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Genome-wide association study on antipsychotic-induced weight gain in Europeans and African-Americans

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ABSTRACT

Background: Antipsychotic (AP) medications are the first line of treatment for schizophrenia. However, most conferr a risk of antipsychotic-induced weight gain (AIWG). The objective of this investigation was to conduct a genome-wide association study (GWAS) of AIWG, followed by comprehensive, post-GWAS approaches.
Methods: We investigated n = 201 schizophrenia or schizoaffective disorder patients of European and African American ancestry who were treated primarily with clozapine or olanzapine. We conducted a genome-wide association analysis for AIWG, defined primarily as a percentage of weight change from baseline.
Results: When examining Europeans (n = 147), we noticed an association between rs62097526 (β = 0.39, p = 3.59 × 10−6, CADD = 2.213) variant, located downstream of the CIDEA gene, which is considered a risk factor for AIWG. In the entire sample, we observed a significant association between rs1525085 (β = 0.411, p = 3.15 × 10−9) variant of the DGKB gene and AIWG. The association was nominally significant in Europeans (β = 0.271, p = 0.002) and African Americans (β = 0.579, p = 5.73 × 10−5) with the same risk allele. Our top genes ($p < 5 \times 10-5$) were enriched in the GWAS catalog for the risk of obesity and interacted with the known risk factors for obesity (G6PD) and diabetes (IRS1). In addition, these genes are targeted by miRNAs related to schizophrenia (mir-34a) and obesity (mir-19b). However, our polygenic risk score analyses did not provide support for major genetic overlap between obesity and the risk of AIWG.
Conclusions: In summary, we propose that the CIDEA and DGKB genes are risk factors for AIWG in transethnic populations. Additionally, our evidence suggests that the G6PD and IRS1 gene-related pathways might be involved in AIWG.

1. Introduction

Schizophrenia (SCZ) is a severe, debilitating disorder with a lifetime prevalence of 1% regardless of gender or ethnic group (Owen et al., 2016). Antipsychotic drugs (APs) are the primary intervention in the treatment of schizophrenia. Despite clinical efficacy, APs are associated with severe side effects including antipsychotic-induced weight gain (AIWG) and correlated metabolic disturbances including type 2 diabetes (T2D) and cardiovascular disorders. AIWG is also one of the leading reasons for patient non-adherence and discontinuation of treatment (MacNeil and Müller, 2016). Significant weight gain (>7% from baseline) is observed in >30% of patients treated with antipsychotic drugs. However, the risk of weight gain varies among antipsychotic medications with clozapine and olanzapine characterized as “high risk” and risperidone and quetiapine characterized as “medium risk” (Lett et al., 2012).

Family and twin studies strongly support the involvement of genetic factors in the onset of AIWG, suggesting it is polygenic and characterized by heritability (h^2) of 0.6–0.8 (Gebhardt et al., 2010). Numerous factors contribute to inter-individual differences in the risk for AIWG, including age, diet, smoking, eating habits, concurrent medications, and most importantly, genetic factors. Previous studies using candidate gene approaches have identified risk variants in several genes, including alpha-ketoglutarate dependent dioxygenase (*FTO*) (Reynolds et al., 2013; H.-T. Song et al., 2014b), leptin (*LEP*) and leptin receptor (*LEPR*) (Ellingrod et al., 2007; Kang et al., 2014),

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serotonin (*HTR2C*) receptor (Opgen-Rhein et al., 2010), the neuropeptide Y (*NPY*) (Tiwari et al., 2013), orexin receptor (Tiwari et al., 2016), NADH-ubiquinone oxidoreductase Fe-S *protein 1* (*NDUFS1*) (Gonçalves et al., 2014), and translocator protein 18 kDa (*TSPO*) (Pouget et al., 2015). Hypothesis-free genome-wide association studies implicated cAMP-dependent protein kinase type II-beta regulatory subunit (*PRKAR2B*), meis homeobox 2 (*MEIS2*) (Adkins et al., 2011), melanocortin 4 receptor (*MC4R*) (Chowdhury et al., 2013; Malhotra et al., 2012), opioid growth factor receptor-like 1 (*OGFRL1*) (Brandl et al., 2016), and protein tyrosine phosphatase and receptor type D (*PTPRD*) (Yu et al., 2016) genes in AIWG. A few GWAS in AIWG have been conducted and despite smaller sample sizes, revealed interesting findings which are noteworthy, considering that effect sizes for pharmacogenetic phenotypes are larger than for complex disease risk (Maranville and Cox, 2016).

It is important to note that the results from genetic association studies vary depending on ethnic groups (Asians vs Europeans), previous drug exposure (drug-naïve patients vs chronic), and length of treatment (short vs long-term effects). For example, the effects of *FTO* variants were significant in chronically exposed SCZ patients of European ancestry (Reynolds et al., 2013) but the effect was the strongest in drug-naïve participants of Han Chinese ancestry (X. Song et al., 2014a). Similarly, leptin influences AIWG in the long term(Templeman et al., 2005), whereas *HTR2C* may have short-term effects (Wallace et al., 2011).

The aim of the current investigation was to conduct a hypothesis-free, genome-wide association study (GWAS) of AIWG in chronic SCZ and schizoaffective disorder (SCA) patients of African American and European ancestry. In a series of secondary analyses, we leveraged a series of post-GWAS approaches to investigate detected signals and understand the multi-omic biological architecture of AIWG and its possible interplay with obesity. We also attempted to replicate our findings in a cohort of children and adolescents treated with risperidone to further elucidate genetic risk factors of metabolic side effects of antipsychotic medications.

2. Subjects and methods

2.1. Discovery (CAMH) sample

For this study, we used a samlpe of patients ages 18–65 years and diagnosed with schizophrenia or schizoaffective disorders using DSM-III/DSM-IV/DSMIV-TR criteria. Detailed information about sites and recruitment protocols are available in our previous studies (Tiwari et al., 2013, 2016). The patients were recruited primarily across four sites: Charite University Medicine, Berlin, Germany (Sample 1, n = 69); Case Western Reserve University, Cleveland, OH, USA (Sample 2, n = 55); Hillside Hospital in Glen Oaks, NY, USA (Sample 3, n = 43), and Centre for Addiction and Mental Health in Toronto, ON, Canada (Sample 4, n = 34). Exclusion criteria included pregnancy, the presence of an organic brain disorder or severe head injuries, previous medical conditions that required treatment and were not stable (e.g., hepatitis C, HIV, thyroid disorder, diabetes mellitus), a history of substance dependence, the presence of clinically-relevant intellectual disability, and a diagnosis of severe personality disorder.

We defined a participant as a 'weight-gainer' if their weight increased by 7% or more from baseline to the last observation carried forward (LOCF) (Lieberman et al., 2005). To avoid spurious associations due to uncorrected population stratification, we restricted our analysis to the two largest ethnic groups of African-Americans and Europeans.

This investigation received approval from the Centre of Addiction and Mental Health Research Ethics Board. All participants gave informed consent to be enrolled in the study.

2.2. Replication (RUPP) sample

In an attempt to validate the findings from our sample, we repeated our analyses on the Research Units on Pediatric Psychopharmacology Autism Network (RUPP) cohort. Youth and adolescents (ages 4–17 years) were assessed using DSM-IV criteria for Autism Spectrum Disorder (ASD) accompanied by severe irritability defined by a score of ≥18 on the Aberrant Behavior Checklist Irritability subscale. Individuals were treated for 8 weeks with risperidone or placebo. To avoid spurious associations due to population stratification, we only investigated participants of European ancestry, treated with risperidone (n = 125; 69.0%). Detailed information about the sample and recruitment methodology is available in a previous study (Nurmi et al., 2013).

2.3. Genotyping

The discovery sample was genotyped on the Illumina Omni2.5 BeadChip at The Centre for Applied Genomics (TCAG) at The Hospital for Sick Children in Toronto, Canada. The RUPP sample was genotyped using the Infinium PsychArray BeadChip (Illumina Inc., San Diego, CA.)

2.4. Quality control

We applied standard quality control (QC) steps based on the protocols described by Anderson (Anderson et al., 2010) and Clarke (Clarke et al., 2011) for the CAMH sample. QC steps for individuals included: heterozygosity rate, relatedness (IBS), and confirmation of self-reported ancestry with genetic ancestry. To determine genetic ancestry, we applied multidimensional scaling (MDS) in PLINK (Purcell et al., 2007) and plotted our sample versus the 1000 Genomes (1000 Genomes Project Consortium et al., 2010) reference populations in R. We defined ancestry outliers as located ±6 SD from the mean (Price et al., 2006). For genetic variants, the following QC criteria were applied: control for minor allele frequency (MAF) >1%; Hardy-Weinberg equilibrium (p > 10–6); genotype call rate (>98%), and individual missingness (<10%). Following these QC steps, n = 144 individuals with verified European and n = 57 of African American ancestries entered our analyses. See Supplementary Fig. 1 for details.

In the case of the RUPP sample, the following QC and imputation steps were applied independently: raw PsychChip array data was called using Illumina's Genomestudio and converted to PLINK bed format. Pre-imputation QC was performed using PLINK and bash scripts. After a first pass removing indels, SNVs, duplicates and SNPs with a variant call rate of less that 95%, a second pass further pruned SNPs with sample and variant call rates each <98% and SNPs not passing a Hardy-Weinberg equilibrium mid p-value exact test with a threshold of 1e-6. Finally, individuals with PI_HAT >0.2, (based on an LD pruned subset with r-squared of 0.1) were excluded. The QC'd genotypes were prephased with SHAPEIT2, after correcting strand errors, and then imputed to 1000 Genomes Phase 3 build 37 using IMPUTE2. The final output was filtered to a call rate of 98% and MAF of 0.05 before use in analysis.

2.5. Exploratory and genome-wide association analysis

Prior to the main association analyses, we ran exploratory analyses to determine how additional demographic/clinical variables affected our phenotypes of interest using Kendall's correlation, and Kruskal-Wallis and Wilcoxon tests. As a result, we corrected for sample site, high-risk or medium/low-risk drug (clozapine and olanzapine were defined as risk drugs), study duration, and the first two principal components from the population stratification analysis. Pairwise genotype-genotype differences were explored using one-way pairwise Wilcoxon rank sum test.

Given our modest sample size, the primary phenotype of interest in the discovery sample was percentage of weight gain, which is quantitative. For the top associated variants, we also explored the association with a secondary, binary phenotype (i.e., presence/absence of weight gain) to ensure the robustness of associations. The

secondary outcome of interest was weight gain status (yes/no), where weight gain was defined as ≥7% of weight increase from baseline. We investigated associations using linear (% of weight change) or logistic (weight gain status) regression under the additive model inheritance in PLINK (Purcell et al., 2007). To increase readability, we reported results for quantitative phenotype and investigated if the effect was robust, i.e. seen in the secondary phenotype. Our initial genetic association study was conducted in the European (n = 144) cohort. As part of secondary analyses, we investigated the combined sample, followed by separate investigations in patients of two ethnic subgroups. For the mixed sample, we only investigated genes if 1) SNP was significant in both mixed sample and two subsamples (Europeans and African Americans); 2) effect showed the same direction (BETAs positive or negative in all three samples); and 3) minor allele was the same for Europeans and African Americans. The number of African Americans (n = 57) enrolled in the study remained too low to rationalize a separate GWAS.

2.6. Functional, post-GWAS characterization of top findings

Given our interest in biological characterization, we conducted additional exploratory, post-GWAS analyses. At first, we explored the possible genetic overlap between the risk of obesity and AIWG. We downloaded summary statistics from GWAS of BMI and obesity (Locke et al., 2015) and conducted polygenic risk score (PRS) analyses using several p-value thresholds (e.g. 0.1; 0.05; 0.01). We calculated weighted polygenic risk score in PRSice (Euesden et al., 2015). To keep consistent with the main study, we fit regression models and corrected for the same covariates. To be consisten with the original study, our weighted polygenic risk score analyses were conducted only in the European subsample.

We annotated our top hits using Combined Annotation Dependent Depletion (CADD) (Kircher et al., 2014) and reported only potentially functional variants, outside of intergenic regions without known functional features (CADD ≥ 2). In the CADD system, scores between 0 and 1 are irrelevant, scores of 2 are often seen for intergenic variants, whereas pathogenic, deleterious variants are characterized by scores of 10–20.

Pathway analysis was conducted to investigate the biological context of our findings. We explored pathways using Gene Ontology (GO) terms in INRICH (Lee et al., 2012) for selected intervals based on clumping in PLINK using minimum variant p-values of 0.0001 and maximum p-values of 0.5, with a range border of 20 kb. For gene annotations, we used Entrez Gene data from NCBI.

Lastly, we applied several in silico methods for additional characterization of top genes. Top genes ($p < 5 \times 10-5$) were fine-mapped using FUMA (Watanabe et al., 2017) where we investigated functional enrichment. In addition, we used Network Analyst (Xia et al., 2015) to investigate protein-protein interactions (PPI) between gene products of top 10 protein-coding genes in a sample of Europeans. Networks were visualized in Cytoscape (Smoot et al., 2011). Functional characterization was conducted for the main phenotype (percentage of weight gain) only for the European subsample.

2.7. Meta-analysis

The initial step included a meta-analysis of the combined sample followed by separate investigations in patients of two ethnic subgroups. As the number of African Americans was low, we did not report the original findings from this sample. For the meta-analysis, we only reported gene variants if 1) SNP was significant in both mixed sample and two subsamples (Europeans and African Americans); 2) effect showed the same direction (BETAs positive or negative in all three samples); and 3) minor allele was the same for Europeans and African Americans. Meta-analysis was conducted in METAL (Willer et al., 2010). Lastly, we meta-analysed Europeans from CAMH and RUPP cohorts.

3. Results

3.1. Sample demographics

Participants were predominantly male (n = 133; 66.2%), and gained 4.75 ± 7.20% of weight during the study (see Table 1). Among all 201 participants, 60 (29.9%) were classified as weight gainers after being 7.83 ± 4.22 weeks in the study. The majority of patients were of European ancestry (n = 144; 71.6%) but ancestry composition differed significantly among four recruitment sites; for example, individuals from Site 3 consisted predominantly of African Americans (n = 33; 76.7%). Participants weighed 79.46 ± 15.59 kg at baseline, but the average weight, the percentage of weight change, and a number of weight gainers differed significantly across samples. African Americans gained significantly more weight than patients of European ancestry (m difference = 4.85, 95% C.I. = [2.01,5.69], p = 0.00032).

3.2. GWAS and pathway analyses in European ancestry subsample

No genome-wide significant hits were observed in this sample (see Fig. 1 and Table 2a). Among the top hits, SNP rs7720513 ($\beta = 0.41$, $p = 1.26 \times 10-6$), located in the upstream region of the stanniocalcin 2 (*STC2*) gene, was putatively functional (CADD = 7.739). Individuals with the AA genotype gained significantly less weight than those with at least one copy of the G allele (m difference = 4.80, 95% C.I. = [2.89, 6.89], $p = 2.1 \times 10-5$, see Fig. S5A). When we investigated weight gain status, individuals with the G allele were in the highest risk of falling into "weight gainer" category (OR = 3.43 95% C.I. = [1.66, 7.07], p = 0.00086).

Other nominal associations included the rs62097526 ($\beta = 0.39$, $p = 3.59 \times 10-6$, CADD = 2.213) variant, located downstream of the cell death-inducing DFFA-like effector (*CIDEA*) gene. Individuals with the TT genotype gained significantly less weight than those with GT (m difference = 3.15, 95% C.I. = [−5.31,−0.99], p = 0.0023) and GG (m difference = −9.66, 95% C.I. = [−15.15, −4.13], p = 0.0081) genotypes as shown at Fig. S5B. Additionally, we noticed an association with weight gain status (OR = 3.49 95% C.I. = [1.66, 7.07], p = 0.0007).

We found no significant enrichment in metabolic pathways in our pathway analyses. Nominal association (p = 0.001; adjusted p = 0.66) was seen for a signal transducer activity (GO:0004871), as described in Supplementary Tables 5–6.

3.3. Functional characterization of top genes in European-ancestry sample

On a SNP level, our polygenic risk score analyses did not provide support for the major genetic overlap between obesity-related traits, such as BMI, and risk of AIWG, as shown in Supplementary Tables S3–S4. The results remained negative for both primary (percentage of weight gain) and secondary (weight gain categories yes/no) phenotypes.

Functional enrichment for top genes showed a significant overrepresentation of genes in the GWAS catalog for obesity-related traits (p = 0.0150; genes: RGS7, SDK1, and MAGI2) and body mass index (p = 0.0197; genes: AKAP6, MAGI2), see Table S5 for details. As for miRNA targets, the top genes targeted by miRNAs were previously associated with obesity (p = 0.01; mir-141) and schizophrenia (p = 0.01; mir-34a), as depicted in Table S6.

Two genes *RGS7* and *SCN2B* are expressed higher in the brain than in other tissues, as shown in Fig. S4. *CIDEA* gene, on the other hand, is highly expressed in adipose tissues and the stomach. No effect of differentially expressed genes was seen in Europeans.

Finally, PPI networks suggested a possible interaction between top genes and obesity and metabolic disturbance-related genes, such as IRS1 and G6DD. Interestingly, the network also captured the leptin receptor (*LEPR*) gene, one of the AIWG candidate genes. A discovered network is presented in Fig. S5.

Table 1
Sample demographics.

Characteristics	All (n = 201)	Sample 1 (n = 69)	Sample 2 (n = 55)	Sample 3 (n = 43)	Sample 4 (n = 34)	P
Age	37.02 ± 10.71	34.76 ± 12.09	33.56 ± 7.99	41.69 ± 7.67	41.35 ± 11.67	<0.001
Study duration*	7.83 ± 4.22	5.00 ± 1.65	6.00 ± 0.00	12.17 ± 3.50	11.52 ± 5.32	<0.001
% of weight change	4.75 ± 7.20	3.27 ± 4.44	5.77 ± 6.90	6.94 ± 8.87	3.34 ± 9.00	0.018
Baseline weight (kg)	79.46 ± 15.59	78.57 ± 13.28	74.63 ± 13.39	85.60 ± 18.76	81.70 ± 16.80	0.045
Weight gainer (>7%)	60 (29.9%)	14 (20.3%)	22 (40.0%)	18 (41.9%)	6 (17.6%)	0.01
Sex (males)	133 (66.2%)	40 (58.0%)	33 (60.0%)	36 (83.7%)	24 (70.6%)	0.019
Ethnicity						<0.001
European	144 (71.6%)	68 (98.6%)	37 (67.3%)	10 (23.3%)	29 (85.3)	
African American	57 (28.4%)	1 (1.4%)	18 (32.7%)	33 (76.7%)	5 (14.7%)	
Medication						<0.001
Clozapine	95 (43.7%)	8 (11.6%)	55 (100%)	11 (25.6%)	21 (61.8%)	
Haloperidol	16 (8.0%)	6 (8.7%)	0	10 (23.3%)	0	
Olanzapine	30 (14.9%)	10 (14.5%)	0	15 (34.9%)	5 (14.7%)	
Risperidone	30 (14.9%)	20 (29.0%)	0	7 (16.3%)	3 (8.8%)	
Other	30 (14.9%)	25 (36.2%)	0	0	5 (14.7%)	

3.4. GWAS and pathway analyses in the combined sample

In the combined sample, we observed a genome-wide significant association of an intronic, putatively functional (CADD = 3.123) variant in the diacylglycerol kinase beta (*DGKB*) gene, rs1525085 (β = 0.411, p = 3.15 × 10−9) and the percentage of weight change (see Fig. 2 and Table 3a for details). This SNP was nominally significant in individuals of both European (β = 0.271, p = 0.002) and African ancestry (β = 0.579, p = 5.73 × 10−5). Individuals with the GG genotype gained significantly less weight than those with at least one copy of the A allele in the whole sample (m difference = −9.01, 95% C.I. = [−6.22,−11.80], p = 6.1 × 10−7) as well as in the European (m difference = −6.94, 95% C.I. = [−2.90,−0.90], p = 0.0048) and African ancestry (m difference = −8.64, 95% C.I. = [−12.69,−4.58], p = 0.0003) subgroups. The QQ plot (see Fig. 1) suggested a presence of inflation (λ = 1.27), which was expected in a sample of mixed ancestry. Additionally, rs1525085 was associated with increased risk of weight gain in Europeans (OR = 5.73 95% C.I. = [1.82, 30.37], p = 0.04), African Americans (OR = 11.87 95% C.I. = [1.32, 107.1], p = 0.028), and combined samples (OR = 8.51 95% C.I. = [2.57, 28.16], p = 0.0004). The same SNP was also suggested as most significant by the meta-analysis (z = 4.79; p = 1.68 × 10−6) (Fig. 3).

3.5. Meta-analysis between African Americans and Europeans

None of the SNPs reached genome-wide significance in our meta-analysis, as shown in Table 3b. However, we captured rs1525085 as the most significant finding (Z = 4.52; p = 6.26 × 10−6). Both meta-analysis and transethnic GWAS suggested a comparable list of most significant SNPs, including rs12460932.

The second most significant SNP in the meta-analysis was the rs1052990 variant located in 3′UTR of the caveolin 2 (*CAV2*) gene. The G allele is a minor allele in both African Americans (MAF = 0.41) and Europeans (MAF = 34). The SNP showed nominally significant associations in Europeans (β = 0.37, p = 1.42 × 10−5), African Americans β = 0.27, p = 0.04) and a combined sample (β = 0.33, p = 3.35 × 10−6).

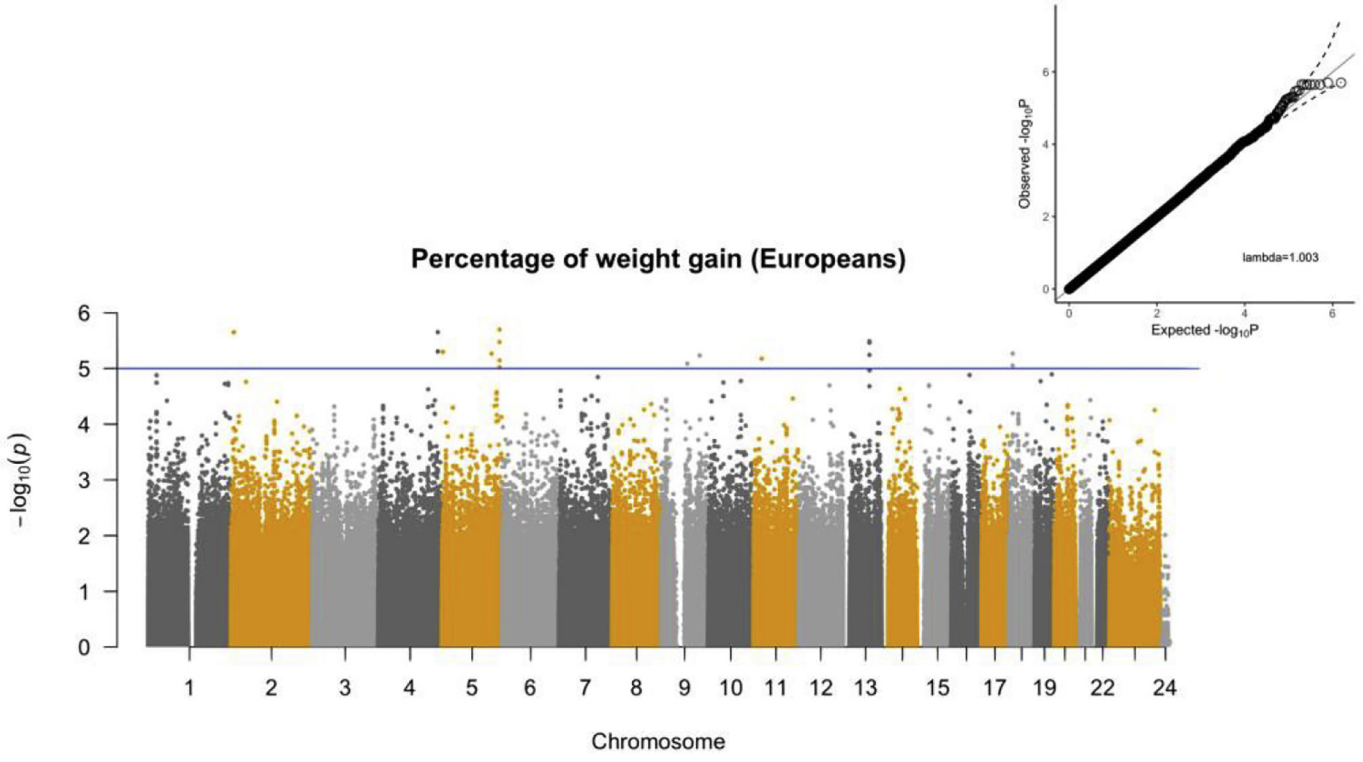

Fig. 1. Manhattan plot (left) and QQ plot (upper right) illustrating genome-wide association analysis between the percentage of weight change in a sample of European ancestry from CAMH cohort.

Table 2
a) Top variants in a subsample of European ancestry; b) Meta-analysis between CAMH and RUPP samples.

CHR	SNP	Ref/Alt	MAF	BETA	P	Annotation	CADD
5	rs7720513	A/G	0.15	0.406	$1.26 \times 10{-}6$	5′ of STC2	7.739
13	rs117433199	G/A	0.03	0.397	$2.20 \times 10{-}6$	3′ of POU4F1	0.785
2	rs78129933	C/T	0.02	0.398	$2.58 \times 10{-}6$	Intergenic	4.15
18	rs62097526	T/G	0.16	0.387	$3.59 \times 10{-}6$	3′ of CIDEA	2.213
4	rs62344853	C/T	0.19	−0.397	$3.61 \times 10{-}6$	RP11-130F10.1	0.189
9	rs74820080	C/T	0.02	0.383	$5.29 \times 10{-}6$	3′ of ZNF883	6.856
11	rs7938982	C/T	0.01	0.381	$5.55 \times 10{-}6$	LUZP2 intron	1.366
5	rs191168	C/T	0.91	0.390	$7.50 \times 10{-}6$	3′ of RP11-35O7.1	1.546
9	rs10114227	T/C	0.41	−0.3723	$1.00 \times 10{-}5$	MIR548H3	2.464
5	rs60232573	G/A	0.06	0.3788	$1.01 \times 10{-}6$	IL17B	3.948

b)

CHR	SNP	Zscore	P	Direction	Ref/Alt	MAF	Annotation	CADD
3	rs1546733	−4.524	$6.08 \times 10{-}6$	−−	C/T	0.57	CBLB intron	2.876
7	rs2192883	4.326	$1.52 \times 10{-}5$	++	C/T	0.35	MAGI2 intron	1.254
1	rs624790	4.227	$2.37 \times 10{-}5$	++	T/G	0.15	5′ of GADD45A	7.223
2	rs9784089	−4.201	$2.66 \times 10{-}5$	−−	T/C	0.09	3′ of ARL4C	1.239
5	rs10038227	4.198	$2.69 \times 10{-}5$	++	T/G	0.12	Intergenic	5.135
5	rs6870782	4.143	$3.43 \times 10{-}5$	++	T/C	0.11	Intergenic	1.2
1	rs7364578	4.139	$3.49 \times 10{-}5$	++	G/A	0.27	NAV1	14.05
6	rs2531815	4.082	$4.47 \times 10{-}5$	++	C/T	0.28	5′ of ZSCAN23	0.238
3	rs9859953	−4.066	$4.78 \times 10{-}5$	−−	C/T	0.29	CBLB intron	0.159
17	rs8071193	4.066	$4.79 \times 10{-}5$	++	A/C	0.48	3′ of SPDYE4	1.08
8	rs4831834	4.065	$4.80 \times 10{-}5$	++	C/A	0.47	5′ of KIAA1456	1.321

3.6. Meta-analysis between CAMH and RUPP samples

None of our top variants were associated with AIWG in the RUPP sample. Our meta-analysis suggested the effect of the potentially functional, intronic rs1546733 variant in the Cbl Proto-Oncogene B (*CBLB*) gene ($Z = -4.52$; $p = 6.08 \times 10^{-6}$, CADD = 2.88), as shown in Table 3A. The second top hit, rs2192883 was located in the intronic variant of WW and PDZ domain containing 2 (*MAGI2*) gene ($Z = 4.33$; $p = 1.52 \times 10^{-5}$, CADD = 1.25), which showed a positive trend in both the CAMH and RUPP cohorts. *MAGI2* rs2192883 is located in the proximity of possible promoters in the anterior caudate, substantia nigra, and hippocampus. However, the most putatively functional variant was rs7364578 ($Z = 4.14$; $p = 3.49 \times 10{-}5$, CADD = 14.05) which is located within the neuron navigator 1 (*NAV1*) gene and lies in the proximity of enhancers and promoters across several tissues including the brain and stomach.

4. Discussion

4.1. GWAS results

None of the gene variants showed genome-wide significant associations with AIWG in our European subsample. The top variant, rs7720513 ($\beta = 0.406$, $p = 1.26 \times 10{-}6$), was located upstream of the

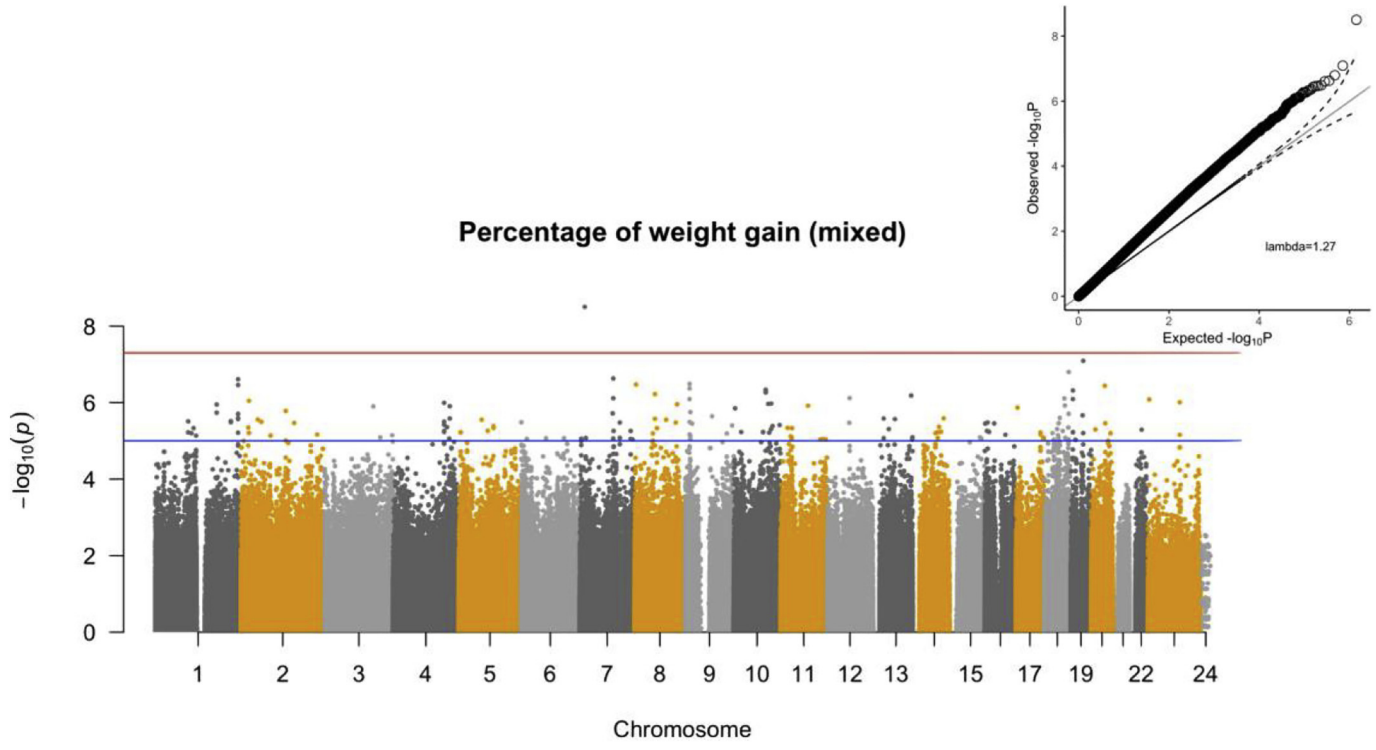

Fig. 2. Manhattan plot (left) and QQ plot (upper right) illustrating genome-wide association analysis between the percentage of weight change in a mixed sample from CAMH cohort.

Table 3
a) Top results for the association in a mixed sample. Only SNPs significantly associated in two ethnic groups are shown. b) Meta-analysis between African American and European samples.

a)

		Mixed			Europeans			African Americans					
CHR	SNP	BETA	P	Permuted P	BETA	P	MAF	BETA	P	MAF	Ref/Alt	Annotation	Phred
7	rs1525085	0.411	3.15E-09	1.00E-06	0.271	1.73E-03	0.02	0.579	3.73E-05	0.12	G/A	DGKB intronic	3.123
19	rs12460932	0.378	8.05E-08	1.00E-06	0.302	4.25E-04	0.14	0.396	7.22E-03	0.37	C/A	DMKN missense	11.11
18	rs4892207	0.376	1.59E-07	1.00E-06	0.321	2.81E-04	0.83	0.298	3.73E-02	0.51	C/A	RP11-231E4.2	1.479
10	rs4586057	0.352	4.62E-07	1.00E-06	0.204	2.28E-02	0.2	0.452	1.03E-03	0.43	T/G	RPP30 intronic	5.469
10	rs11186358	0.351	5.38E-07	2.00E-06	0.204	2.28E-02	0.2	0.482	3.76E-04	0.35	T/C	RPP30 3′-UTR	NA
10	rs11186359	0.351	5.38E-07	2.00E-06	0.204	2.28E-02	0.2	0.482	3.76E-04	0.35	T/C	RPP30 3′-UTR	0.38
10	rs7903584	0.351	5.38E-07	2.00E-06	0.204	2.28E-02	0.2	0.482	3.76E-04	0.36	C/T	RPP30 3′-UTR	0.659
8	rs10086387	0.358	6.00E-07	1.00E-06	0.195	2.74E-02	0.03	0.399	6.45E-03	0.4	G/A	24 kb 5′ of RP11-44D19.1	2.318
9	rs10809837	0.354	8.09E-07	1.00E-06	0.239	6.85E-03	0.13	0.421	2.70E-03	0.36	C/T	RP11-3L8.3 intronic	NA
4	rs7693115	0.359	1.25E-06	1.00E-06	0.259	2.98E-03	0.96	0.351	2.65E-02	0.59	A/G	MARCH1 intronic	2.341

b)

chr	Marker	Weight	Z score	P	Direction	Ref/Alt	AFR MAF	EUR MAF	Annotation	CADD
7	rs1525085	191	4.789	$1.68 \times 10-6$	++	G/A	0.12	0.02	DGKB intron	3.123
7	rs1052990	191	4.764	$1.90 \times 10-6$	++	T/G	0.41	0.34	CAV2 3′-UTR	2.318
9	rs10114227	191	−4.642	$3.45 \times 10-6$	–	T/C	0.23	0.41	MIR548H3	0.157
7	rs3779511	191	4.605	$4.12 \times 10-6$	++	T/G	0.36	0.34	CAV2 intron	7.929
20	rs73909111	190	4.595	$4.32 \times 10-6$	++	A/C	0.05	0.03	5′ of TOP1	4.467
11	rs7938982	191	4.58	$4.65 \times 10-6$	++	C/T	0.28	0.01	LUZP2 intron	1.41
19	rs12460932	190	4.517	$6.26 \times 10-6$	++	C/A	0.37	0.14	DMKN missense	2.829
13	rs56910685	189	4.512	$6.42 \times 10-6$	++	A/G	0.06	0.05	3′ of POU4F1	0.841
13	rs1411552	191	4.491	$7.09 \times 10-6$	++	A/C	0.9	0.89	5′ of IRS2	8.224

STC2 gene. The STC2 protein plays a role in the regulation of renal and intestinal calcium and phosphate transport, cell metabolism, and cellular calcium/phosphate homeostasis. *STC2* is expressed at low levels in many tissues, with higher levels at the substantia nigra, mammary tissue, and transformed fibroblasts. Existing literature linked *STC2* to malignancies including colorectal cancer (Hashemzadeh et al., 2014), hepatocellular carcinoma (Zhang et al., 2014) and lung cancer (Na et al., 2015). Other studies connected *STC2* with insulin-like growth factor in transgenic mice (Jepsen et al., 2015), and height in adults (Marouli et al., 2017). In summary, *STC2* seemed to be a less plausible hit for AIWG but more research is needed to investigate its potential role in AIWG. The second top variant was rs62097526 ($\beta = 0.386$, $p = 3.59 \times 10-6$, CADD = 2.213), located 3′ of *CIDEA*. Other studies suggested that *CIDEA* variants rs1154588, rs4796955, rs8092502, and rs12962340 were associated with the risk of obesity in the Han-Chinese population (Wu et al., 2013), and metabolic syndrome in Chinese, Japanese, and Swedish cohorts (Zhang et al., 2011). However, none of these *CIDEA* variants showed associations with AIWG ($p > 0.05$) in our sample, which might be related to ethnic differences among samples.

Our transethnic GWAS revealed potentially significant associations between the *DGKB* variant (rs1525085, $\beta = 0.411$, $p = 3.15 \times 10-9$) and the percentage of weight change in a combined sample of African Americans and Europeans, as well as in both ethnically homogenous subsamples. When we conducted meta-analysis, rs1525085 was the most significant finding ($Z = 4.79$; $p = 1.68 \times 10-6$).

Although our top variant in *DGKB* is still pending replication, existing literature supports its potential as a plausible risk gene for AIWG. *DGKB* is predominantly expressed in the brain and codes for a protein that phosphorylate diacylglycerol (DAG) to phosphatidic acid. Notably, a meta-analysis reported an association between the rs10241087 variant in *DGKB* and insulin clearance in Hispanics (Goodarzi et al., 2013). A more recent study of African Americans provided evidence that interactions between the *DGKB* rs978989 variant and individual insulin secretion significantly influenced the risk of type 2 diabetes (Keaton et al., 2017).

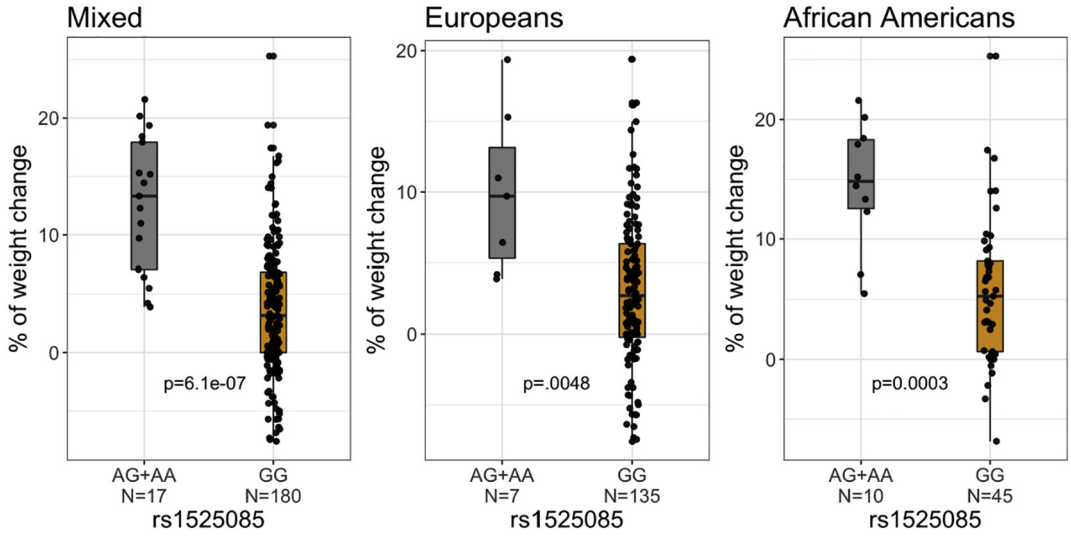

Fig. 3. Boxplot to illustrate associations between the percentage of weight change and genotypes of rs1525085 from CAMH cohort.

4.2. Results from external RUPP sample

None of our top SNPs showed an association in the RUPP sample, though meta-analysis revealed a few suggestive hits with the same direction of the effect.

The most significant SNP, rs1546733 ($z = -4.52$; $p = 6.08 \times 10-6$), was located in the *CBLB* gene, previously implicated in diabetes. Mice that were Cbl-b deficient and exposed to a high fat diet showed higher insulin resistance, suggesting the critical role of Cbl-b in obesity-related insulin resistance (Abe et al., 2013, 2014). This gene has been implicated in risk of diabetes type 1 (T1D) in a Japanese population characterized by younger age at onset (Matsuda and Yokota, 2008). Moreover, *CBLB* has been upregulated after exercise intervention in T2D individuals (Hansen et al., 2015). The second most significant variant, rs2192883 ($z = 4.33$; $p = 1.52 \times 10-5$), was located in the *MAGI2* gene. This gene is highly expressed across different tissues including the brain. Large deletions in *MAGI2* were previously reported to increase the risk of schizophrenia and bipolar disorder (Karlsson et al., 2012), cognitive impairment in schizophrenia (Koide et al., 2012), and response to lurasidone when investigated as a part of genetic risk score (Li et al., 2018). Existing literature suggests that *MAGI2* may be a promising gene associated with antipsychotic response and the risk of side effects, whereas CBLB might be implicated in the risk of metabolic side effects of AP exposure.

4.3. Additional characterization of top SNPs

Our additional analyses, when applied to SNPs, provided no suggestions for pathways or enrichment. None of our top SNPs were previously reported in GWAS studies. Negative results might be either due to a modest sample size or the fact that our top SNPs were located outside of coding genes.

4.4. Additional characterization of top genes

Our top genes ($p < 5 * 10-5$) for Europeans (*MAGI2*, *RGS7*) were previously noted in GWAS studies for obesity-related traits. The relationship between obesity and schizophrenia is well known and goes beyond AIWG (Manu et al., 2015; Subramaniam et al., 2014). It seems that we were able to capture the known risk factors for obesity and AIWG on a gene level but not at SNP level. In addition, we noticed that our top genes were targeted by miRNAs known for their involvement in obesity and schizophrenia (e.g. mir-34a). Mir-34a has been proposed as a biomarker for schizophrenia (Lai et al., 2016) and together with mir-7 might be associated with antipsychotic response (H.-T. Song et al., 2014b). A recent study of antidepressant response showed a possible role of miRNAs as predictors of treatment response across different medications (Lopez et al., 2017). Therefore, mir-34a might be an interesting biomarker to be followed up in AIWG.

Finally, when we investigated networks of experimentally validated PPRs for our top genes, we noticed interactions with *G6PD*, *LEPR*, and *IRS1*. *G6PD* plays important roles in redox regulation and de novo lipogenesis. Mice models suggested that its aberrant upregulation leads to insulin resistance in obesity (Park et al., 2005; Wang et al., 2012). In humans, *G6PD* has been implicated in adipose tissue inflammation and systemic insulin resistance in obesity (Park et al., 2017). Some studies have suggested the role of *G6PD* in psychiatric disorders (Bocchetta, 2003; Maiocchi and Bernardi, 2012; Singh et al., 2012). Furthermore, the *LEPR* gene has been suggested as AIWG-risk gene (Brandl et al., 2012; Gregoor et al., 2009; Vasudev et al., 2017). Top genes and protein-protein interactions provided suggestions for possible hypothesis-driven studies. Such preselection of regions, using GWAS and prioritization methods, might allow us to find significant signals in smaller samples.

5. Conclusions

In our study, we investigated genetic risk variants and mechanisms that contribute to the metabolic side effects of antipsychotic medications. In our GWAS, we investigated both European and transethnic, African American and European cohorts to find nominally significant associations in CIDEA (European) and genome-wide significant variant in DGKB (combined sample) - two genes that have been previously implicated in risk of diabetes and obesity. Meta-analysis between our sample and a sample of adolescents treated with risperidone suggests a role of MAGI2 gene previously implicated in SCZ and antipsychotic response. Finally, post-GWAS analyses suggested a possible interaction with the known risk factors for obesity (G6PD) and previously identified risk genes of AIWG (LEPR). Overall, we propose that potential, genetic contributors of AIWG may be implicated in obersity- and diabetes-related pathways.

5.1. Limitations

Our study has several limitations that should be kept in mind. The observations are based on a relatively small sample ($n = 201$) and were not replicated in an independent sample. Compared to the CAMH sample, the RUPP sample is clinically different. Firstly, this is a sample of youths, as opposed to adults, who were previously exposed to antipsychotics. Secondly, RUPP participants were treated with risperidone which is a “medium risk” medication for AIWG, instead of “high risk” medications, like clozapine or olanzapine. Our sample was heterogeneous and of moderate size ($n = 201$), but GWAS in AIWG have been conducted on even smaller sample sizes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.022.

References

1000 Genomes Project Consortium, Abecasis, G.R., Altshuler, D., Auton, A., Brooks, L.D., Durbin, R.M., Gibbs, R.A., Hurles, M.E., McVean, G.A., 2010. A map of human genome variation from population-scale sequencing. Nature 467, 1061–1073.

Abe, T., Hirasaka, K., Kagawa, S., Kohno, S., Ochi, A., Utsunomiya, K., Sakai, A., Ohno, A., Teshima-Kondo, S., Okumura, Y., Oarada, M., Maekawa, Y., Terao, J., Mills, E.M., Nikawa, T., 2013. Cbl-b is a critical regulator of macrophage activation associated with obesity-induced insulin resistance in mice. Diabetes 62, 1957–1969.

Abe, T., Hirasaka, K., Kohno, S., Ochi, A., Yamagishi, N., Ohno, A., Teshima-Kondo, S., Nikawa, T., 2014. Ubiquitin ligase Cbl-b and obesity-induced insulin resistance. Endocr. J. 61, 529–538.

Adkins, D.E., Aberg, K., McClay, J.L., Bukszár, J., Zhao, Z., Jia, P., Stroup, T.S., Perkins, D., McEvoy, J.P., Lieberman, J.A., Sullivan, P.F., van den Oord, E.J.C.G., 2011. Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs. Mol. Psychiatry 16, 321–332.

Anderson, C.A., Pettersson, F.H., Clarke, G.M., Cardon, L.R., Morris, A.P., Zondervan, K.T., 2010. Data quality control in genetic case-control association studies. Nat. Protoc. 5, 1564–1573.

Bocchetta, A., 2003. Psychotic mania in glucose-6-phosphate-dehydrogenase-deficient subjects. Ann. Gen Hosp. Psychiatry 2, 6.

Brandl, E.J., Frydrychowicz, C., Tiwari, A.K., Lett, T.A.P., Kitzrow, W., Büttner, S., Ehrlich, S., Meltzer, H.Y., Lieberman, J.A., Kennedy, J.L., Müller, D.J., Puls, I., 2012. Association study of polymorphisms in leptin and leptin receptor genes with antipsychotic-induced body weight gain. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 38, 134–141.

Brandl, E.J., Tiwari, A.K., Zai, C.C., Nurmi, E.L., Chowdhury, N.I., Arenovich, T., Sanches, M., Goncalves, V.F., Shen, J.J., Lieberman, J.A., Meltzer, H.Y., Kennedy, J.L., Müller, D.J., 2016. Genome-wide association study on antipsychotic-induced weight gain in the CATIE sample. Pharmacogenomics J 16, 352–356.
Chowdhury, N.I., Tiwari, A.K., Souza, R.P., Zai, C.C., Shaikh, S.A., Chen, S., Liu, F., Lieberman, J.A., Meltzer, H.Y., Malhotra, A.K., Kennedy, J.L., Müller, D.J., 2013. Genetic association study between antipsychotic-induced weight gain and the melanocortin-4 receptor gene. Pharmacogenomics J 13, 272–279.
Clarke, G.M., Anderson, C.A., Pettersson, F.H., Cardon, L.R., Morris, A.P., Zondervan, K.T., 2011. Basic statistical analysis in genetic case-control studies. Nat. Protoc. 6, 121–133.
Ellingrod, V.L., Bishop, J.R., Moline, J., Lin, Y.-C., Miller, D.D., 2007. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. Psychopharmacol. Bull. 40, 57–62.
Euesden, J., Lewis, C.M., O'Reilly, P.F., 2015. PRSice: polygenic risk score software. Bioinformatics 31, 1466–1468.
Gebhardt, S., Theisen, F.M., Haberhausen, M., Heinzel-Gutenbrunner, M., Wehmeier, P.M., Krieg, J.-C., Kühnau, W., Schmidtke, J., Remschmidt, H., Hebebrand, J., 2010. Body weight gain induced by atypical antipsychotics: an extension of the monocygotic twin and sib pair study. J. Clin. Pharm. Ther. 35, 207–211.
Gonçalves, V.F., Zai, C.C., Tiwari, A.K., Brandl, E.J., Derkach, A., Meltzer, H.Y., Lieberman, J.A., Müller, D.J., Sun, L., Kennedy, J.L., 2014. A hypothesis-driven association study of 28 nuclear-encoded mitochondrial genes with antipsychotic-induced weight gain in schizophrenia. Neuropsychopharmacology 39, 1347–1354.
Goodarzi, M.O., Guo, X., Cui, J., Jones, M.R., Haritunians, T., Xiang, A.H., Chen, Y.-D.I., Taylor, K.D., Buchanan, T.A., Hsueh, W.A., Raffel, L.J., Rotter, J.I., 2013. Systematic evaluation of validated type 2 diabetes and glycaemic trait loci for association with insulin clearance. Diabetologia 56, 1282–1290.
Gregoor, J.G., van der Weide, J., Mulder, H., Cohen, D., van Megen, H.J.G.M., Egberts, A.C.G., Heerdink, E.R., 2009. Polymorphisms of the LEP- and LEPR gene and obesity in patients using antipsychotic medication. J. Clin. Psychopharmacol. 29, 21–25.
Hansen, J.S., Zhao, X., Irmler, M., Liu, X., Hoene, M., Scheler, M., Li, Y., Beckers, J., Hrabě de Angelis, M., Häring, H.-U., Pedersen, B.K., Lehmann, R., Xu, G., Plomgaard, P., Weigert, C., 2015. Type 2 diabetes alters metabolic and transcriptional signatures of glucose and amino acid metabolism during exercise and recovery. Diabetologia 58, 1845–1854.
Hashemzadeh, S., Arabzadeh, A.A., Estiar, M.A., Sakhinia, M., Mesbahi, N., Emrahi, L., Ghojazadeh, M., Sakhinia, E., 2014. Clinical utility of measuring expression levels of Stanniocalcin 2 in patients with colorectal cancer. Med. Oncol. 31, 237.
Jepsen, M.R., Kløverpris, S., Mikkelsen, J.H., Pedersen, J.H., Füchtbauer, E.-M., Laursen, L.S., Oxvig, C., 2015. Stanniocalcin-2 inhibits mammalian growth by proteolytic inhibition of the insulin-like growth factor axis. J. Biol. Chem. 290, 3430–3439.
Kang, S.H., Lee, J.-I., Han, H.R., Soh, M., Hong, J.P., 2014. Polymorphisms of the leptin and HTR2C genes and clozapine-induced weight change and baseline BMI in patients with chronic schizophrenia. Psychiatr. Genet. 24, 249–256.
Karlsson, R., Graae, L., Lekman, M., Wang, D., Favis, R., Axelsson, T., Galter, D., Belin, A.C., Paddock, S., 2012. MAGI1 copy number variation in bipolar affective disorder and schizophrenia. Biol. Psychiatry 71, 922–930.
Keaton, J.M., Hellwege, J.N., Ng, M.C.Y., Palmer, N.D., Pankow, J.S., Fornage, M., Wilson, J.G., Correa, A., Rasmussen-Torvik, L.J., Rotter, J.I., Chen, Y.-D.I., Taylor, K.D., Rich, S.S., Wagenknecht, L.E., Freedman, B.I., Bowden, D.W., 2017. Genome-wide interaction with selected type 2 diabetes loci reveals novel loci for type 2 diabetes in African Americans. Pac. Symp. Biocomput. 22, 242–253.
Kircher, M., Witten, D.M., Jain, P., O'Roak, B.J., Cooper, G.M., Shendure, J., 2014. A general framework for estimating the relative pathogenicity of human genetic variants. Nat. Genet. 46, 310–315.
Koide, T., Banno, M., Aleksic, B., Yamashita, S., Kikuchi, T., Kohmura, K., Adachi, Y., Kawano, N., Kushima, I., Nakamura, Y., Okada, T., Ikeda, M., Ohi, K., Yasuda, Y., Hashimoto, R., Inada, T., Ujike, H., Iidaka, T., Suzuki, M., Takeda, M., Iwata, N., Ozaki, N., 2012. Common variants in MAGI2 gene are associated with increased risk for cognitive impairment in schizophrenic patients. PLoS One 7, e36836.
Lai, C.-Y., Lee, S.-Y., Scarr, E., Yu, Y.-H., Lin, Y.-T., Liu, C.-M., Hwang, T.-J., Hsieh, M.H., Liu, C.-C., Chien, Y.-L., Udawela, M., Gibbons, A.S., Everall, I.P., Hwu, H.-G., Dean, B., Chen, W.J., 2016. Aberrant expression of microRNAs as biomarker for schizophrenia: from acute state to partial remission, and from peripheral blood to cortical tissue. Transl. Psychiatry 6, e717.
Lee, P.H., O'Dushlaine, C., Thomas, B., Purcell, S.M., 2012. INRICH: interval-based enrichment analysis for genome-wide association studies. Bioinformatics 28, 1797–1799.
Lett, T.A.P., Wallace, T.J.M., Chowdhury, N.I., Tiwari, A.K., Kennedy, J.L., Müller, D.J., 2012. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. Mol. Psychiatry 17, 242–266.
Li, J., Yoshikawa, A., Brennan, M.D., Ramsey, T.L., Meltzer, H.Y., 2018. Genetic predictors of antipsychotic response to lurasidone identified in a genome wide association study and by schizophrenia risk genes. Schizophr. Res. 192, 194–204.
Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S.E., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators, 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223.
Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S., Buchkovich, M.L., Yang, J., Croteau-Chonka, D.C., Esko, T., Fall, T., Ferreira, T., Gustafsson, S., Kutalik, Z., Luan, J. 'an, Mägi, R., Randall, J.C., Winkler, T.W., Wood, A.R., Workalemahu, T., Faul, J.D., Smith, J.A., Zhao, J.H., Zhao, W., Chen, J., Fehrmann, R., Hedman, Å.K., Karjalainen, J., Schmidt, E.M., Absher, D., Amin, N., Anderson, D., Beekman, M., Bolton, J.L., Bragg-Gresham, J.L., Buyske, S., Demirkan, A., Deng, G., Ehret, G.B., Feenstra, B., Feitosa, M.F., Fischer, K., Goel, A., Gong, J., Jackson, A.U., Kanoni, S., Kleber, M.E., Kristiansson, K., Lim, U., Lotay, V., Mangino, M., Leach, I.M., Medina-Gomez, C., Medland, S.E., Nalls, M.A., Palmer, C.D., Pasko, D., Pechlivanis, S., Peters, M.J., Prokopenko, I., Shungin, D., Stančáková, A., Strawbridge, R.J., Sung, Y.J., Tanaka, T., Teumer, A., Trompet, S., van der Laan, S.W., van Setten, J., Van Vliet-Ostaptchouk, J.V., Wang, Z., Yengo, L., Zhang, W., Isaacs, A., Albrecht, E., Ärnlöv, J., Arscott, G.M., Attwood, A.P., Bandinelli, S., Barrett, A., Bas, I.N., Bellis, C., Bennett, A.J., Berne, C., Blagieva, R., Blüher, M., Böhringer, S., Bonnycastle, L.L., Böttcher, Y., Boyd, H.A., Bruinenberg, M., Caspersen, I.H., Chen, Y.-D.I., Clarke, R., Daw, E.W., de Craen, A.J.M., Delgado, G., Dimitriou, M., Doney, A.S.F., Eklund, N., Estrada, K., Eury, E., Folkersen, L., Fraser, R.M., Garcia, M.E., Geller, F., Giedraitis, V., Gigante, B., Go, A.S., Golay, A., Goodall, A.H., Gordon, S.D., Gorski, M., Grabe, H.-J., Grallert, H., Grammer, T.B., Gräßler, J., Grönberg, H., Groves, C.J., Gusto, G., Haessler, J., Hall, P., Haller, T., Hallmans, G., Hartman, C.A., Hassinen, M., Hayward, C., Heard-Costa, N.L., Helmer, Q., Hengstenberg, C., Holmen, O., Hottenga, J.-J., James, A.L., Jeff, J.M., Johansson, Å., Jolley, J., Juliusdottir, T., Kinnunen, L., Koenig, W., Koskenvuo, M., Kratzer, W., Laitinen, J., Lamina, C., Leander, K., Lee, N.R., Lichtner, P., Lind, L., Lindström, J., Lo, K.S., Lobbens, S., Lorbeer, R., Lu, Y., Mach, F., Magnusson, P.K.E., Mahajan, A., McArdle, W.L., McLachlan, S., Menni, C., Merger, S., Mihailov, E., Milani, L., Moayyeri, A., Monda, K.L., Morken, M.A., Mulas, A., Müller, G., Müller-Nurasyid, M., Musk, A.W., Nagaraja, R., Nöthen, M.M., Nolte, I.M., Pilz, S., Rayner, N.W., Renstrom, F., Rettig, R., Ried, J.S., Ripke, S., Robertson, N.R., Rose, L.M., Sanna, S., Scharnagl, H., Scholtens, S., Schumacher, F.R., Scott, W.R., Seufferlein, T., Shi, J., Smith, A.V., Smolonska, J., Stanton, A.V., Steinthorsdottir, V., Stirrups, K., Stringham, H.M., Sundström, J., Swertz, M.A., Swift, A.J., Syvänen, A.-C., Tan, S.-T., Tayo, B.O., Thorand, B., Thorleifsson, G., Tyrer, J.P., Uh, H.-W., Vandenput, L., Verhulst, F.C., Vermeulen, S.H., Verweij, N., Vonk, J.M., Waite, L.L., Warren, H.R., Waterworth, D., Weedon, M.N., Wilkens, L.R., Willenborg, C., Wilsgaard, T., Wojczynski, M.K., Wong, A., Wright, A.F., Zhang, Q., LifeLines Cohort Study, Brennan, E.P., Choi, M., Dastani, Z., Drong, A.W., Eriksson, P., Franco-Cereceda, A., Gådin, J.R., Gharavi, A.G., Goddard, M.E., Handsaker, R.E., Huang, J., Karpe, F., Kathiresan, S., Keildson, S., Kiryluk, K., Kubo, M., Lee, J.-Y., Liang, L., Lifton, R.P., Ma, B., McCarroll, S.A., McKnight, A.J., Min, J.L., Moffatt, M.F., Montgomery, G.W., Murabito, J.M., Nicholson, G., Nyholt, D.R., Okada, Y., Perry, J.R.B., Dorajoo, R., Reinmaa, E., Salem, R.M., Sandholm, N., Scott, R.A., Stolk, L., Takahashi, A., Tanaka, T., van 't Hooft, F.M., Vinkhuyzen, A.A.E., Westra, H.-J., Zheng, W., Zondervan, K.T., ADIPOGen Consortium, AGEN-BMI Working Group, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GLGC, ICBP, MAGIC Investigators, MuTHER Consortium, MIGen Consortium, PAGE Consortium, ReproGen Consortium, GENIE Consortium, International Endogene Consortium, Heath, A.C., Arveiler, D., Bakker, S.J.L., Beilby, J., Bergman, R.N., Blangero, J., Bovet, P., Campbell, H., Caulfield, M.J., Cesana, G., Chakravarti, A., Chasman, D.I., Chines, P.S., Collins, F.S., Crawford, D.C., Cupples, L.A., Cusi, D., Danesh, J., de Faire, U., den Ruijter, H.M., Dominiczak, A.F., Erbel, R., Erdmann, J., Eriksson, J.G., Farrall, M., Felix, S.B., Ferrannini, E., Ferrières, J., Ford, I., Forouhi, N.G., Forrester, T., Franco, O.H., Gansevoort, R.T., Gejman, P.V., Gieger, C., Gottesman, O., Gudnason, V., Gyllensten, U., Hall, A.S., Harris, T.B., Hattersley, A.T., Hicks, A.A., Hindorff, L.A., Hingorani, A.D., Hofman, A., Homuth, G., Hovingh, G.K., Humphries, S.E., Hunt, S.C., Hyppönen, E., Illig, T., Jacobs, K.B., Jarvelin, M.-R., Jöckel, K.-H., Johansen, B., Jousilahti, P., Jukema, J.W., Jula, A.M., Kaprio, J., Kastelein, J.J.P., Keinanen-Kiukaanniemi, S.M., Kiemeney, L.A., Knekt, P., Kooner, J.S., Kooperberg, C., Kovacs, P., Kraja, A.T., Kumari, M., Kuusisto, J., Lakka, T.A., Langenberg, C., Marchand, L.L., Lehtimäki, T., Lyssenko, V., Männistö, S., Marette, A., Matise, T.C., McKenzie, C.A., McKnight, B., Moll, F.L., Morris, A.D., Morris, A.P., Murray, J.C., Nelis, M., Ohlsson, C., Oldehinkel, A.J., Ong, K.K., Madden, P.A.F., Pasterkamp, G., Peden, J.F., Peters, A., Postma, D.S., Pramstaller, P.P., Price, J.F., Qi, L., Raitakari, O.T., Rankinen, T., Rao, D.C., Rice, T.K., Ridker, P.M., Rioux, J.D., Ritchie, M.D., Rudan, I., Salomaa, V., Samani, N.J., Saramies, J., Sarzynski, M.A., Schunkert, H., Schwarz, P.E.H., Sever, P., Shuldiner, A.R., Sinisalo, J., Stolk, R.P., Strauch, K., Tönjes, A., Trégouët, D.-A., Tremblay, A., Tremoli, E., Virtamo, J., Vohl, M.-C., Völker, U., Waeber, G., Willemsen, G., Witteman, J.C., Zillikens, M.C., Adair, L.S., Amouyel, P., Asselbergs, F.W., Assimes, T.L., Bochud, M., Boehm, B.O., Boerwinkle, E., Bornstein, S.R., Bottinger, E.P., Bouchard, C., Cauchi, S., Chambers, J.C., Chanock, S.J., Cooper, R.S., de Bakker, P.I.W., Dedoussis, G., Ferrucci, L., Franks, P.W., Froguel, P., Groop, L.C., Haiman, C.A., Hamsten, A., Hui, J., Hunter, D.J., Hveem, K., Kaplan, R.C., Kivimaki, M., Kuh, D., Laakso, M., Liu, Y., Martin, N.G., März, W., Melbye, M., Metspalu, A., Moebus, S., Munroe, P.B., Njølstad, I., Oostra, B.A., Palmer, C.N.A., Pedersen, N.L., Perola, M., Pérusse, L., Peters, U., Power, C., Quertermous, T., Rauramaa, R., Rivadeneira, F., Saaristo, T.E., Saleheen, D., Sattar, N., Schadt, E.E., Schlessinger, D., Slagboom, P.E., Snieder, H., Spector, T.D., Thorsteinsdottir, U., Stumvoll, M., Tuomilehto, J., Uitterlinden, A.G., Uusitupa, M., van der Harst, P., Walker, M., Wallaschofski, H., Wareham, N.J., Watkins, H., Weir, D.R., Wichmann, H.-E., Wilson, J.F., Zanen, P., Borecki, I.B., Deloukas, P., Fox, C.S., Heid, I.M., O'Connell, J.R., Strachan, D.P., Stefansson, K., van Duijn, C.M., Abecasis, G.R., Franke, L., Frayling, T.M., McCarthy, M.I., Visscher, P.M., Scherag, A., Willer, C.J., Boehnke, M., Mohlke, K.L., Lindgren, C.M., Beckmann, J.S., Barroso, I., North, K.E., Ingelsson, E., Hirschhorn, J.N., Loos, R.J.F., Speliotes, E.K., 2015. Genetic studies of body mass index yield new insights for obesity biology. Nature 518, 197–206.
Lopez, J.P., Fiori, L.M., Cruceanu, C., Lin, R., Labonte, B., Cates, H.M., Heller, E.A., Vialou, V., Ku, S.M., Gerald, C., Han, M.-H., Foster, J., Frey, B.N., Soares, C.N., Müller, D.J., Farzan, F., Leri, F., MacQueen, G.M., Feilotter, H., Tyryshkin, K., Evans, K.R., Giacobbe, P., Blier, P., Lam, R.W., Milev, R., Parikh, S.V., Rotzinger, S., Strother, S.C., Lewis, C.M., Aitchison, K.J., Wittenberg, G.M., Mechawar, N., Nestler, E.J., Uher, R., Kennedy, S.H., Turecki, G., 2017. MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. Nat. Commun. 8, 15497.
MacNeil, R.R., Müller, D.J., 2016. Genetics of common antipsychotic-induced adverse effects. Mol Neuropsychiatry 2, 61–78.

Maiocchi, L., Bernardi, E., 2012. Acute anterior compartment syndrome associated with psychogenic polydipsia. Australas. Psychiatry 20, 159–161.
Malhotra, A.K., Correll, C.U., Chowdhury, N.I., Müller, D.J., Gregersen, P.K., Lee, A.T., Tiwari, A.K., Kane, J.M., Fleischhacker, W.W., Kahn, R.S., Ophoff, R.A., Meltzer, H.Y., Lencz, T., Kennedy, J.L., 2012. Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. Arch. Gen. Psychiatry 69, 904–912.
Manu, P., Dima, L., Shulman, M., Vancampfort, D., De Hert, M., Correll, C.U., 2015. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. Acta Psychiatr. Scand. 132, 97–108.
Maranville, J.C., Cox, N.J., 2016. Pharmacogenomic variants have larger effect sizes than genetic variants associated with other dichotomous complex traits. Pharmacogenomics J 16, 388–392.
Marouli, E., Graff, M., Medina-Gomez, C., Lo, K.S., Wood, A.R., Kjaer, T.R., Fine, R.S., Lu, Y., Schurmann, C., Highland, H.M., Rüeger, S., Thorleifsson, G., Justice, A.E., Lamparter, D., Stirrups, K.E., Turcot, V., Young, K.L., Winkler, T.W., Esko, T., Karaderi, T., Locke, A.E., Masca, N.G.D., Ng, M.C.Y., Mudgal, P., Rivas, M.A., Vedantam, S., Mahajan, A., Guo, X., Abecasis, G., Aben, K.K., Adair, L.S., Alam, D.S., Albrecht, E., Allin, K.H., Allison, M., Amouyel, P., Appel, E.V., Arveiler, D., Asselbergs, F.W., Auer, P.L., Balkau, B., Banas, B., Bang, L.E., Benn, M., Bergmann, S., Bielak, L.F., Blüher, M., Boeing, H., Boerwinkle, E., Böger, C.A., Bonnycastle, L.L., Bork-Jensen, J., Bots, M.L., Bottinger, E.P., Bowden, D.W., Brandslund, I., Breen, G., Brilliant, M.H., Broer, L., Burt, A.A., Butterworth, A.S., Carey, D.J., Caulfield, M.J., Chambers, J.C., Chasman, D.I., Chen, Y.-D.I., Chowdhury, R., Christensen, C., Chu, A.Y., Cocca, M., Collins, F.S., Cook, J.P., Corley, J., Galbany, J.C., Cox, A.J., Cuellar-Partida, G., Danesh, J., Davies, G., de Bakker, P.I.W., de Borst, G.J., de Denus, S., de Groot, M.C.H., de Mutsert, R., Deary, I.J., Dedoussis, G., Demerath, E.W., den Hollander, A.I., Dennis, J.G., Di Angelantonio, E., Drenos, F., Du, M., Dunning, A.M., Easton, D.F., Ebeling, T., Edwards, T.L., Ellinor, P.T., Elliott, P., Evangelou, E., Farmaki, A.-E., Faul, J.D., Feitosa, M.F., Feng, S., Ferrannini, E., Ferrario, M.M., Ferrieres, J., Florez, J.C., Ford, I., Fornage, M., Franks, P.W., Frikke-Schmidt, R., Galesloot, T.E., Gan, W., Gandin, I., Gasparini, P., Giedraitis, V., Giri, A., Girotto, G., Gordon, S.D., Gordon-Larsen, P., Gorski, M., Grarup, N., Grove, M.L., Gudnason, V., Gustafsson, S., Hansen, T., Harris, K.M., Harris, T.B., Hattersley, A.T., Hayward, C., He, L., Heid, I.M., Heikkilä, K., Helgeland, Ø., Hernesniemi, J., Hewitt, A.W., Hocking, L.J., Hollensted, M., Holmen, O.L., Hovingh, G.K., Howson, J.M.M., Hoyng, C.B., Huang, P.L., Hveem, K., Ikram, M.A., Ingelsson, E., Jackson, A.U., Jansson, J.-H., Jarvik, G.P., Jensen, G.B., Jhun, M.A., Jia, Y., Jiang, X., Johansson, S., Jørgensen, M.E., Jørgensen, T., Jousilahti, P., Jukema, J.W., Kahali, B., Kahn, R.S., Kähönen, M., Kamstrup, P.R., Kanoni, S., Kaprio, J., Karaleftheri, M., Kardia, S.L.R., Karpe, F., Kee, F., Keeman, R., Kiemeney, L.A., Kitajima, H., Kluivers, K.B., Kocher, T., Komulainen, P., Kontto, J., Kooner, J.S., Kooperberg, C., Kovacs, P., Kriebel, J., Kuivaniemi, H., Küry, S., Kuusisto, J., La Bianca, M., Laakso, M., Lakka, T.A., Lange, E.M., Lange, L.A., Langefeld, C.D., Langenberg, C., Larson, E.B., Lee, I.-T., Lehtimäki, T., Lewis, C.E., Li, H., Li, J., Li-Gao, R., Lin, H., Lin, L.-A., Lin, X., Lind, L., Lindström, J., Linneberg, A., Liu, Y., Liu, Y., Lophatananon, A., Luan, J. 'an, Lubitz, S.A., Lyytikäinen, L.-P., Mackey, D.A., Madden, P.A.F., Manning, A.K., Männistö, S., Marenne, G., Marten, J., Martin, N.G., Mazul, A.L., Meidtner, K., Metspalu, A., Mitchell, P., Mohlke, K.L., Mook-Kanamori, D.O., Morgan, A., Morris, A.D., Morris, A.P., Müller-Nurasyid, M., Munroe, P.B., Nalls, M.A., Nauck, M., Nelson, C.P., Neville, M., Nielsen, S.F., Nikus, K., Njølstad, P.R., Nordestgaard, B.G., Ntalla, I., O'Connel, J.R., Oksa, H., Loohuis, L.M.O., Ophoff, R.A., Owen, K.R., Packard, C.J., Padmanabhan, S., Palmer, C.N.A., Pasterkamp, G., Patel, A.P., Pattie, A., Pedersen, O., Peissig, P.L., Peloso, G.M., Pennell, C.E., Perola, M., Perry, J.A., Perry, J.R.B., Person, T.N., Pirie, A., Polasek, O., Posthuma, D., Raitakari, O.T., Rasheed, A., Rauramaa, R., Reilly, D.F., Reiner, A.P., Renström, F., Ridker, P.M., Rioux, J.D., Robertson, N., Robino, A., Rolandsson, O., Rudan, I., Ruth, K.S., Saleheen, D., Salomaa, V., Samani, N.J., Sandow, K., Sapkota, Y., Sattar, N., Schmidt, M.K., Schreiner, P.J., Schulze, M.B., Scott, R.A., Segura-Lepe, M.P., Shah, S., Sim, X., Sivapalaratnam, S., Small, K.S., Smith, A.V., Smith, J.A., Southam, L., Spector, T.D., Speliotes, E.K., Starr, J.M., Steinthorsdottir, V., Stringham, H.M., Stumvoll, M., Surendran, P., 't Hart, L.M., Tansey, K.E., Tardif, J.-C., Taylor, K.D., Teumer, A., Thompson, D.J., Thorsteinsdottir, U., Thuesen, B.H., Tönjes, A., Tromp, G., Trompet, S., Tsafantakis, E., Tuomilehto, J., Tybjaerg-Hansen, A., Tyrer, J.P., Uher, R., Uitterlinden, A.G., Ulivi, S., van der Laan, S.W., Van Der Leij, A.R., van Duijn, C.M., van Schoor, N.M., van Setten, J., Varbo, A., Varga, T.V., Varma, R., Edwards, D.R.V., Vermeulen, S.H., Vestergaard, H., Vitart, V., Vogt, T.F., Vozzi, D., Walker, M., Wang, F., Wang, C.A., Wang, S., Wang, Y., Wareham, N.J., Warren, H.R., Wessel, J., Willems, S.M., Wilson, J.G., Witte, D.R., Woods, M.O., Wu, Y., Yaghootkar, H., Yao, J., Yao, P., Yerges-Armstrong, L.M., Young, R., Zeggini, E., Zhan, X., Zhang, W., Zhao, J.H., Zhao, W., Zhao, W., Zheng, H., Zhou, W., EPIC-InterAct Consortium, CHD Exome+ Consortium, ExomeBP Consortium, T2D-Genes Consortium, GoT2D Genes Consortium, Global Lipids Genetics Consortium, ReproGen Consortium, MAGIC Investigators, Rotter, J.I., Boehnke, M., Kathiresan, S., McCarthy, M.I., Willer, C.J., Stefansson, K., Borecki, I.B., Liu, D.J., North, K.E., Heard-Costa, N.L., Pers, T.H., Lindgren, C.M., Oxvig, C., Kutalik, Z., Rivadeneira, F., Loos, R.J.F., Frayling, T.M., Hirschhorn, J.N., Deloukas, P., Lettre, G., 2017. Rare and low-frequency coding variants alter human adult height. Nature 542, 186–190.
Matsuda, J., Yokota, I., 2008. Cblb gene analysis in Japanese type 1 diabetes with younger age of onset. Clin. Pediatr. Endocrinol. 17, 31–38.
Na, S.-S., Aldonza, M.B., Sung, H.-J., Kim, Y.-I., Son, Y.S., Cho, S., Cho, J.-Y., 2015. Stanniocalcin-2 (STC2): a potential lung cancer biomarker promotes lung cancer metastasis and progression. Biochim. Biophys. Acta 1854, 668–676.
Nurmi, E.L., Spilman, S.L., Whelan, F., Scahill, L.L., Aman, M.G., McDougle, C.J., Arnold, L.E., Handen, B., Johnson, C., Sukhodolsky, D.G., Posey, D.J., Lecavalier, L., Stigler, K.A., Ritz, L., Tierney, E., Vitiello, B., McCracken, J.T., Research Units on Pediatric Psychopharmacology Autism Network, 2013. Moderation of antipsychotic-induced weight gain by energy balance gene variants in the RUPP autism network risperidone studies. Transl. Psychiatry 3, e274.
Opgen-Rhein, C., Brandl, E.J., Müller, D.J., Neuhaus, A.H., Tiwari, A.K., Sander, T., Dettling, M., 2010. Association of HTR2C, but not LEP or INSIG2, genes with antipsychotic-induced weight gain in a German sample. Pharmacogenomics 11, 773–780.
Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. Lancet 388, 86–97.
Park, J., Rho, H.K., Kim, K.H., Choe, S.S., Lee, Y.S., Kim, J.B., 2005. Overexpression of glucose-6-phosphate dehydrogenase is associated with lipid dysregulation and insulin resistance in obesity. Mol. Cell. Biol. 25, 5146–5157.
Park, Y.J., Choe, S.S., Sohn, J.H., Kim, J.B., 2017. The role of glucose-6-phosphate dehydrogenase in adipose tissue inflammation in obesity. Adipocyte 6, 147–153.
Pouget, J.G., Gonçalves, V.F., Nurmi, E.L., P Laughlin, C., Mallya, K.S., McCracken, J.T., Aman, M.G., McDougle, C.J., Scahill, L., Misener, V.L., Tiwari, A.K., Zai, C.C., Brandl, E.J., Felsky, D., Leung, A.Q., Lieberman, J.A., Meltzer, H.Y., Potkin, S.G., Niedling, C., Steimer, W., Leucht, S., Knight, J., Müller, D.J., Kennedy, J.L., 2015. Investigation of TSPO variants in schizophrenia and antipsychotic treatment outcomes. Pharmacogenomics 16, 5–22.
Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., Reich, D., 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat. Genet. 38, 904–909.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P., de Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81, 559–575.
Reynolds, G.P., Yevtushenko, O.O., Gordon, S., Arranz, B., San, L., Cooper, S.J., 2013. The obesity risk gene FTO influences body mass in chronic schizophrenia but not initial antipsychotic drug-induced weight gain in first-episode patients. Int. J. Neuropsychopharmacol. 16, 1421–1425.
Singh, V., Kishore, N., Kumar, D., Sengupta, S., 2012. Glucose-6 phosphate dehydrogenase deficiency and psychotic illness. Indian J. Psychol. Med. 34, 270–272.
Smoot, M.E., Ono, K., Ruscheinski, J., Wang, P.-L., Ideker, T., 2011. Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics 27, 431–432.
Song, X., Pang, L., Feng, Y., Fan, X., Li, X., Zhang, W., Gao, J., Zhang, J., Nemani, K., Zhang, H., Lv, L., 2014. Fat-mass and obesity-associated gene polymorphisms and weight gain after risperidone treatment in first episode schizophrenia. Behav. Brain Funct. 10, 35.
Song, H.-T., Sun, X.-Y., Zhang, L., Zhao, L., Guo, Z.-M., Fan, H.-M., Zhong, A.-F., Niu, W., Dai, Y.-H., Zhang, L.-Y., Shi, Z., Liu, X.-P., Lu, J., 2014. A preliminary analysis of association between the down-regulation of microRNA-181b expression and symptomatology improvement in schizophrenia patients before and after antipsychotic treatment. J. Psychiatr. Res. 54, 134–140.
Subramaniam, M., Lam, M., Guo, M.E., He, V.Y.F., Lee, J., Verma, S., Chong, S.A., 2014. Body mass index, obesity, and psychopathology in patients with schizophrenia. J. Clin. Psychopharmacol. 34, 40–46.
Templeman, L.A., Reynolds, G.P., Arranz, B., San, L., 2005. Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenet. Genomics 15, 195.
Tiwari, A.K., Brandl, E.J., Weber, C., Likhodi, O., Zai, C.C., Hahn, M.K., Lieberman, J.A., Meltzer, H.Y., Kennedy, J.L., Müller, D.J., 2013. Association of a functional polymorphism in neuropeptide Y with antipsychotic-induced weight gain in schizophrenia patients. J. Clin. Psychopharmacol. 33, 11–17.
Tiwari, A.K., Brandl, E.J., Zai, C.C., Goncalves, V.F., Chowdhury, N.I., Freeman, N., Lieberman, J.A., Meltzer, H.Y., Kennedy, J.L., Müller, D.J., 2016. Association of orexin receptor polymorphisms with antipsychotic-induced weight gain. World J. Biol. Psychiatry 17, 221–229.
Vasudev, K., Choi, Y.-H., Norman, R., Kim, R.B., Schwarz, U.I., 2017. Genetic determinants of clozapine-induced metabolic side effects. Can. J. Psychiatr. 62, 138–149.
Wallace, T.J., Zai, C.C., Brandl, E.J., Müller, D.J., 2011. Role of 5-HT(2C) receptor gene variants in antipsychotic-induced weight gain. Pharmgenomics. Pers. Med. 4, 83–93.
Wang, F., Zhao, Y., Niu, Y., Wang, C., Wang, M., Li, Y., Sun, C., 2012. Activated glucose-6-phosphate dehydrogenase is associated with insulin resistance by upregulating pentose and pentosidine in diet-induced obesity of rats. Horm. Metab. Res. 44, 938–942.
Watanabe, K., Taskesen, E., van Bochoven, A., Posthuma, D., 2017. Functional mapping and annotation of genetic associations with FUMA. Nat. Commun. 8, 1826.
Willer, C.J., Li, Y., Abecasis, G.R., 2010. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics 26, 2190–2191.
Wu, J., Zhang, L., Zhang, J., Dai, Y., Bian, L., Song, M., Russell, A., Wang, W., 2013. The genetic contribution of CIDEA polymorphisms, haplotypes and loci interaction to obesity in a Han Chinese population. Mol. Biol. Rep. 40, 5691–5699.
Xia, J., Gill, E.E., Hancock, R.E.W., 2015. NetworkAnalyst for statistical, visual and network-based meta-analysis of gene expression data. Nat. Protoc. 10, 823–844.
Yu, H., Wang, L., Lv, L., Ma, C., Du, B., Lu, T., Jin, C., Yan, H., Yang, Y., Li, W., Ruan, Y., Zhang, H., Zhang, H., Mi, W., Mowry, B., Ma, W., Li, K., Zhang, D., Yue, W., 2016. Genome-wide association study suggested the PTPRD polymorphisms were associated with weight gain effects of atypical antipsychotic medications. Schizophr. Bull. 42, 814–823.
Zhang, L., Dai, Y., Bian, L., Wang, W., Muramatsu, M., Hua, Q., 2011. Association of the cell death-inducing DNA fragmentation factor alpha-like effector A (CIDEA) gene V115F (G/T) polymorphism with phenotypes of metabolic syndrome in a Chinese population. Diabetes Res. Clin. Pract. 91, 233–238.
Zhang, Z.-H., Wu, Y.-G., Qin, C.-K., Rong, Z.-H., Su, Z.-X., Xian, G.-Z., 2014. Stanniocalcin 2 expression predicts poor prognosis of hepatocellular carcinoma. Oncol. Lett. 8, 2160–2164.