.
7. Robinson DG, Woerner MG, Napolitano B, Patel RC, Sevy SM, Gunduz-Bruce H, Soto-Perello JM, Mendelowitz A, Khadivi A, Miller R, McCormack J, Lorell BS, Lesser ML, Schooler NR, Kane JM. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. *Am J Psychiatry*. 2006;163(12):2096-2102.
8. Kane JM. Treatment adherence and long-term outcomes. *CNS Spectr*. 2007;12 (10)(suppl 17):21-26.
9. Adkins DE, Aberg K, McClay JL, Bukszár J, Zhao Z, Jia P, Stroup TS, Perkins D, McEvoy JP, Lieberman JA, Sullivan PF, van den Oord EJ. Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs. *Mol Psychiatry*. 2011;16(3):321-332.
10. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085-1097.
11. Contopoulos-Ioannidis DG, Kouri I, Ioannidis JP. Pharmacogenetics of the response to beta 2 agonist drugs: a systematic overview of the field. *Pharmacogenomics*. 2007;8(8):933-958.
12. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007; 81(3):559-575.
13. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38(8):904-909.
14. Tiwari AK, Zai CC, Likhodi O, Lisker A, Singh D, Souza RP, Batra P, Zaidi SHE, Chen S, Liu F, Puls I, Meltzer HY, Lieberman JA, Kennedy JL, Müller DJ. A common polymorphism in the cannabinoid receptor 1 (CNR1) gene is associated with antipsychotic-induced weight gain in Schizophrenia. *Neuropsychopharmacology*. 2010;35(6):1315-1324.
15. Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, Inouye M, Freathy RM, Attwood AP, Beckmann JS, Berndt SI, Jacobs KB, Chanock SJ, Hayes RB, Bergmann S, Bennett AJ, Bingham SA, Bochud M, Brown M, Cauchi S, Connell JM, Cooper C, Smith GD, Day I, Dina C, De S, Dermitzakis ET, Doney AS, Elliott KS, Elliott P, Evans DM, Sadaf Farooqi I, Froguel P, Ghori J, Groves CJ, Gwilliam R, Hadley D, Hall AS, Hattersley AT, Hebebrand J, Heid IM, Lamina C, Gieger C, Illig T, Meitinger T, Wichmann HE, Herrera B, Hinney A, Hunt SE, Jarvelin MR, Johnson T, Jolley JD, Karpe F, Keniry A, Khaw KT, Luben RN, Mangino M, Marchini J, McArdle WL, McGinnis R, Meyre D, Munroe PB, Morris AD, Ness AR, Neville MJ, Nica AC, Ong KK, O'Rahilly S, Owen KR, Palmer CN, Papadakis K, Potter S, Pouta A, Qi L, Randall JC, Rayner NW, Ring SM, Sandhu MS, Scherag A, Sims MA, Song K, Soranzo N, Speliotes EK, Syddall HE, Teichmann SA, Timpson NJ, Tobias JH, Uda M, Vogel CI, Wallace C, Waterworth DM, Weedon MN, Willer CJ, Wraight, Yuan X, Zeggini E, Hirschhorn JN, Strachan DP, Ouwehand WH, Caulfield MJ, Samani NJ, Frayling TM, Vollenweider P, Waeber G, Mooser V, Deloukas P, McCarthy MI, Wareham NJ, Barroso I, Jacobs KB, Chanock SJ, Hayes RB, Lamina C, Gieger C, Illig T, Meitinger T, Wichmann HE, Kraft P, Hankinson SE, Hunter DJ, Hu FB, Lyon HN, Voight BF, Ridderstrale M, Groop L, Scheet P, Sanna S, Abecasis GR, Albai G, Nagaraja R, Schlessinger D, Jackson AU, Tuomilehto J, Collins FS, Boehnke M, Mohlke KL; Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial; KORA; Nurses' Health Study; Diabetes Genetics Initiative; SardiNIA Study; Wellcome Trust Case Control Consortium; FUSION. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet*. 2008;40(6):768-775.
16. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, Balding D, Scott J, Kooner JS. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat Genet*. 2008;40(6):716-718.
17. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, Lee F. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell*. 1997;88(1):131-141.
18. Daly AK, Donaldson PT, Bhatnagar P, Shen Y, Pe'er I, Floratos A, Daly MJ, Goldstein DB, John S, Nelson MR, Graham J, Park BK, Dillon JF, Bernal W, Cordell HJ, Pirmohamed M, Aithal GP, Day CP; DILIGEN Study; International SAE Consortium. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet*. 2009;41(7):816-819.
19. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302(8):849-857.
20. Heard-Costa NL, Zillikens MC, Monda KL, Johansson A, Harris TB, Fu M, Haritunians T, Feitosa MF, Aspelund T, Eiriksdottir G, Garcia M, Launer LJ, Smith AV, Mitchell BD, McArdle PF, Shuldiner AR, Bielinski SJ, Boerwinkle E, Brancati F, Demerath EW, Pankow JS, Arnold AM, Chen YDI, Glazer NL, McKnight B, Psaty BM, Rotter JI, Amin N, Campbell H, Gyllensten U, Pattaro C, Pramstaller PP, Rudan I, Struchalin M, Vitart V, Gao X, Kraja A, Province MA, Zhang Q, Atwood LD, Dupuis J, Hirschhorn JN, Jaquish CE, O'Donnell CJ, Vasan RS, White CC, Aulchenko YS, Estrada K, Hofman A, Rivadeneira F, Uitterlinden AG, Witteman JCM, Oostra BA, Kaplan RC, Gudnason V, O'Connell JR, Borecki IB, van Duijn CM, Cupples LA, Fox CS, North KE. NRXN3 is a novel locus for waist circumference: a genome-wide association study from the CHARGE Consortium. *PLoS Genet*. 2009;5 (6):e1000539.
21. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, Styrkarsdottir U, Gretarsdottir S, Thorlacius S, Jonsdottir I, Jonsdottir T, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Jonsson F, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T, Lauritzen T, Aben KK, Verbeek AL, Roeleveld N, Kampman E, Yanek LR, Becker LC, Tryggvadottir L, Rafnar T, Becker DM, Gulcher J, Kiemeney LA, Pedersen O, Kong A, Thorsteinsdottir U, Stefansson K. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. 2009;41(1):18-24.
22. Zabaneh D, Balding DJ. A genome-wide association study of the metabolic syndrome in Indian Asian men. *PLoS One*. 2010;5(8):e11961.
23. Meyre D, Delplanque J, Chèvre JC, Lecoeur C, Lobbens S, Gallina S, Durand E, Vatin V, Degraeve F, Proença C, Gaget S, Körner A, Kovacs P, Kiess W, Tichet J, Marre M, Hartikainen AL, Horber F, Potoczna N, Hercberg S, Levy-Marchal C, Pattou F, Heude B, Tauber M, McCarthy MI, Blakemore AI, Montpetit A, Polychronakos C, Weill J, Coin LJ, Asher J, Elliott P, Järvelin MR, Visvikis-Siest S, Balkau B, Sladek R, Balding D, Walley A, Dina C, Froguel P. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet*. 2009;41(2):157-159.

24. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burtt NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennison EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jacobs KB, Johnson T, Jousilahti P, Jovanovic Z, Khaw KT, Kraft P, Kuokkanen M, Kuusisto J, Laitinen J, Lakatta EG, Luan J, Luben RN, Mangino M, McArdle WL, Meitinger T, Mulas A, Munroe PB, Narisu N, Ness AR, Northstone K, O'Rahilly S, Purmann C, Rees MG, Ridderstråle M, Ring SM, Rivadeneira F, Ruokonen A, Sandhu MS, Saramies J, Scott LJ, Scuteri A, Silander K, Sims MA, Song K, Stephens J, Stevens S, Stringham HM, Tung YC, Valle TT, Van Duijn CM, Vimaleswaran KS, Vollenweider P, Waeber G, Wallace C, Watanabe RM, Waterworth DM, Watkins N, Witteman JC, Zeggini E, Zhai G, Zillikens MC, Altshuler D, Caulfield MJ, Chanock SJ, Farooqi IS, Ferrucci L, Guralnik JM, Hattersley AT, Hu FB, Jarvelin MR, Laakso M, Mooser V, Ong KK, Ouwehand WH, Salomaa V, Samani NJ, Spector TD, Tuomi T, Tuomilehto J, Uda M, Uitterlinden AG, Wareham NJ, Deloukas P, Frayling TM, Groop LC, Hayes RB, Hunter DJ, Mohlke KL, Peltonen L, Schlessinger D, Strachan DP, Wichmann HE, McCarthy MI, Boehnke M, Barroso I, Abecasis GR, Hirschhorn JN; Wellcome Trust Case Control Consortium; Genetic Investigation of ANthropometric Traits Consortium. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009;41(1):25-34.
25. Scherag A, Dina C, Hinney A, Vatin V, Scherag S, Vogel CI, Müller TD, Grallert H, Wichmann HE, Balkau B, Heude B, Jarvelin MR, Hartikainen AL, Levy-Marchal C, Weill J, Delplanque J, Körner A, Kiess W, Kovacs P, Rayner NW, Prokopenko I, McCarthy MI, Schäfer H, Jarick I, Boeing H, Fisher E, Reinehr T, Heinrich J, Rzehak P, Berdel D, Borte M, Biebermann H, Krude H, Rosskopf D, Rimmbach C, Rief W, Fromme T, Klingenspor M, Schürmann A, Schulz N, Nöthen MM, Mühleisen TW, Erbel R, Jöckel KH, Moebus S, Boes T, Illig T, Froguel P, Hebebrand J, Meyre D. Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. *PLoS Genet*. 2010;6(4):e1000916.
26. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, Allen HL, Lindgren CM, Luan J, Mägi R, Randall JC, Vedantam S, Winkler TW, Qi L, Workalemahu T, Heid IM, Steinthorsdottir V, Stringham HM, Weedon MN, Wheeler E, Wood AR, Ferreira T, Weyant RJ, Segrè AV, Estrada K, Liang L, Nemesh J, Park JH, Gustafsson S, Kilpeläinen TO, Yang J, Bouatia-Naji N, Esko T, Feitosa MF, Kutalik Z, Mangino M, Raychaudhuri S, Scherag A, Smith AV, Welch R, Zhao JH, Aben KK, Absher DM, Amin N, Dixon AL, Fisher E, Glazer NL, Goddard ME, Heard-Costa NL, Hoesel V, Hottenga JJ, Johansson A, Johnson T, Ketkar S, Lamina C, Li S, Moffatt MF, Myers RH, Narisu N, Perry JR, Peters MJ, Preuss M, Ripatti S, Rivadeneira F, Sandholt C, Scott LJ, Timpson NJ, Tyrer JP, van Wingerden S, Watanabe RM, White CC, Wiklund F, Barlassina C, Chasman DI, Cooper MN, Jansson JO, Lawrence RW, Pellikka N, Prokopenko I, Shi J, Thiering E, Alavere H, Alibrandi MT, Almgren P, Arnold AM, Aspelund T, Atwood LD, Balkau B, Balmforth AJ, Bennett AJ, Ben-Shlomo Y, Bergman RN, Bergmann S, Biebermann H, Blakemore AI, Boes T, Bonnycastle LL, Bornstein SR, Brown MJ, Buchanan TA, Busonero F, Campbell H, Cappuccio FP, Cavalcanti-Proença C, Chen YD, Chen CM, Chines PS, Clarke R, Coin L, Connell J, Day IN, den Heijer M, Duan J, Ebrahim S, Elliott P, Elosua R, Eiriksdottir G, Erdos MR, Eriksson JG, Facheris MF, Felix SB, Fischer-Posovszky P, Folsom AR, Friedrich N, Freimer NB, Fu M, Gaget S, Gejman PV, Geus EJ, Gieger C, Gjesing AP, Goel A, Goyette P, Grallert H, Grässler J, Greenawalt DM, Groves CJ, Gudnason V, Guiducci C, Hartikainen AL, Hassanali N, Hall AS, Havulinna AS, Hayward C, Heath AC, Hengstenberg C, Hicks AA, Hinney A, Hofman A, Homuth G, Hui J, Igl W, Iribarren C, Isomaa B, Jacobs KB, Jarick I, Jewell E, John U, Jørgensen T, Jousilahti P, Jula A, Kaakinen M, Kajantie E, Kaplan LM, Kathiresan S, Kettunen J, Kinnunen L, Knowles JW, Kolcic I, König IR, Koskinen S, Kovacs P, Kuusisto J, Kraft P, Kvaløy K, Laitinen J, Lantieri O, Lanzani C, Launer LJ, Lecoeur C, Lehtimäki T, Lettre G, Liu J, Lokki ML, Lorentzon M, Luben RN, Ludwig B, Manunta P, Marek D, Marre M, Martin NG, McArdle WL, McCarthy A, McKnight B, Meitinger T, Melander O, Meyre D, Midthjell K, Montgomery GW, Morken MA, Morris AP, Mulic R, Ngwa JS, Nelis M, Neville MJ, Nyholt DR, O'Donnell CJ, O'Rahilly S, Ong KK, Oostra B, Paré G, Parker AN, Perola M, Pichler I, Pietiläinen KH, Platou CG, Polasek O, Pouta A, Rafelt S, Raitakari O, Rayner NW, Ridderstråle M, Rief W, Ruokonen A, Robertson NR, Rzehak P, Salomaa V, Sanders AR, Sandhu MS, Sanna S, Saramies J, Savolainen MJ, Scherag S, Schipf S, Schreiber S, Schunkert H, Silander K, Sinisalo J, Siscovick DS, Smit JH, Soranzo N, Sovio U, Stephens J, Surakka I, Swift AJ, Tammesoo ML, Tardif JC, Teder-Laving M, Teslovich TM, Thompson JR, Thomson B, Tönjes A, Tuomi T, van Meurs JB, van Ommen GJ, Vatin V, Viikari J, Visvikis-Siest S, Vitart V, Vogel CI, Voight BF, Waite LL, Wallaschofski H, Walters GB, Widen E, Wiegand S, Wild SH, Willemsen G, Witte DR, Witteman JC, Xu J, Zhang Q, Zgaga L, Ziegler A, Zitting P, Beilby JP, Farooqi IS, Hebebrand J, Huikuri HV, James AL, Kähönen M, Levinson DF, Macciardi F, Nieminen MS, Ohlsson C, Palmer LJ, Ridker PM, Stumvoll M, Beckmann JS, Boeing H, Boerwinkle E, Boomsma DI, Caulfield MJ, Chanock SJ, Collins FS, Cupples LA, Smith GD, Erdmann J, Froguel P, Grönberg H, Gyllensten U, Hall P, Hansen T, Harris TB, Hattersley AT, Hayes RB, Heinrich J, Hu FB, Hveem K, Illig T, Jarvelin MR, Kaprio J, Karpe F, Khaw KT, Kiemeney LA, Krude H, Laakso M, Lawlor DA, Metspalu A, Munroe PB, Ouwehand WH, Pedersen O, Penninx BW, Peters A, Pramstaller PP, Quertermous T, Reinehr T, Rissanen A, Rudan I, Samani NJ, Schwarz PE, Shuldiner AR, Spector TD, Tuomilehto J, Uda M, Uitterlinden A, Valle TT, Wabitsch M, Waeber G, Wareham NJ, Watkins H, Wilson JF, Wright AF, Zillikens MC, Chatterjee N, McCarroll SA, Purcell S, Schadt EE, Visscher PM, Assimes TL, Borecki IB, Deloukas P, Fox CS, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, Mohlke KL, O'Connell JR, Peltonen L, Schlessinger D, Strachan DP, van Duijn CM, Wichmann HE, Frayling TM, Thorsteinsdottir U, Abecasis GR, Barroso I, Boehnke M, Stefansson K, North KE, McCarthy MI, Hirschhorn JN, Ingelsson E, Loos RJ; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937-948.
27. Kang SJ, Chiang CW, Palmer CD, Tayo BO, Lettre G, Butler JL, Hackett R, Adeyemo AA, Guiducci C, Berzins I, Nguyen TT, Feng T, Luke A, Shriner D, Ardlie K, Rotimi C, Wilks R, Forrester T, McKenzie CA, Lyon HN, Cooper RS, Zhu X, Hirschhorn JN. Genome-wide association of anthropometric traits in African- and African-derived populations. *Hum Mol Genet*. 2010;19(13):2725-2738.
28. Liu G, Zhu H, Lagou V, Gutin B, Barbeau P, Treiber FA, Dong Y, Snieder H. Common variants near melanocortin 4 receptor are associated with general and visceral adiposity in European- and African-American youth. *J Pediatr*. 2010;156(4):598.e1-605.e1.
29. Scherag A, Jarick I, Grothe J, Biebermann H, Scherag S, Volckmar AL, Vogel CIG, Greene B, Hebebrand J, Hinney A. Investigation of a genome wide association signal for obesity: synthetic association and haplotype analyses at the melanocortin 4 receptor gene locus. *PLoS One*. 2010;5(11):e13967.
30. Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. *Am J Psychiatry*. 2011;168(10):1057-1065.
31. Nargund RP, Strack AM, Fong TM. Melanocortin-4 receptor (MC4R) agonists for the treatment of obesity. *J Med Chem*. 2006;49(14):4035-4043.