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# Association of variants in *SH2B1* and *RABEP1* with worsening of low-density lipoprotein and glucose parameters in patients treated with psychotropic drugs

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**ABSTRACT**

Genetic factors associated with Body Mass Index (BMI) have been widely studied over the last decade. We examined whether genetic variants previously associated with BMI in the general population are associated with cardiometabolic parameter worsening in the psychiatric population receiving psychotropic drugs, a high-risk group for metabolic disturbances. Classification And Regression Trees (CARTs) were used as a tool capable of describing hierarchical associations, to pinpoint genetic variants best predicting worsening of cardiometabolic parameters (i.e total, HDL and LDL-cholesterol, triglycerides, body mass index, waist circumference, fasting glucose, and blood pressure) following prescription of psychotropic drugs inducing weight gain in a discovery sample of 357 Caucasian patients. Significant findings were tested for replication in a second Caucasian psychiatric sample (n=140).

*SH2B1* rs3888190C>A was significantly associated with LDL levels in the discovery and in the replication sample, with A-allele carriers having 0.2 mmol/l (p=0.005) and 0.36 mmol/l (p=0.007) higher LDL levels compared to others, respectively. G-allele carriers of *RABEP1* rs1000940A>G had lower fasting glucose levels compared to others in both samples (-0.16 mmol/l; p<0.001 and -0.77 mmol/l; p=0.03 respectively). The present study is the first to observe such associations in human subjects, which may in part be explained by a high risk towards dyslipidemia and diabetes in psychiatric patients receiving psychotropic treatments compared to population-based individuals. These results may therefore give new insight into the etiology of LDL-cholesterol and glucose regulation in psychiatric patients under psychotropic drug therapy.

## INTRODUCTION

Cardiovascular diseases constitute a major health concern associated with high morbidity and mortality. Comorbidities such as obesity, dyslipidemia, diabetes and hypertension are complex clinical conditions and major contributing risk factors for the development of cardiovascular diseases. Such medical conditions result from the interaction between numerous genetic and environmental factors (e.g. sedentary lifestyle with excessive dietary intake) (1, 2). Genetic risk factors were actually reported to account for up to 40 to 70% of inter-individual variability for the most extensively studied obesity-related phenotype, namely the BMI (3, 4). The largest meta-analysis of Genome-Wide Association Studies (GWAS) to date has reported 97 different loci associated with BMI in 339,224 individuals (5).

In psychiatry, patients suffering from severe mental illness have a reduced life expectancy of 10 to 25 years compared to the general population due mainly to cardiovascular diseases resulting from the psychiatric disorder and/or comorbidities, but also from the prescription of psychotropic treatments (6). Thus, many antipsychotics, in particular atypical antipsychotics, some mood stabilizers and antidepressants induce metabolic dysfunctions by inducing weight gain (7), dyslipidemia (8), type 2 diabetes (9-11), and/or hypertension (12) to varying degrees. For instance, clozapine and olanzapine are associated with the greatest risk for developing weight gain and other metabolic effects (7). All of these factors result in serious morbidity such as cardiovascular diseases (13) and a decreased medication adherence. Dyslipidemia, type 2 diabetes and hypertension can develop either as a direct or collateral consequence of the use of psychotropic drugs. Although precise mechanisms underlying metabolic side effects induced by psychotropic drugs are only partially elucidated to

date, the dual antagonism on serotonin and dopamine receptors was shown to stimulate appetite leading to weight gain and other long-term comorbidities (14). Furthermore, independent antagonism actions on adrenergic and muscarinic receptors were directly related with decreasing insulin secretion and pancreatic β-cell response (15). Over the last decade, pharmacogenetics of psychotropic-induced weight gain has been extensively studied using candidate gene approaches, in particular within dopamine and serotonin receptors (16, 17). In addition, numerous single nucleotide polymorphisms (SNPs) within genes involved in other pathways of metabolism regulation (e.g. enzymes, receptors or transcriptional coactivators involved in leptin-melanocortin pathways, genes involved in cholesterol and/or in glucose homeostasis) were also associated with weight gain in psychiatric patients taking psychotropic drugs (18-22).

A growing body of evidence suggests that obesity and psychiatric diseases share common etiological pathways, which may be illustrated by the observed synergistic influence of genes associated with obesity and with psychiatric illness on cardiometabolic parameters (23). In addition, recent pharmacogenetic studies have shown stronger influence on obesity phenotypes of some BMI-associated genes in the psychiatric population treated with weight gain inducing psychotropic drugs compared to the general population (19-21). Unfortunately, it is unknown to which extent the 97 variants associated with BMI in the general population are associated with other cardiometabolic phenotypes in the psychiatric population, despite that such populations are at very high risk for cardiometabolic disorders. Because cardiometabolic traits have a complex etiology, with an important variability, the aim of the present study was to determine whether population-based genetic variants related to BMI are associated with cardiometabolic phenotypes in patients from two psychiatric samples who were

prescribed known weight gain inducing psychotropic drugs. The analyses were performed using methods capable of detecting hierarchical associations, in order to further refine the underlying biological mechanisms of cardiometabolic phenotypes in psychiatry.

## MATERIALS AND METHODS

### Psychiatric samples

A prospective cohort study is ongoing in the Lausanne Psychiatric University Hospital since 2007. Patients treated with atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, paliperidone, risperidone), mood stabilizers (lithium, valproate) or/and mirtazapine were included. Baseline and follow-up clinical observations (1, 3, 6 and/or 12 months) were obtained during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis (24). Blood samples were collected at $1^{st}$, $3^{rd}$ and $12^{th}$ months. Most patients had already received other psychotropic treatments before the current treatment. Ethnicity data were obtained from medical files. Diagnoses were based on the *ICD-10* classification (F00-F09 organic disorder; F20.0-F24.9 and F28-F29 psychotic disorders; F25.0-F25.9 schizoaffective disorder; F30.0-F31.9 bipolar disorder; F32.0-F33.9 depressive disorder). Written informed consents for inclusion in the study and also for the genetic analyses were obtained from patients or their legal representatives. The study was approved by the Ethics Committee of Lausanne University Hospital. Further description of the cohort study was published elsewhere (22, 25).

#### *Discovery and replication samples*

97 SNPs associated with BMI in a recent population-based meta-analysis (5) were tested for association with worsening of cardiometabolic variables in the discovery sample. The discovery sample consisted of 357 Caucasian patients from the above-described prospective cohort study, with available clinical data for at least two periods including baseline data. Positive results (i.e. for a smaller subset of SNPs) were tested for replication in the replication sample, composed of 140 Caucasian patients from the same cohort study, with available clinical data for at least two periods of treatment but without baseline data (all patients with baseline data were already included in the discovery sample). Changes of metabolic parameters are more important at the beginning of treatment and including patients with baseline data in the discovery cohort increases the power to detect significant associations between SNPs and cardiometabolic parameters. Thereafter, only the strongest signals were confirmed using the replication sample.

**SNP selection and genotyping**

97 SNPs were selected according to the previously mentioned population-based meta-analysis (5). DNA from blood samples of psychiatric patients was extracted using the Flexigene DNA Kit or QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland) as described by the manufacturers's instructions. Genotypes of 96 SNPs were available in the Illumina 200K CardioMetaboChip (26). The CardioMetabochip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200'000 SNPs from regions identified by large scale meta-analyses of genome wide association studies (GWAS) for metabolic and cardiovascular traits. CardioMetabochip genotyping was performed at the iGE3 genomics platform of the University of Geneva

(http://www.ige3.unige.ch/genomics-platform.php). Quality control excluded samples from the analysis if gender was inconsistent with genetic data from X-linked markers, if autosomal heterozygosity was extreme, genotype call rate <0.96, Gene Call (GC) score <0.15 and/or minor allele frequency (MAF) <0.10. The one remaining SNP not available in the CardioMetaboChip, namely rs11847697, was analysed using a TaqMan SNP Genotyping Assay (C_1293175_10) on ViiA™ 7 Real-Time PCR System, as described by the manufacturer instructions.

**Functional assessment of significant SNPs**

***eQTL analysis***

Cis-association data of the influence of significant SNPs on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations in the general population (Illumina OMNI 5M SNP Array)(27).

***RegulomeDB annotation***

The Regulome database (http://www.regulomedb.org/) was used to assess the functional activity of significant SNPs (28). This database defines SNPs with known and/or predicted regulatory elements located in intergenic regions of the human genome. Known and predicted regulatory elements include regions of DNAase hypersensitivity, binding sites of transcription factors and promoter regions biochemically characterized to the regulation of transcription. Sources for these data include public datasets from GEO, the ENCODE project and the published literature.

**Statistical analyses**

Statistical analyses were performed using Stata 12 (StataCorp, College Station TX, USA) and R version 3.1.1. Hardy-Weinberg equilibrium (HWE) testing was performed for the 97 SNPs using Pearson's chi-squared test. SNPs for which p-value was higher than 0.05 were considered in HWE.

Classification And Regression Trees (CARTs) are used to segregate SNPs that best predict the worsening of cardiometabolic variables during different periods of the psychotropic treatment. CARTs can be grown using the so called Recursive Partitioning and Regression Trees algorithms (29). These algorithms are implemented in a few softwares including R environment for statistical programming and data analysis (rpart library). At each node, the split rule is applied which is based on the Generalized Gini index, the split can be performed if number of observations exceeds a certain threshold (the threshold in this study was 20). Pruning can be used in function of the desired complexity of the tree. Complexity of the constructed tree at each node is represented by the so called Complexity Parameter which is equivalent to the decrease in relative error rate of the tree if the split at each that node survives after the tree is pruned.

CARTs were first performed on the discovery sample to identify clinical (age, sex, smoking status) and genetic (97 SNPs) variables best predicting worsening of cardiometabolic features during the psychotropic treatment (i.e. increase of BMI, waist circumference (WC), total cholesterol (TC), fasting triglycerides (TG), low-density lipoprotein (LDL), fasting glucose (GLC), systolic blood pressure (SBP) and/or of diastolic blood pressure (DBP), and/or decrease of high-density lipoprotein (HDL)). Of note, patients receiving lipid-lowering, antidiabetic and/or antihypertensive drugs were

excluded from TC, TG, LDL, HDL analyses, GLC analyses and SBP and DBP analyses, respectively (**S1 Table**). In order to determine short- and long-term risk factors associated with metabolic disturbances, CARTs were performed at several periods of treatment (i.e. from ≥10 to <45 days; from ≥45 to <135 days and from ≥135 to <535 days of psychotropic treatment). Variables in the first three layers of the CART tree structure for each cardiometabolic phenotype and each period of psychotropic treatment were considered in further covariate-adjusted statistical analyses. Associations between the most important SNPs (in the first three layers) and cardiometabolic variables were assessed in the discovery sample (using a dominant or recessive model according to CART results) by fitting a generalized additive mixed model (GAMM) adjusting for possible confounders such as age, sex and smoking status (30), allowing a smooth trend for the response in time based on multiple observations for each patient. Significant associations were then tested in the replication sample using the same model. GAMMs were fitted using the mgcv package of R, in which parameter uncertainties (confidence intervals and p-values) were computed using bootstrap (1000 replicates or 10000 replicates whenever possible with replacement, performed on patient level). P-values of two-sided models ≤ 0.05 were considered as statistically significant.

## RESULTS

### Characteristics of psychiatric samples

**S2 Table** displays demographic and clinical characteristics of the two psychiatric Caucasian samples. As published elsewhere (25), values of cardiometabolic parameters in both psychiatric samples generally increased during the psychotropic treatment.

Patients were slightly older in the replication sample (median of 52 years) compared to the discovery sample (median of 47 years; p=0.04). Psychotic (F20.0-F24.9 and F28-F29) was the most frequent diagnosis (37% in the combined sample), and quetiapine was the most frequently prescribed psychotropic drug (33% in the combined sample). No difference of clinical or of demographical variables was observed between the discovery and replication samples (p>0.05), except in the second psychotropic treatment period, namely between 45 and 135 days of treatment, in which BMI and waist circumference were higher in the replication sample (25.5 kg/$m^2$; 95 cm) compared to the discovery sample (23.7 kg/$m^2$; 91 cm; p-values=0.04 and 0.03, respectively).

**Variables predicting cardiometabolic phenotype worsening in the discovery sample**

Three out of the 97 SNPs were not in Hardy Weinberg equilibrium and were therefore not used in analyses (i.e rs1075847, rs13201877 and rs657452). CARTs fitted on the different cardiometabolic phenotypes (i.e. BMI, WC, HDL, TC, TG, LDL, GLC, SBP and DBP) highlighted 57 different SNPs that best predicted worsening of at least one of the latter-mentioned cardiometabolic variable in the discovery sample during three distinct consecutive periods of psychotropic treatment. An example of a CART is presented in **S1 Fig,** showing, for instance, that patients carrying the variant allele of *ADCY3* rs10182181A>G (i.e. G) have a mean TC increase of 3.9%, whereas those who carry the AA genotype have a mean TC increase of 13.7% during the first period of psychotropic treatment. A summary of CART results is displayed in **Table 1**.

**Association of SNPs with cardiometabolic phenotypes in psychiatric samples**

In the discovery sample, 18 out of the 57 different SNPs were significantly associated with at least one cardiometabolic phenotype using multiple linear models adjusted for age, sex, BMI and smoking status ($p<0.05$) (**Table 2**). Two out of the 18 SNPs were significantly replicated in the replication sample, with *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G being significantly associated with LDL levels ($p=0.007$) and FG levels ($p=0.03$), respectively (**Table 3**). The 16 remaining SNPs were not replicated (data not shown) and were therefore not considered in further analyses. Genotype frequencies of *SH2B1* rs3888190C>A (GRCh38.p7 16:28878165) and *RABEP1* rs1000940A>G (GRCh38.p7 17:5379957) in the discovery and replication samples are presented in the **S3 Table**. Both SNPs were in HWE in the two psychiatric samples, and their MAF were in accordance with those reported in HapMap for Caucasians.

***Association of SH2B1 rs3888190C>A with LDL levels in psychiatric samples***

In the discovery sample, rs3888190C>A was significantly associated with LDL levels, with A-allele carriers having 0.20 [0.07; 0.36] mmol/l higher LDL levels compared to patients carrying the CC genotype ($p=0.005$) (**Table 3**). This observation was replicated in the second psychiatric sample (0.36 [0.08; 0.66] mmol/l; $p=0.007$) (**Table 3**). **S2 Fig.a** illustrates the evolution of abnormal LDL level (i.e. LDL levels ≥ 3 mmol/l and/or with any prescribed lipid-lowering drug) prevalence according to rs3888190C>A genotypes during psychotropic treatment in the combined sample. During psychotropic treatment, the proportion of patients with abnormal LDL values significantly increased for both rs3888190-CC (from 40% at baseline to 54% in the last treatment period; $p=0.04$) and rs3888190-A allele carriers (from 46% to 60%, respectively; $p=0.02$), reflecting the development of dyslipidemia-induced psychotropic drug. Within subperiods of treatment,

no difference of abnormal LDL proportion was detected across rs3888190C>A genotypes, possibly due to insufficient power. In contrast, when considering all observations from multiple treatment periods together (**S2 Fig.b**), the overall proportion of patients with abnormal LDL levels was lower for rs3888190-CC carriers (47%) compared to rs3888190-A allele carriers (53%; p=0.03).

***Association of RABEP1 rs1000940A>G with fasting glucose levels in psychiatric samples***

In the discovery sample, rs1000940A>G was significantly associated with fasting glucose. G-allele carriers had 0.16 [0.06; 0.28] mmol/l lower fasting glucose levels compared to patients carrying the AA genotype (p<0.001) and this association was replicated in the second psychiatric sample (0.77 [0.03; 1.39] mmol/l; p=0.03) (**Table 3**). **S3 Fig.a** displays the prevalence of abnormal fasting glucose levels (i.e. fasting GLC levels ≥ 5.6 mmol/l and/or with any prescribed antidiabetic drug) according to rs1000940A>G during the psychotropic treatment. As for *SH2B1* rs3888190C>A and LDL, no significant difference of abnormal glucose level prevalence across rs1000940A>G genotypes was observed in subperiods of psychotropic treatment. However, the overall proportion of patients with abnormal glucose levels was significantly lower for patients carrying rs1000940-G allele (20%) compared to those carrying the AA genotype (27%; p=0.03) when considering all periods of treatment together (**S3 Fig.b**). Moreover, when considering each genotype separately (i.e. in carriers of rs1000940 AA genotype and in carriers of rs1000940 G allele), there was no significant difference of the prevalence of hyperglycemia after a short or after a longer period of treatment (p=0.77 and 0.96 for AA and G allele carriers, respectively), possibly

explained by a worsening of glycemia profile occurring during a longer period of treatment than the one taken into account during the present study.

Even though being non significant due to non-adjusted analyses as well as an insufficient number of observation, **S2** and **S3 Fig** suggest that both *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G could exert an influence on LDL and on glucose, respectively, already before the current psychotropic treatment initiation. These baseline differences may possibly be explained, at least in part, by the fact that most patients were not drug naïve when starting the current psychotropic treatment. Of note, no difference of LDL nor of glucose levels were observed between psychotropic medication groups (constructed according to their propensity to induce metabolic alterations, i.e. high-risk group (olanzapine, clozapine and valproate) versus medium-risk group (quetiapine, risperidone, mirtazapine, lithium) versus low-risk group (amisulpride, aripiprazole)), data not shown.

Although neither *SH2B1* rs3888190C>A nor *RABEP1* rs1000940A>G were detected as having a possible influence on BMI in CART analyses, both SNPs were tested for association with BMI in the discovery psychiatric sample. No significant association was observed between these two SNPs and BMI in the discovery sample (data not shown).

## DISCUSSION

The present study aimed to explore whether SNPs previously associated with BMI and other cardiometabolic variables in the general population (5) are associated with the worsening of cardiometabolic phenotypes in a psychiatric population receiving weight gain inducing psychotropic treatments. In particular, we aimed to better refine underlying

mechanisms linking and/or discerning genetics of BMI with regard to other cardiometabolic comorbidities in the psychiatric population, considering that the prevalence of metabolic syndrome has been reported twice as high in this population compared to the general population (31).

Our preliminary exploration using CART analyses highlighted and ranked 57 different SNPs that predicted the best metabolic parameter worsening during psychotropic treatment in the discovery sample. In the latter sample, 18 SNPs were significantly associated with cardiometabolic phenotypes but the remaining 39 SNPs were not, probably due to adjustment for covariates (i.e. age, sex, BMI and/or smoking status) in GAMM analyses, which was not performed in exploratory CART analyses. Out of the 18 SNPs, *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G were replicated in the second psychiatric replication sample. The 16 remaining SNPs were not replicated, possibly due to the lower sample size of the latter sample compared to the discovery sample and the probable minor influence of these SNPs on cardiometabolic variables.

Thus, *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G were significantly associated with low-density lipoprotein levels and fasting glucose levels, respectively, in two separate psychiatric samples. As recent population-based studies did not observe such associations (5, 32) this is, to our knowledge, the first genetic study that suggested an influence of *SH2B1* rs3888190C>A on LDL as well as of *RABEP1* rs1000940A>G on fasting glucose levels. These different results between general and psychiatric populations may in part be explained by a lower risk towards dyslipidemia and diabetes in population-based individuals compared to psychiatric patients receiving psychotropic treatments(33). Of note, since a 1% reduction in LDL-cholesterol on average was shown to reduce risks for hard coronary heart disease events by approximately 1% in short-

term controlled trials (34), the observed difference of LDL levels between *SH2B1* rs3888190C>A genotypes appears clinically relevant.

In order to differentiate SNPs according to their short- and/or long-term influence on metabolic features, CART analyses were conducted after several distinct periods of psychotropic treatment. Both *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G appeared to exert an influence already before the current psychotropic treatment initiation, which may be explained by the fact that most patients were not drug naïve when starting the current psychotropic treatment. Further studies are required to characterize how these genetic variants influence these two metabolic parameters in drug naïve patients. It is of particular interest to note that our results within this observational psychiatric sample reflect real clinical conditions.

The LDL-increasing allele of *SH2B1* rs3888190C>A in the psychiatric population, namely the A allele was associated with higher BMI values (0.03 $kg/m^2$; $p=3.14*10^{-23}$) in population-based samples (5), which is in accordance with epidemiological expectations. On the other hand, the glucose-increasing genotype of *RABEP1* rs1000940A>G in the psychiatric population, namely AA was associated with lower BMI values in the general population (-0.019 $kg/m^2$; $p=1.3*10^{-8}$) (5). This unexpected result may be explained by a differential influence of *RABEP1* rs1000940A>G on these two cardiometabolic parameters between population-based and psychiatric samples. Despite BMI being a well-described parameter associated with metabolic comorbidities including fasting glycemia in large prospective population studies (35), some recent conflicting genetic association results have been described in population-based samples (32). Thus, several loci have a more pronounced effect on body fat percentage than on BMI, suggesting a specific effect on adiposity rather than on overall body mass (32). For

instance, a genetic polymorphism 500kb upstream of *IRS1* and influencing its expression was on one hand significantly associated with an increased overall adiposity (body fat percentage) and, on the other hand, associated with a protective effect on cardiometabolic health, including a reduced risk of type 2 diabetes and cardiovascular diseases (32). These unexpected results were explained by an effect on fat distribution, as the body fat percentage increasing allele was associated with increased subcutaneous but not with metabolically more harmful visceral fat (36). Many other similar inconsistent cross-phenotypic genetic associations were described in population-based GWAS meta-analyses (5, 32) and strikingly, most of inconsistent cross-phenotypic genetic associations encompass genes that influence insulin receptor signaling (32). Further studies are therefore needed to elucidate underlying biological mechanisms of such unexpected cross-phenotypic associations, in particular between adiposity and insulin resistance disorders.

An increasing number of studies indicate that metabolic and psychiatric diseases share common etiological pathways and have related neurobiological bases (23). *SH2B1* rs3888190C>A as well as its 77 proxies lie in a highly conserved genetic region displaying a considerable regulatory function. *SH2B1* rs3888190C>A may alter the expression of many genes involved in cholesterol homeostasis, including Interleukin 27 (*IL27*), *SH2B1* and Apolipoprotein B receptor (*APOBR*) (S4 Fig) (37-43), either through a cis-effect in the liver and/or through methylation-mediated long-range interaction with its promoter (44). Apart from being involved in the regulation of atherosclerosis, this cytokine was associated with LDL levels in mice and humans (40-42). Besides, some genes involved in the immune system have been associated with schizophrenia, bipolar disorder and major depressive disorder (MDD) in two recent genome-wide association

studies (45, 46), suggesting that cytokines may play a role in psychiatric disorders. Similarly, a recent meta-analysis reported analogies in the pattern of cytokine alterations in the above mentioned psychiatric disorders (47). Taken together, published results suggest that LDL regulation and psychiatric illnesses may share common regulatory genes including *IL27*, which constitutes a possible candidate to explain the specific influence of *SH2B1* rs3888190C>A on LDL in patients with psychiatric disorders but not in individuals from the general population. A growing body of evidence suggest that *RABEP1* rs1000940A>G and its 7 proxies ($r^2$>0.95) may be involved in the regulation of glucose. RABEP1 was shown to interact with RAB5a, a protein required for the regulation of gluconeogenic gene (48) and for insulin sensitivity (49, 50). Additionally, NUP88 was shown to interact with several proteins including the CREB binding protein (CREBBP) involved in insulin sensitivity (51). In addition, eQTL data of these SNPs showed higher expression of *NUP88* in the brain (cerebellar hemisphere) and a lower expression of *RABEP1* in the thyroid and the pituitary, two genes (tagged in part by rs1000940A>G) interacting with different proteins involved in insulin sensitivity (S5 Fig) (48-51). Within the large genetic region of *RABEP1* rs1000940A>G, three proxies may influence expression levels of *ATF2*, a transcription factor involved in part in the regulation of insulin resistance (51-55). Interestingly, an overexpression of the latter transcription factor in nucleus accumbens of rats enhanced antidepressant-like responses, suggesting that this transcription factor plays a role in the regulation of emotional behavior as well (56). Likewise, chronic administration of antidepressants impaired levels of ATF2 in the prefrontal cortex in rats, and similarly, levels of phosphorylated ATF2 were decreased in patients medicated with antidepressants compared to non-medicated patients in post-mortem human brains (57). The latter

studies illustrate the possible role of *ATF2* in the complex interminglement between glucose homeostasis and psychiatric illnesses and may therefore explain the specific influence of *RABEP1* rs1000940A>G on glucose levels in particular in patients with psychiatric disorders but not in individuals from the general population. More studies with larger psychiatric samples are needed to confirm our findings and to identify true causal variants, which will help to better understand mechanisms underlying the metabolic regulation of cholesterol and glucose, in particular in the psychiatric population.

Several limitations of the present study should be considered. Firstly, this study was limited to Caucasian patients and results cannot be generalized to other ethnicities. Secondly, the functional activity of *SH2B1* rs3888190C>A and of *RABEP1* rs1000940A>G could not be assessed in the psychiatric population. Third, association with *SH2B1* rs3888190C>A did not survive to multiple testing correction. However, the present results were replicated in a second psychiatric sample and functional analyses strengthen the validity of our data. Moreover, our results within this observational psychiatric sample reflect real clinical conditions.

In conclusion, this is the first genetic study to identify an association between *SH2B1* rs3888190C>A and LDL levels as well as between *RABEP1* rs1000940A>G and glucose levels. Our results are in agreement with the previously reported roles of the many probable affected genes in metabolism and provide new insight into the implication of these genes in the human regulation of cholesterol and glucose, in particular in the psychiatric population receiving psychotropic drugs. Finally, the considerable regulatory function of these genetic regions emphasizes the probable involvement of many regulatory genes and supports further studies to better understand

mechanisms underlying the metabolic regulation of cholesterol and glucose, in particular in the psychiatric population.

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## Table 1. SNPs and cardiometabolic variables: CART analyses.

| TC | | HDL | | LDL | | TG | | BMI | | WC | | FG | | SBP | | DBP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** | **SNP** | **gene[1]** |
| rs10182181 | *ADCY3* | rs10132280 | *STXBP6* | rs1000940 | *RABEP1* | rs1000940 | *RABEP1* | rs1016287 | *LINC01122* | rs11583200 | *ELAVL4* | rs1000940 | *RABEP1* | rs10132280 | *STXBP6* | rs1000940 | *RABEP1* |
| rs10968576 | *LINGO2* | rs10968576 | *LINGO2* | rs10182181 | *ADCY3* | rs11688816 | *EHBP1* | rs10182181 | *ADCY3* | rs12429545 | *OLFM4* | rs11688816 | *EHBP1* | rs10182181 | *ADCY3* | rs10938397 | *GNPDA2* |
| rs11688816 | *EHBP1* | rs11165643 | *PTBP2* | rs10968576 | *LINGO2* | rs12429545 | *OLFM4* | rs11688816 | *EHBP1* | rs1808579 | *C18orf8* | rs17203016 | *CREB1* | rs1441264 | *MIR548A2* | rs10968576 | *LINGO2* |
| rs12401738 | *FUBP1* | rs11688816 | *EHBP1* | rs1441264 | *MIR548A2* | rs1528435 | *UBE2E3* | rs12885454 | *PRKD1* | rs2033529 | *TDRG1* | rs17405819 | *HNF4G* | rs17203016 | *CREB1* | rs10968576 | *LINGO2* |
| rs17024393 | *GNAT2* | rs1441264 | *MIR548A2* | rs2176598 | *HSD17B12* | rs29941 | *KCTD15* | rs12940622 | *RPTOR* | rs2033732 | *RALYL* | rs2820292 | *NAV1* | rs29941 | *KCTD15* | rs1167827 | *HIP1* |
| rs17094222 | *HIF1AN* | rs1460676 | *FIGN* | rs2287019 | *QPCTL* | rs3101336 | *NEGR1* | rs1441264 | *MIR548A2* | rs205262 | *C6orf106* | rs3101336 | *NEGR1* | rs3810291 | *ZC3H4* | rs17405819 | *HNF4G* |
| rs1808579 | *C18orf8* | rs1514175 | *TNNI3K* | rs3736485 | *DMXL2* | rs3888190 | *SH2B1* | rs1808579 | *C18orf8* | rs2241420 | *MAP2K5* | rs543874 | *SEC16B* | rs7164727 | *LOC100287559* | rs17724992 | *PGPEP1* |
| rs1928295 | *TLR4* | rs16907751 | *ZBTB10* | rs3888190 | *SH2B1* | rs5014937 | *CALCR* | rs2033732 | *RALYL* | rs29941 | *KCTD15* | rs6567160 | *MC4R* | | | rs3810291 | *ZC3H4* |
| rs205262 | *C6orf106* | rs2112347 | *POC5* | rs492400 | *USP37* | rs7103411 | *BDNF* | rs4740619 | *C9orf93* | rs492400 | *USP37* | rs7164727 | *LOC100287559* | | | rs3849570 | *GBE1* |
| rs492400 | *USP37* | rs29941 | *KCTD15* | rs7164727 | *LOC100287559* | | | rs7903146 | *TCF7L2* | | | rs7239883 | *LOC284260* | | | rs4787491 | *INO80E* |
| rs7164727 | *LOC100287559* | rs4787491 | *INO80E* | rs7243357 | *GRP* | | | rs9400239 | *FOXO3* | | | rs7903146 | *TCF7L2* | | | rs7113874 | *TRIM66* |
| rs7903146 | *TCF7L2* | rs6804842 | *RARB* | rs7715256 | *GALNT10* | | | | | | | | | | | | |
| rs9914578 | *SMG6* | rs7103411 | *BDNF* | rs9374842 | *LOC285762* | | | | | | | | | | | | |
| | | rs7715256 | *GALNT10* | | | | | | | | | | | | | | |
| | | rs7903146 | *TCF7L2* | | | | | | | | | | | | | | |

TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TG: triglycerides; BMI: body mass index; WC: waist circumference; FG: fasting glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure.
This table displays the 57 SNPs predicting the best worsening of cardiometabolic parameters (within the first three layers) according to CART analyses in the discovery sample.
[1]Nearest gene for each SNP.

## Table 2. SNPs and cardiometabolic variables: discovery sample.

| TC | | HDL | | LDL | | TG | | BMI | | WC | | FG | | SBP | | DBP | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n=309 | | n=306 | | n=301 | | n=290 | | n=330 | | n=325 | | n=287 | | n=268 | | n=268 | |
| SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value | SNP<br>β | gene(s)[1]<br>p-value |
| rs17094222 T>C | *HIF1AN* | rs1441264 G>A | *MIR548A2* | rs3888190 C>A | *SH2B1; APOBR; ATXN2L; SBK1; SULT1A2; TUFM* | rs7103411 C>T | *BDNF* | rs1016287 T>C | *LINC01122* | rs2241420 G>A | *MAP2K5; LBXCOR1* | rs1000940 A>G | *RABEP1* | rs29941 A>G | *KCTD15* | rs1000940 A>G | *RABEP1* |
| ref :TT<br>0.17 (-0.04-0.35) | 0.05 | ref :GG<br>0.07 (0.02-0.12) | 0.01 | ref :CC<br>0.20 (0.07-0.36) | 0.005 | ref :CC<br>0.12 (0.01-0.25) | 0.01 | ref :TT/TC<br>1.33 (-0.28-2.85) | 0.05 | ref :GG/GA<br>-7.37 (-10.54 - (-)2.90) | <0.001 | ref :AA<br>-0.16 (-0.28 - (-)0.06) | <0.001 | ref :AA/AG<br>6.78 (-0.42-12.2) | 0.05 | ref :AA<br>-3.34 (-5.76 - (-)1.72) | <0.001 |
| rs205262 A>G | *C6orf106; SNRPC* | rs7103411 C>T | *BDNF* | rs2287019 C>T | *QPCTL; GIPR* | rs3888190 C>A | *SH2B1; APOBR; ATXN2L; SBK1; SULT1A2; TUFM* | rs9400239 T>C | *FOXO3; HSS00296402* | rs12429545 G>A | *OLFM4* | rs7903146 C>T | *TCF7L2* | | | rs3810291 G>A | *ZC3H4* |
| ref :AA<br>-0.22 (-0.37 - (-)0.05) | 0.01 | ref :CC/CT<br>-0.23 (-0.31 - (-)0.14) | <0.001 | ref :CC<br>-0.11 (-0.24 - 0.02) | 0.05 | ref :CC/CA<br>0.13 (-0.04-0.29) | 0.05 | ref :TT<br>0.99 (0.22-1.88) | 0.009 | ref :GG<br>-2.18 (-4.05 - (-)0.17) | 0.02 | ref :CC/CT<br>0.15 (-0.01-0.31) | 0.03 | | | ref :GG<br>-1.63 (-4.07 - 0.32) | 0.04 |
| rs11688816 G>A | *EHBP1* | | | | | rs11688816 G>A | *EHBP1* | | | | | | | | | rs1167827 G>A | *HIP1; PMS2L3; PMS2P5; WBSCR16* |
| ref:GG/GA<br>0.24 (0.06-0.47) | 0.01 | | | | | ref :GG/GA<br>0.19 (0.01-0.37) | 0.02 | | | | | | | | | ref :GG<br>2.20 (0.04-3.88) | 0.03 |

Among SNPs from CART analyses (in Table 1), 18 SNPs were significantly associated with cardiometabolic variables in the discovery sample using GAMM models, with SNPs considered as dominant or recessive according to CART results.
[1]All notable genes related to corresponding SNPs (i.e. nearest gene, gene with biological relevance to metabolic parameters, eQTL SNPs, etc) (5).

## Table 3. Association of SNPs with metabolic phenotypes in two independent Caucasian psychiatric samples

| SNP | Phenotype | n | Discovery sample β (95% CI) (mmol/l) | p-value | n | Replication sample β (95% CI) (mmol/l) | p-value |
|---|---|---|---|---|---|---|---|
| *SH2B1* rs3888190C>A<br>CC<br>CA/AA | LDL | 301 | ref<br>0.20 (0.07 - 0.36) | 0.005 | 105 | ref<br>0.36 (0.08 - 0.66) | 0.007 |
| *RABEP1* rs1000940A>G<br>AA<br>AG/GG | FG | 287 | ref<br>-0.16 (-0.28 - -0.06) | <0.001 | 82 | ref<br>-0.77 (-1.39 - 0.03) | 0.03 |

In this Table, 2 SNPs significantly associated with cardiometabolic variables in the replication sample using GAMM models are displayed. For clarity purpose, results for these 2 SNPs in the discovery sample are repeated. These 2 SNPs appeared in the second layer of CART analyses on LDL and fasting glucose levels.
Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex, body mass index and smoking status.
β: estimate; ref: reference; LDL:low-density lipoprotein; FG: fasting glucose.
Patients taking lipid-lowering or antidiabetic medications were excluded from LDL and FG analyses, respectively.
For FG analyses, patients in non fasting conditions were excluded from analyses.

**S1 Table. Lipid-lowering drugs, antidiabetic drugs and antihypertensive drugs considered to characterize dyslipidemia, type 2 diabetes and/or hypertension.**

| Lipid-lowering drugs | Antidiabetic drugs | Antihypertensive drugs |
|---|---|---|
| Atorvastatin | Desmopressin | Aliskiren |
| Ezetimibe | Glibenclamid | Amiloride hydrochlorothiazide |
| Fenofibrate | Gliclazide | Amlodipin |
| Fluvastatin | Glimepiride | Atenolol |
| Pravastatin | Insulin | Bisoprolol |
| Rosuvastatin | Metformin | Bosentan |
| Simvastatin | Pioglitazone | Candesartan |
| | Rosiglitazone | Captopril |
| | Sitagliptin | Carvedilol |
| | Vildagliptin | Celiprolol |
| | | Dilitiazem |
| | | Enalapril |
| | | Eplerenone |
| | | Felodipine |
| | | Furosemide |
| | | Hydrochlorothiazide |
| | | Irbesartan |
| | | Lercanidipine |
| | | Lisinopril |
| | | Losartan |
| | | Metolazone |
| | | Metoprolol |
| | | Midodrine |
| | | Molsidomine |
| | | Nebivolol |
| | | Nifedipine |
| | | Nitroglycerin |
| | | Olmesartan |
| | | Perindopril |
| | | Propranolol |
| | | Ramipril |
| | | Spironolactone |
| | | Telmisartan |
| | | Torasemide |
| | | Trandolapril |
| | | Valsartan |
| | | Verapamil |

The list was extracted from (1)

## S2 Table. Characteristics of psychiatric samples: discovery and replication samples

| Characteristics | Discovery sample | | Replication sample | | p-value[7] |
|---|---|---|---|---|---|
| | n | median (range) | n | median (range) | |
| Male (%) | 356 | 156 (43.8) | 140 | 58 (41.4) | 0.63 |
| Age, years | 356 | 47 (12-96) | 140 | 52 (15-97) | **0.04** |
| Medication, n(%) | 356 | | 140 | | 0.74 |
| Amisulpride | | 28 (7.9) | | 13 (9.3) | |
| Aripiprazole | | 32 (9) | | 10 (7.2) | |
| Clozapine | | 25 (7.0) | | 11 (7.9) | |
| Lithium | | 31 (8.6) | | 8 (5.7) | |
| Mirtazapine | | 15 (4.2) | | 8 (5.7) | |
| Olanzapine | | 41 (11.5) | | 12 (8.6) | |
| Quetiapine | | 115 (32.4) | | 47 (33.8) | |
| Risperidone | | 52(14.6) | | 26 (18.7) | |
| Valproate | | 17 (4.8) | | 4 (2.9) | |
| Main diagnosis, n(%) | 269 | | 90 | | 0.42 |
| Organic mental disorders | | 10 (3.7) | | 8 (8.9) | |
| Psychotic disorders | | 107 (39.8) | | 25 (27.8) | |
| Schizoaffective disorders | | 21 (7.8) | | 10 (11.1) | |
| Bipolar disorders | | 65 (24.2) | | 21 (23.3) | |
| Depressive disorder | | 66 (24.5) | | 26 (28.9) | |
| Treatment duration, months | 356 | 3 (1-12) | 140 | 3 (1-12) | 0.63 |
| **Treatment duration[1]: 0** | | | | | |
| Total cholesterol, *mmol/l* | 355 | 4.6 (2.1-8.4) | | | |
| Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2] | | 166 (46.8) | | | |
| High-density lipoprotein, *mmol/l* | 348 | 1.4 (0.6-3.3) | | | |
| Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2] | | 77 (22.1) | | | |
| Low-density lipoprotein, *mmol/l* | 338 | 2.6 (0.6-6.1) | | | |
| Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2] | | 148 (43.8) | | | |
| Triglycerides, *mmol/l* [3] | 279 | 1.1 (0.4-8.5) | | | |
| Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3] | | 51 (18.3) | | | |
| Glucose, *mmol/l* | 272 | 5.1 (3.5-10.3) | | | |
| Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4] | | 71 (26.1) | | | |
| Body mass index, $kg/m^2$ | 343 | 23.0 (13.3-42.5) | | | |
| Obesity (≥30 $kg/m^2$), n(%) | | 45 (13.1) | | | |
| Waist circumference, *cm* | 310 | 86 (54-136) | | | |
| Obesity in women (≥80 *cm)* ,n(%) [5] | | 112 (64) | | | |
| Obesity in men (≥94 *cm)* ,n(%) [5] | | 52 (38.5) | | | |

| | | | | | |
|---|---|---|---|---|---|
| Systolic blood pressure, *mm Hg*<br>Hypertension (≥140 *mm Hg)* ,n(%) [6] | 320 | 123 (70-214)<br>102 (31.9) | | | |
| Diastolic blood pressure, *mm Hg*<br>Hypertension (≥90 *mm Hg)* ,n(%) [6] | 320 | 75 (47-150)<br>90 (28.1) | | | |
| **Treatment duration[1]: 1** | | | | | |
| Total cholesterol, *mmol/l*<br>Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2] | 207 | 4.8 (2.4-8.6)<br>109 (52.7) | 86 | 5.1 (2.8-7.7)<br>54 (62.8) | 0.21<br>0.11 |
| High-density lipoprotein, *mmol/l*<br>Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2] | 206 | 1.4 (0.6-3.2)<br>55 (26.7) | 87 | 1.4 (0.7-2.8)<br>20 (23.0) | 0.19<br>0.5 |
| Low-density lipoprotein, *mmol/l*<br>Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2] | 199 | 2.8 (0.5-6.3)<br>96 (48.2) | 81 | 3.0 (0.8-5.3)<br>47 (58) | 0.25<br>0.13 |
| Triglycerides, *mmol/l* [3]<br>Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3] | 177 | 1.1 (0.3-6.5)<br>41 (23.1) | 65 | 1.2 (0.4-4.6)<br>18 (27.7) | 0.68<br>0.46 |
| Glucose, *mmol/l*<br>Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4] | 115 | 4.9 (2.9-18.7)<br>20 (17.4) | 44 | 5.0 (4.1-20.8)<br>11 (25.0) | 0.06<br>0.28 |
| Body mass index, *kg/m²*<br>Obesity (≥30 *kg/m²)*, n(%) | 200 | 23.6 (13.4-43.5)<br>27 (13.5) | 77 | 24.3 (14.7-40.6)<br>14 (18.2) | 0.57<br>0.32 |
| Waist circumference, *cm*<br>Obesity in women (≥80 *cm)* ,n(%) [5]<br>Obesity in men (≥94 *cm)* ,n(%) [5] | 187 | 88 (62-142)<br>65 (67)<br>33 (36.7) | 69 | 88 (58-126)<br>29 (70.7)<br>28 (46.4) | 0.47<br>0.67<br>0.35 |
| Systolic blood pressure, *mm Hg*<br>Hypertension (≥140 *mm Hg)* ,n(%) [6] | 38 | 119.5 (98-155)<br>8 (21) | 20 | 122 (100-170)<br>7 (35) | 0.47<br>0.25 |
| Diastolic blood pressure, *mm Hg*<br>Hypertension (≥90 *mm Hg)* ,n(%) [6] | 38 | 75.5 (54-103)<br>9 (23.7) | 20 | 75 (60-115)<br>7 (35) | 0.92<br>0.36 |
| **Treatment duration[1]: 2** | | | | | |
| Total cholesterol, *mmol/l*<br>Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2] | 233 | 4.9 (2.1-8.9)<br>134 (57.5) | 103 | 5 (2.7-8.6)<br>58 (56.3) | 0.29<br>0.84 |
| High-density lipoprotein, *mmol/l*<br>Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2] | 232 | 1.3 (0.6-2.8)<br>61 (26.3) | 103 | 1.4 (0.6-2.7)<br>24 (23.3) | 0.53<br>0.56 |
| Low-density lipoprotein, *mmol/l*<br>Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2] | 219 | 2.8 (0.6-6)<br>114 (52) | 99 | 3 (1.4-6.2)<br>55 (55.5) | 0.19<br>0.56 |
| Triglycerides, *mmol/l* [3]<br>Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3] | 178 | 1.2 (0.3-6.8)<br>45 (25.3) | 73 | 1.2 (0.4-4.1)<br>19 (26) | 0.74<br>0.9 |
| Glucose, *mmol/l* | 147 | 4.9 (3.5-7.9) | 69 | 5.1 (2.7-11.2) | 0.32 |

| | | | | | |
|---|---|---|---|---|---|
| Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4] | | 29 (19.7) | | 13 (18.8) | 0.88 |
| Body mass index, *kg/m²* | 229 | 23.7 (16.1-44.1) | 98 | 25.5 (14.3-50.2) | **0.04** |
| Obesity (≥30 *kg/m²)*, n(%) | | 36 (15.7) | | 29 (29.6) | **0.004** |
| Waist circumference, *cm* | 201 | 91 (67-147) | 95 | 95 (66-162) | **0.03** |
| Obesity in women (≥80 *cm)* ,n(%) [5] | | 77 (78.6) | | 42 (77.8) | 0.91 |
| Obesity in men (≥94 *cm)* ,n(%) [5] | | 51 (49.5) | | 26 63.4) | 0.13 |
| Systolic blood pressure, *mm Hg* | 145 | 120 (85-180) | 76 | 120 (84-162) | 0.77 |
| Hypertension (≥140 *mm Hg)* ,n(%) [6] | | 27 (18.6) | | 18 (23.7) | 0.37 |
| Diastolic blood pressure, *mm Hg* | 144 | 76 (48-120) | 76 | 77.5 (56-110) | 0.36 |
| Hypertension (≥90 *mm Hg)* ,n(%) [6] | | 34 (23.6) | | 22 (28.9) | 0.38 |
| **Treatment duration[1]: 3** | | | | | |
| Total cholesterol, *mmol/l* | 166 | 5.1 (2.3-8.7) | 73 | 5.2 (3.3-8.2) | 0.25 |
| Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2] | | 103 (62) | | 50 (68.5) | 0.34 |
| High-density lipoprotein, *mmol/l* | 161 | 1.3 (0.6-2.7) | 71 | 1.3 (0.7-4.8) | 0.29 |
| Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2] | | 47 (29.2) | | 17 (23.9) | 0.41 |
| Low-density lipoprotein, *mmol/l* | 147 | 3 (0.7-6) | 69 | 3.1 (0.6-6.4) | 0.75 |
| Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2] | | 85 (57.8) | | 39 (56.5) | 0.86 |
| Triglycerides, *mmol/l* [3] | 125 | 1.2 (0.3-6.1) | 56 | 1.2 (0.5-3.7) | 0.69 |
| Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3] | | 32 (25.6) | | 16 (28.6) | 0.67 |
| Glucose, *mmol/l* | 122 | 5.2 (3.1-7.6) | 54 | 5.2 (3.1-13.6) | 0.9 |
| Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4] | | 33 (27.1) | | 15 (27.8) | 0.92 |
| Body mass index, *kg/m²* | 160 | 24.9 (15.2-47.2) | 62 | 25.5 (15.3-41.2) | 0.77 |
| Obesity (≥30 *kg/m²)*, n(%) | | 34 (21.2) | | 15 (24.2) | 0.63 |
| Waist circumference, *cm* | 150 | 92 (64-155) | 61 | 92 (48-137) | 0.46 |
| Obesity in women (≥80 *cm)* ,n(%) [5] | | 58 (71.6) | | 21 (65.6) | 0.53 |
| Obesity in men (≥94 *cm)* ,n(%) [5] | | 39 (56.5) | | 18 (62.1) | 0.61 |
| Systolic blood pressure, *mm Hg* | 135 | 120 (91-182) | 63 | 120 (88-177) | 0.76 |
| Hypertension (≥140 *mm Hg)* ,n(%) [6] | | 32 (23.7) | | 16 (25.4) | 0.79 |
| Diastolic blood pressure, *mm Hg* | 135 | 76 (50-113) | 63 | 77 (58-106) | 0.5 |
| Hypertension (≥90 *mm Hg)* ,n(%) [6] | | 35 (25.9) | | 18 (28.6) | 0.69 |

[1] Treatment duration: period of the current psychotropic treatment. This variable was categorized into four categories according to the number of days of psychotropic treatment as follow: 0: 0 days i.e baseline before the prescription of the studied drug; 1: from ≥10 to <45 days; 2: from ≥45 to <135 days; 3: from ≥135 to <535 days.

[2] Lipid levels thresholds were defined according to ESH/ESC guidelines(2). Patients with treated dyslipidemia (S2 Table) were also included in the abnormal lipid levels category.

[3] Triglyceride levels were collected in fasting conditions.

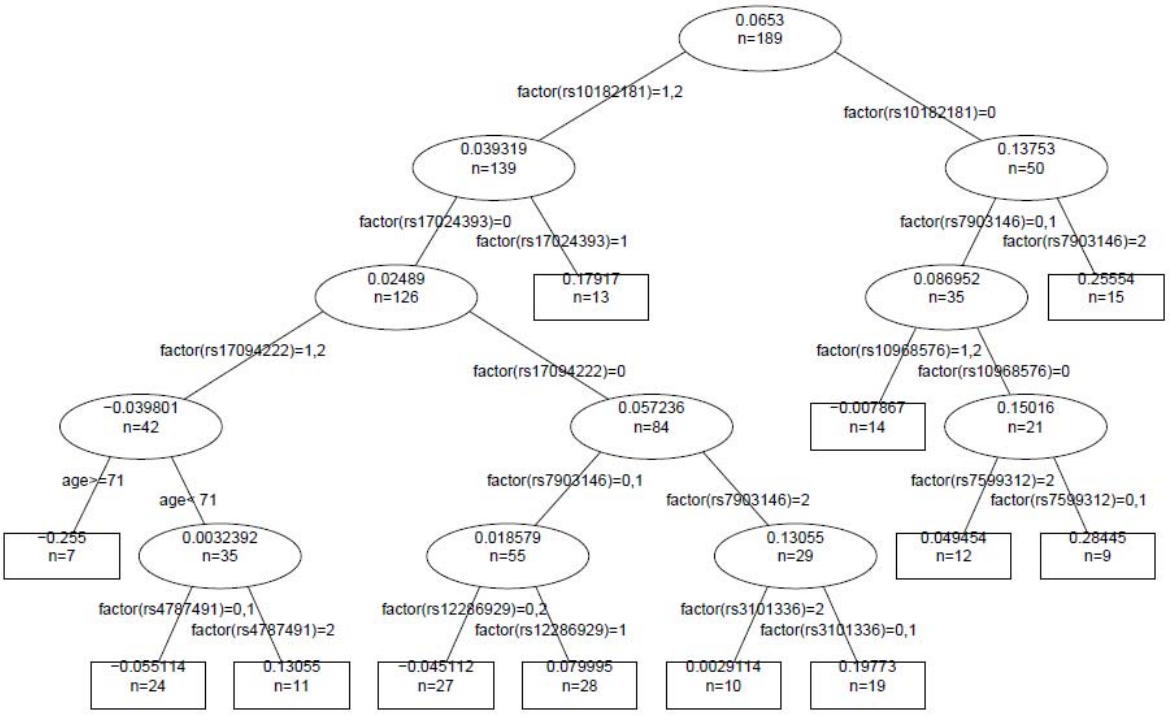
[4] Threshold for fasting glucose levels (≥5.6 mmol/l) was defined according to IDF definition(3). Patients with treated diabetes (S2 Table) were also included in the abnormal glucose levels category.

[5] Waist circumference thresholds (≥80 cm for women and ≥94 cm for men) were defined according to IDF definition(3).
[6] Hypertension thresholds (≥140 mm Hg for systolic blood pressure and ≥ 90 mm Hg for diastolic blood pressure) were defined according to ESH/ESC guidelines(2). Patients with treated hypertension (S2 Table) were also included in the abnormal hypertension category.
[7] P values were calculated using Wilcoxon-Mann-Whitney tests or Chi2 tests between the two psychiatric samples. Values in bold are significant.
Abbreviations: IDF: International Diabetes Federation.ESH/ESC: European Society of Hypertension/European Society of Cardiology.

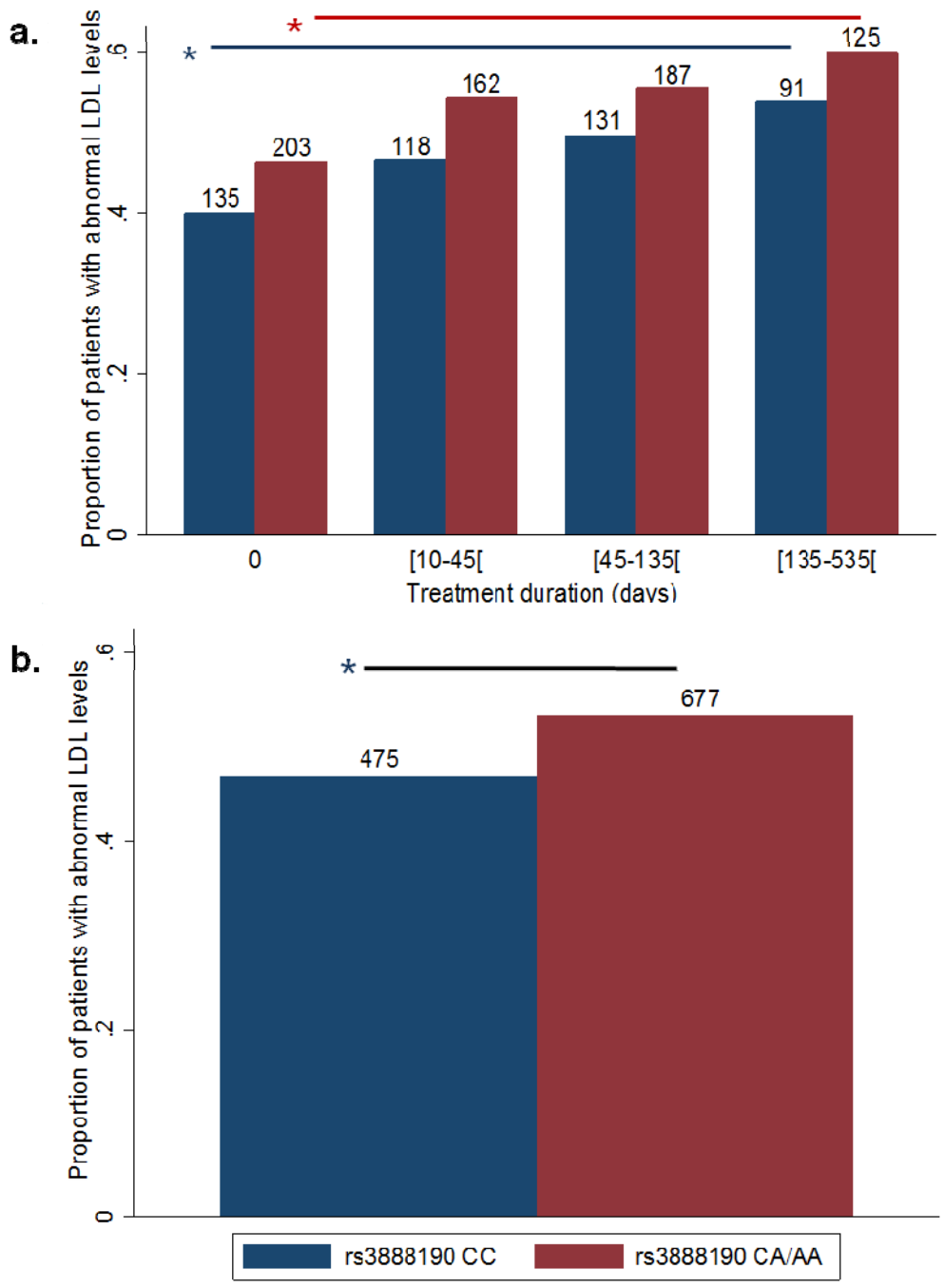
## S3 Table. Genotype frequencies in two Caucasian psychiatric samples.

| Psychiatric sample | Total (n) | n (%) | | | HWE | MAF | MAF Hap Map CEU |
|---|---|---|---|---|---|---|---|
| ***SH2B1* rs3888190 C>A** | | **CC** | **CA** | **AA** | | | **0.36** |
| Discovery sample | 356 | 143 (40.3) | 171 (47.9) | 42 (11.7) | 0.39 | 0.36 | |
| Replication sample | 140 | 66 (47.14) | 57 (40.71) | 17 (12.14) | 0.39 | 0.32 | |
| ***RABEP1* rs1000940A>G** | | **AA** | **AG** | **GG** | | | **0.35** |
| Discovery sample | 356 | 185 (51.9) | 141 (39.6) | 30 (8.4) | 0.67 | 0.28 | |
| Replication sample | 140 | 67 (48.2) | 59 (42.4) | 13 (9.3) | 0.93 | 0.30 | |

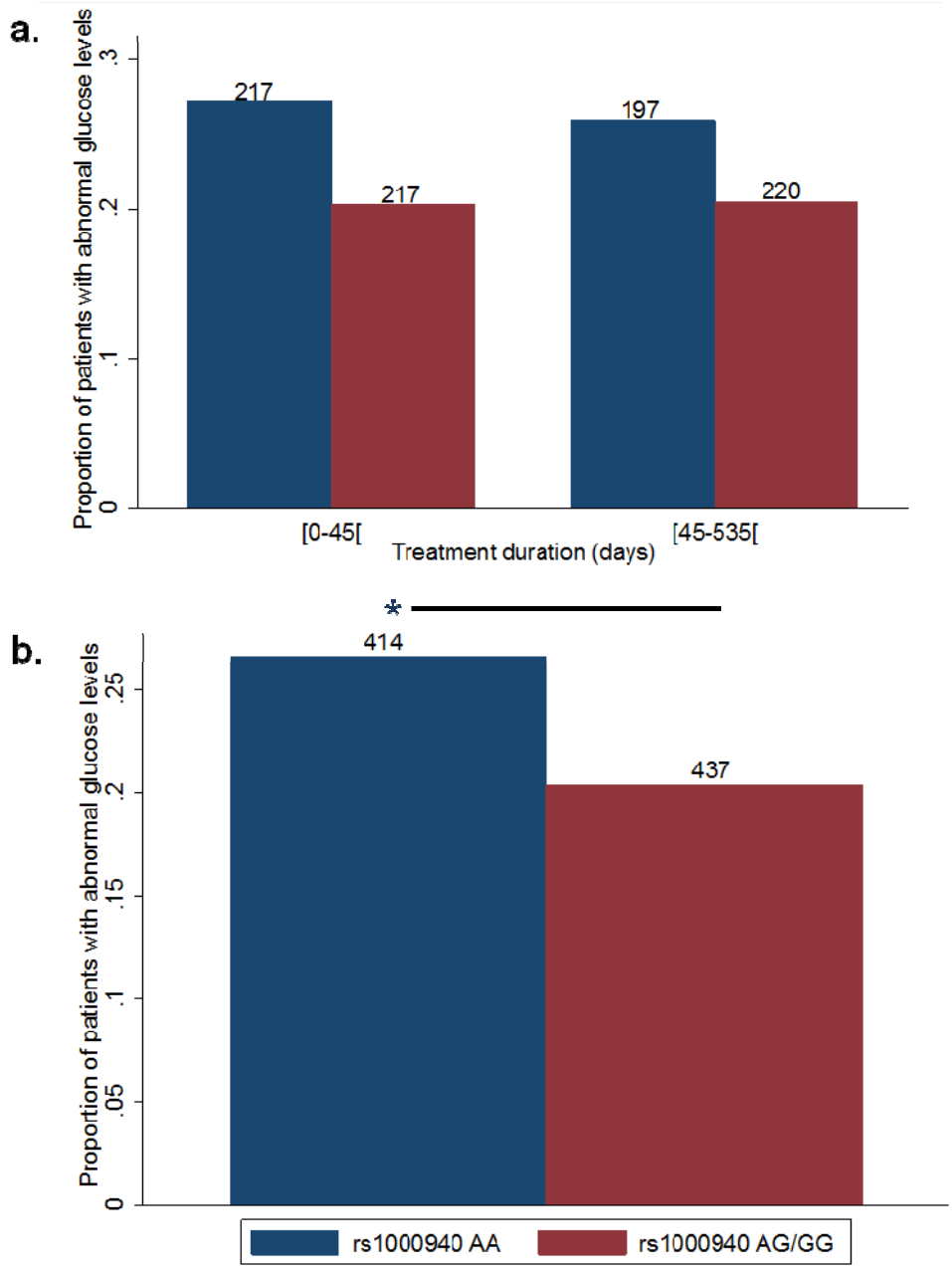
Deviation from Hardy Weinberg Equilibrium (HWE) and minor allele frequencies (MAF) observed in our samples and referred in HapMap are indicated.




**S1 Fig. Tree structure of the classification and regression tree (CART) analysis for the evolution of TC levels within the first category of psychotropic treatment duration (i.e from 10 to 45 days of treatment). Each node indicates the mean of TC difference (within the current psychotropic treatment duration) and the number of observations.**




**S2 Fig. a. Evolution of the proportion of patients with abnormal LDL values (≥3mmol/l or prescription of a lipid-lowering medication) during psychotropic treatment according to rs3888190C>A genotype. b. Overall proportion of patients with abnormal LDL values (≥3mmol/l or prescription of a lipid-lowering medication) according to rs3888190C>A genotype. Numbers of observations are indicated above each category. *:p-value of $Chi^2$ test≤0.05.**




**S3 Fig. a. Evolution of the proportion of patients with abnormal fasting glucose values (≥5.6mmol/l or prescription of an antidiabetic medication) during psychotropic treatment according to rs1000940A>G genotype. The first two periods, as well as the last two periods of psychotropic treatment were pooled together for statistical power purposes. b. Overall proportion of patients with abnormal fasting glucose values (≥5.6mmol/l or prescription of an antidiabetic medication) according to rs1000940A>G genotype.**
**Numbers of observations are indicated above each category. *:p-value of $Chi^2$ test≤0.05.**

| TISSUE | CDC37P1 | | | EIF3C | | | EIF3CL | | | SH2B1 | | | SULT1A2 | | | TUFM | | | IL27 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β |
| Adipose - Subcutaneous | rs3888190 | 2.00E-23 | 0.78 | rs3888190 | 0.0000023 | 0.32 | rs3888190 | 7.80E-10 | 0.39 | rs3888190 | 7.70E-11 | -0.2 | rs3888190 | 1.10E-16 | 0.53 | rs3888190 | 2.00E-10 | 0.31 | | | |
| | rs62037371 | 1.90E-24 | 0.8 | rs62037371 | 0.0000015 | 0.32 | rs62037371 | 3.20E-10 | 0.4 | rs62037371 | 4.20E-11 | -0.2 | rs62037371 | 3.10E-17 | 0.54 | rs62037371 | 3.70E-10 | 0.31 | | | |
| | rs8055138 | 1.60E-24 | 0.8 | rs8055138 | 0.0000015 | 0.32 | rs8055138 | 3.00E-10 | 0.4 | rs8055138 | 4.30E-11 | -0.2 | rs8055138 | 2.90E-17 | 0.54 | rs8055138 | 4.00E-10 | 0.31 | | | |
| | rs7498555 | 6.70E-21 | 0.77 | rs7498555 | 1.60E-07 | 0.36 | rs7498555 | 1.30E-11 | 0.44 | rs7498555 | 1.40E-09 | -0.19 | rs7498555 | 1.20E-17 | 0.57 | rs7498555 | 1.00E-10 | 0.33 | | | |
| | rs8061590 | 1.50E-24 | 0.81 | rs8061590 | 7.80E-07 | 0.33 | rs8061590 | 5.20E-11 | 0.42 | rs8061590 | 1.20E-10 | -0.2 | rs8061590 | 1.70E-16 | 0.54 | rs8061590 | 1.40E-09 | 0.3 | | | |
| | rs62037369 | 1.10E-20 | 0.76 | rs62037369 | 1.50E-07 | 0.36 | rs62037369 | 1.90E-11 | 0.44 | rs62037369 | 1.10E-09 | -0.19 | rs62037369 | 1.70E-17 | 0.56 | rs62037369 | 5.50E-11 | 0.33 | | | |
| | rs7498665 | 1.90E-24 | 0.8 | rs7498665 | 0.0000015 | 0.32 | rs7498665 | 3.20E-10 | 0.4 | rs7498665 | 4.20E-11 | -0.2 | rs7498665 | 3.10E-17 | 0.54 | rs7498665 | 3.70E-10 | 0.31 | | | |
| | rs8055982 | 1.90E-24 | 0.8 | rs8055982 | 0.0000015 | 0.32 | rs8055982 | 3.20E-10 | 0.4 | rs8055982 | 4.20E-11 | -0.2 | rs8055982 | 3.10E-17 | 0.54 | rs8055982 | 3.70E-10 | 0.31 | | | |
| | rs7198606 | 1.90E-24 | 0.8 | rs7198606 | 0.0000015 | 0.32 | rs7198606 | 3.20E-10 | 0.4 | rs7198606 | 4.20E-11 | -0.2 | rs7198606 | 3.10E-17 | 0.54 | rs7198606 | 3.70E-10 | 0.31 | | | |
| | rs62037367 | 1.90E-24 | 0.8 | rs62037367 | 0.0000015 | 0.32 | rs62037367 | 3.20E-10 | 0.4 | rs62037367 | 4.20E-11 | -0.2 | rs62037367 | 3.10E-17 | 0.54 | rs62037367 | 3.70E-10 | 0.31 | | | |
| | rs4788102 | 1.10E-23 | 0.79 | rs4788102 | 0.0000012 | 0.33 | rs4788102 | 2.00E-10 | 0.41 | rs4788102 | 6.70E-11 | -0.2 | rs4788102 | 1.50E-17 | 0.55 | rs4788102 | 4.00E-10 | 0.31 | | | |
| | rs11861174 | 1.90E-24 | 0.8 | rs11861174 | 0.0000015 | 0.32 | rs11861174 | 3.20E-10 | 0.4 | rs11861174 | 4.20E-11 | -0.2 | rs11861174 | 3.10E-17 | 0.54 | rs11861174 | 3.70E-10 | 0.31 | | | |
| | rs12446589 | 1.50E-21 | 0.77 | rs12446589 | 1.10E-07 | 0.36 | rs12446589 | 2.80E-11 | 0.43 | rs12446589 | 1.90E-09 | -0.19 | rs12446589 | 1.50E-17 | 0.56 | rs12446589 | 1.40E-10 | 0.32 | | | |
| | rs62037365 | 1.90E-24 | 0.8 | rs62037365 | 0.0000015 | 0.32 | rs62037365 | 3.20E-10 | 0.4 | rs62037365 | 4.20E-11 | -0.2 | rs62037365 | 3.10E-17 | 0.54 | rs62037365 | 3.70E-10 | 0.31 | | | |
| | rs62037364 | 8.90E-24 | 0.79 | rs62037364 | 0.0000013 | 0.33 | rs62037364 | 4.50E-10 | 0.4 | rs62037364 | 1.80E-10 | -0.19 | rs62037364 | 5.40E-17 | 0.54 | rs62037364 | 5.00E-10 | 0.31 | | | |
| | rs4788101 | 1.90E-24 | 0.8 | rs4788101 | 0.0000015 | 0.32 | rs4788101 | 3.20E-10 | 0.4 | rs4788101 | 4.20E-11 | -0.2 | rs4788101 | 3.10E-17 | 0.54 | rs4788101 | 3.70E-10 | 0.31 | | | |
| | rs7205323 | 1.30E-24 | 0.8 | rs7205323 | 0.0000012 | 0.33 | rs7205323 | 2.30E-10 | 0.4 | rs7205323 | 3.30E-11 | -0.2 | rs7205323 | 8.60E-17 | 0.54 | rs7205323 | 7.10E-10 | 0.3 | | | |
| | rs80275162 | 1.50E-24 | 0.81 | rs80275162 | 0.0000071 | 0.31 | rs80275162 | 3.00E-09 | 0.39 | rs80275162 | 6.10E-11 | -0.2 | rs80275162 | 2.50E-16 | 0.54 | rs80275162 | 4.00E-10 | 0.31 | | | |
| | rs9972693 | 1.90E-24 | 0.8 | rs9972693 | 0.0000015 | 0.32 | rs9972693 | 3.20E-10 | 0.4 | rs9972693 | 4.20E-11 | -0.2 | rs9972693 | 3.10E-17 | 0.54 | rs9972693 | 3.70E-10 | 0.31 | | | |
| | rs7187776 | 1.60E-17 | 0.66 | rs4788099 | 0.0000015 | 0.32 | rs7187776 | 2.40E-08 | 0.34 | rs7187776 | 2.10E-08 | -0.17 | rs7187776 | 6.80E-15 | 0.49 | rs7187776 | 9.40E-16 | 0.37 | | | |
| | rs4788099 | 1.90E-24 | 0.8 | rs61737565 | 0.0000015 | 0.32 | rs4788099 | 3.20E-10 | 0.4 | rs4788099 | 4.20E-11 | -0.2 | rs4788099 | 3.10E-17 | 0.54 | rs4788099 | 3.70E-10 | 0.31 | | | |
| | rs61737565 | 1.90E-24 | 0.8 | rs28403629 | 0.0000015 | 0.32 | rs61737565 | 3.20E-10 | 0.4 | rs61737565 | 4.20E-11 | -0.2 | rs61737565 | 3.10E-17 | 0.54 | rs61737565 | 3.70E-10 | 0.31 | | | |
| | rs28403629 | 1.90E-24 | 0.8 | rs3088215 | 0.0000015 | 0.32 | rs28403629 | 3.20E-10 | 0.4 | rs28403629 | 4.20E-11 | -0.2 | rs28403629 | 3.10E-17 | 0.54 | rs28403629 | 3.70E-10 | 0.31 | | | |
| | rs3088215 | 1.90E-24 | 0.8 | rs12325113 | 1.50E-07 | 0.36 | rs3088215 | 3.20E-10 | 0.4 | rs3088215 | 4.20E-11 | -0.2 | rs3088215 | 3.10E-17 | 0.54 | rs3088215 | 3.70E-10 | 0.31 | | | |
| | rs12325113 | 1.10E-20 | 0.76 | rs55830740 | 0.0000015 | 0.32 | rs12325113 | 1.90E-11 | 0.44 | rs12325113 | 1.10E-09 | -0.19 | rs12325113 | 1.70E-17 | 0.56 | rs12325113 | 5.50E-11 | 0.33 | | | |
| | rs55830740 | 1.90E-24 | 0.8 | rs55719896 | 0.0000015 | 0.32 | rs55830740 | 3.20E-10 | 0.4 | rs55830740 | 4.20E-11 | -0.2 | rs55830740 | 3.10E-17 | 0.54 | rs55830740 | 3.70E-10 | 0.31 | | | |
| | rs55719896 | 1.90E-24 | 0.8 | rs56404918 | 0.0000015 | 0.32 | rs55719896 | 3.20E-10 | 0.4 | rs55719896 | 4.20E-11 | -0.2 | rs55719896 | 3.10E-17 | 0.54 | rs55719896 | 3.70E-10 | 0.31 | | | |
| | rs56404918 | 1.90E-24 | 0.8 | rs12444171 | 0.0000015 | 0.32 | rs56404918 | 3.20E-10 | 0.4 | rs56404918 | 4.20E-11 | -0.2 | rs56404918 | 3.10E-17 | 0.54 | rs56404918 | 3.70E-10 | 0.31 | | | |
| | rs12444171 | 1.90E-24 | 0.8 | rs62036657 | 0.0000015 | 0.32 | rs12444171 | 3.20E-10 | 0.4 | rs12444171 | 4.20E-11 | -0.2 | rs12444171 | 3.10E-17 | 0.54 | rs12444171 | 3.70E-10 | 0.31 | | | |
| | rs62036657 | 1.90E-24 | 0.8 | rs62036626 | 0.0000015 | 0.32 | rs62036657 | 3.20E-10 | 0.4 | rs62036657 | 4.20E-11 | -0.2 | rs62036657 | 3.10E-17 | 0.54 | rs62036657 | 3.70E-10 | 0.31 | | | |
| | rs62036626 | 1.90E-24 | 0.8 | rs56358680 | 0.0000015 | 0.32 | rs62036626 | 3.20E-10 | 0.4 | rs62036626 | 4.20E-11 | -0.2 | rs62036626 | 3.10E-17 | 0.54 | rs62036626 | 3.70E-10 | 0.31 | | | |
| | rs56358680 | 1.90E-24 | 0.8 | rs55991577 | 0.0000015 | 0.32 | rs56358680 | 3.20E-10 | 0.4 | rs56358680 | 4.20E-11 | -0.2 | rs56358680 | 3.10E-17 | 0.54 | rs56358680 | 3.70E-10 | 0.31 | | | |
| | rs55991577 | 1.90E-24 | 0.8 | rs12443881 | 1.60E-07 | 0.36 | rs55991577 | 3.20E-10 | 0.4 | rs55991577 | 4.20E-11 | -0.2 | rs55991577 | 3.10E-17 | 0.54 | rs55991577 | 3.70E-10 | 0.31 | | | |
| | rs12443881 | 5.00E-21 | 0.77 | rs72793812 | 1.40E-07 | 0.36 | rs12443881 | 2.30E-11 | 0.44 | rs12443881 | 9.00E-10 | -0.19 | rs12443881 | 2.30E-17 | 0.56 | rs12443881 | 5.10E-11 | 0.33 | | | |
| | rs72793812 | 7.30E-21 | 0.77 | rs62036624 | 0.0000014 | 0.33 | rs72793812 | 1.80E-11 | 0.44 | rs72793812 | 1.20E-09 | -0.19 | rs72793812 | 2.00E-17 | 0.56 | rs72793812 | 5.90E-11 | 0.33 | | | |
| | rs62036624 | 2.70E-24 | 0.8 | rs72793811 | 1.50E-07 | 0.36 | rs62036624 | 2.80E-10 | 0.4 | rs62036624 | 4.60E-11 | -0.2 | rs62036624 | 2.40E-17 | 0.55 | rs62036624 | 3.70E-10 | 0.31 | | | |
| | rs72793811 | 1.10E-20 | 0.76 | rs8062405 | 0.0000012 | 0.33 | rs72793811 | 1.90E-11 | 0.44 | rs72793811 | 1.10E-09 | -0.19 | rs72793811 | 1.70E-17 | 0.56 | rs72793811 | 5.50E-11 | 0.33 | | | |
| | rs0062405 | 6.00E-24 | 0.79 | rs62036622 | 7.50E-08 | 0.37 | rs0062405 | 2.20E-10 | 0.4 | rs0062405 | 6.50E-11 | -0.2 | rs0062405 | 2.00E-17 | 0.54 | rs0062405 | 1.10E-10 | 0.32 | | | |
| | rs62036622 | 1.40E-21 | 0.78 | rs4451951 | 0.0000012 | 0.32 | rs62036622 | 6.70E-12 | 0.45 | rs62036622 | 9.80E-10 | -0.19 | rs62036622 | 1.00E-17 | 0.57 | rs62036622 | 1.30E-10 | 0.33 | | | |
| | rs4451951 | 3.70E-26 | 0.8 | rs62036621 | 8.20E-07 | 0.33 | rs4451951 | 1.40E-10 | 0.4 | rs4451951 | 4.50E-12 | -0.2 | rs4451951 | 6.70E-17 | 0.52 | rs4451951 | 6.30E-10 | 0.3 | | | |
| | rs62036621 | 1.80E-25 | 0.81 | rs62036620 | 8.20E-07 | 0.33 | rs62036621 | 1.30E-10 | 0.41 | rs62036621 | 3.60E-11 | -0.2 | rs62036621 | 1.90E-17 | 0.55 | rs62036621 | 8.20E-10 | 0.3 | | | |
| | rs62036620 | 1.80E-25 | 0.81 | rs4788095 | 8.20E-07 | 0.33 | rs62036620 | 1.30E-10 | 0.41 | rs62036620 | 3.60E-11 | -0.2 | rs62036620 | 1.90E-17 | 0.55 | rs62036620 | 8.20E-10 | 0.3 | | | |
| | rs4788095 | 1.80E-25 | 0.81 | rs62036617 | 8.20E-07 | 0.33 | rs4788095 | 1.30E-10 | 0.41 | rs4788095 | 3.60E-11 | -0.2 | rs4788095 | 1.90E-17 | 0.55 | rs4788095 | 8.20E-10 | 0.3 | | | |
| | rs62036617 | 1.90E-25 | 0.81 | rs62036616 | 3.30E-08 | 0.38 | rs62036617 | 1.30E-10 | 0.41 | rs62036617 | 3.60E-11 | -0.2 | rs62036617 | 1.90E-17 | 0.55 | rs62036617 | 7.80E-10 | 0.3 | | | |
| | rs62036616 | 3.10E-22 | 0.79 | rs1987472 | 8.20E-07 | 0.33 | rs62036616 | 2.10E-12 | 0.46 | rs62036616 | 8.90E-10 | -0.19 | rs62036616 | 5.10E-17 | 0.56 | rs62036616 | 1.30E-10 | 0.33 | | | |
| | rs1987472 | 1.90E-25 | 0.81 | rs2008514 | 8.20E-07 | 0.33 | rs1987472 | 1.30E-10 | 0.41 | rs1987472 | 3.60E-11 | -0.2 | rs1987472 | 1.90E-17 | 0.55 | rs1987472 | 8.20E-10 | 0.3 | | | |
| | rs2008514 | 1.80E-25 | 0.81 | rs7359397 | 1.50E-07 | 0.36 | rs2008514 | 1.30E-10 | 0.41 | rs2008514 | 3.60E-11 | -0.2 | rs2008514 | 2.00E-17 | 0.55 | rs2008514 | 8.20E-10 | 0.3 | | | |
| | rs7359397 | 1.10E-20 | 0.76 | rs62037363 | 0.0000012 | 0.33 | rs7359397 | 1.90E-11 | 0.44 | rs7359397 | 1.10E-09 | -0.19 | rs7359397 | 1.70E-17 | 0.56 | rs7359397 | 5.50E-11 | 0.33 | | | |
| | rs62037363 | 7.70E-25 | 0.8 | rs56040780 | 0.0000015 | 0.32 | rs62037363 | 2.20E-10 | 0.4 | rs62037363 | 3.50E-11 | -0.2 | rs62037363 | 1.10E-16 | 0.53 | rs62037363 | 7.40E-10 | 0.3 | | | |
| | rs56040780 | 1.90E-24 | 0.8 | rs11864107 | 0.0000018 | 0.32 | rs56040780 | 3.20E-10 | 0.4 | rs56040780 | 4.20E-11 | -0.2 | rs56040780 | 3.10E-17 | 0.54 | rs56040780 | 3.60E-10 | 0.31 | | | |
| | rs8049439 | 2.40E-18 | 0.67 | rs7193733 | 0.0000015 | 0.32 | rs8049439 | 9.60E-09 | 0.35 | rs8049439 | 1.80E-08 | -0.17 | rs8049439 | 1.30E-15 | 0.5 | rs8049439 | 2.10E-15 | 0.37 | | | |
| | rs11864107 | 4.80E-24 | 0.79 | rs12448902 | 3.30E-07 | 0.35 | rs11864107 | 5.60E-10 | 0.39 | rs11864107 | 1.40E-10 | -0.19 | rs11864107 | 1.60E-16 | 0.53 | rs11864107 | 4.30E-10 | 0.31 | | | |
| | rs7193733 | 4.40E-25 | 0.81 | rs7187333 | 1.60E-07 | 0.36 | rs7193733 | 2.70E-10 | 0.4 | rs7193733 | 6.10E-11 | -0.2 | rs7193733 | 5.10E-18 | 0.55 | rs7193733 | 8.40E-10 | 0.3 | | | |
| | rs12448902 | 1.40E-20 | 0.76 | rs9972768 | 0.0000015 | 0.32 | rs12448902 | 1.10E-10 | 0.42 | rs12448902 | 1.90E-09 | -0.19 | rs12448902 | 1.10E-16 | 0.55 | rs12448902 | 2.00E-11 | 0.34 | | | |
| | rs7187333 | 1.70E-21 | 0.77 | rs78613234 | 0.0000014 | 0.33 | rs7187333 | 2.40E-11 | 0.43 | rs7187333 | 6.00E-10 | -0.19 | rs7187333 | 1.20E-16 | 0.55 | rs7187333 | 1.10E-10 | 0.33 | | | |
| | rs9972768 | 1.90E-24 | 0.8 | rs72793809 | 8.20E-07 | 0.33 | rs9972768 | 3.20E-10 | 0.4 | rs9972768 | 4.20E-11 | -0.2 | rs9972768 | 3.10E-17 | 0.54 | rs9972768 | 3.70E-10 | 0.31 | | | |
| | rs78613234 | 2.50E-24 | 0.8 | rs11860513 | 6.90E-07 | 0.33 | rs78613234 | 2.90E-10 | 0.4 | rs78613234 | 4.50E-11 | -0.2 | rs78613234 | 2.60E-17 | 0.54 | rs78613234 | 3.70E-10 | 0.31 | | | |
| | rs72793809 | 1.80E-25 | 0.81 | rs62036614 | 2.20E-08 | 0.39 | rs72793809 | 1.30E-10 | 0.41 | rs72793809 | 3.60E-11 | -0.2 | rs72793809 | 1.90E-17 | 0.55 | rs72793809 | 8.20E-10 | 0.3 | | | |
| | rs11860513 | 4.60E-25 | 0.81 | rs12928404 | 0.000014 | 0.27 | rs11860513 | 1.20E-10 | 0.41 | rs11860513 | 3.70E-11 | -0.2 | rs11860513 | 1.30E-17 | 0.55 | rs11860513 | 5.30E-10 | 0.31 | | | |
| | rs62036614 | 5.50E-22 | 0.79 | rs11864750 | 0.000002 | 0.32 | rs62036614 | 3.90E-12 | 0.46 | rs62036614 | 1.70E-09 | -0.19 | rs62036614 | 2.50E-17 | 0.56 | rs62036614 | 2.30E-10 | 0.33 | | | |
| | rs12928404 | 4.70E-16 | 0.61 | rs11150609 | 0.0000015 | 0.32 | rs12928404 | 7.10E-09 | 0.35 | rs12928404 | 1.40E-07 | -0.15 | rs12928404 | 4.90E-15 | 0.47 | rs12928404 | 9.30E-15 | 0.35 | | | |
| | rs11864750 | 7.00E-24 | 0.79 | rs62036658 | 3.60E-07 | 0.35 | rs11864750 | 3.30E-10 | 0.4 | rs11864750 | 8.50E-11 | -0.2 | rs11864750 | 9.40E-17 | 0.54 | rs11864750 | 1.20E-09 | 0.3 | | | |
| | rs11150609 | 1.90E-24 | 0.8 | rs56186137 | 8.20E-07 | 0.33 | rs11150609 | 3.20E-10 | 0.4 | rs11150609 | 4.20E-11 | -0.2 | rs11150609 | 3.10E-17 | 0.54 | rs11150609 | 3.70E-10 | 0.31 | | | |
| | rs62036658 | 4.00E-19 | 0.74 | | | | rs62036658 | 3.60E-11 | 0.44 | rs62036658 | 2.60E-09 | -0.19 | rs62036658 | 3.50E-17 | 0.56 | rs62036658 | 6.80E-10 | 0.32 | | | |
| | rs56186137 | 1.90E-25 | 0.81 | | | | rs56186137 | 1.30E-10 | 0.41 | rs56186137 | 3.60E-11 | -0.2 | rs56186137 | 1.90E-17 | 0.55 | rs56186137 | 8.10E-10 | 0.3 | | | |
| | rs7191618 | 3.80E-19 | 0.71 | | | | rs7191618 | 0.0000024 | 0.3 | rs7191618 | 1.40E-08 | -0.17 | rs7191618 | 1.20E-24 | 0.63 | rs7191618 | 4.60E-08 | 0.27 | | | |
| | rs4788083 | 2.40E-19 | 0.72 | | | | rs4788083 | 0.0000022 | 0.31 | rs4788083 | 2.70E-09 | -0.18 | rs4788083 | 1.80E-24 | 0.63 | rs4788083 | 3.00E-08 | 0.28 | | | |
| | rs4788084 | 5.90E-21 | 0.75 | | | | rs4788084 | 6.30E-07 | 0.33 | rs4788084 | 2.30E-09 | -0.18 | rs4788084 | 3.00E-23 | 0.63 | rs4788084 | 3.10E-09 | 0.3 | | | |
| | rs62034326 | 7.60E-21 | 0.75 | | | | rs62034326 | 7.20E-07 | 0.32 | rs62034326 | 2.60E-09 | -0.18 | rs62034326 | 3.50E-23 | 0.63 | rs62034326 | 3.30E-09 | 0.3 | | | |
| | rs62034324 | 6.40E-20 | 0.75 | | | | rs62034324 | 3.50E-07 | 0.34 | rs62034324 | 3.10E-09 | -0.19 | rs62034324 | 1.00E-22 | 0.63 | rs62034324 | 9.00E-09 | 0.29 | | | |
| | rs28772958 | 1.00E-19 | 0.73 | | | | rs28772958 | 7.60E-07 | 0.32 | rs28772958 | 4.40E-09 | -0.18 | rs28772958 | 5.00E-23 | 0.62 | rs28772958 | 5.50E-08 | 0.27 | | | |
| | rs4788085 | 1.00E-19 | 0.72 | | | | rs4788085 | 7.40E-07 | 0.32 | rs4788085 | 4.80E-09 | -0.18 | rs4788085 | 4.90E-23 | 0.62 | rs4788085 | 6.10E-08 | 0.27 | | | |
| | rs28698667 | 7.50E-21 | 0.75 | | | | rs28698667 | 7.00E-07 | 0.32 | rs28698667 | 2.50E-09 | -0.18 | rs28698667 | 3.20E-23 | 0.63 | rs28698667 | 3.30E-09 | 0.3 | | | |
| | rs62034319 | 1.60E-21 | 0.75 | | | | rs62034319 | 6.50E-07 | 0.32 | rs62034319 | 8.10E-09 | -0.18 | rs62034319 | 4.10E-24 | 0.63 | rs62034319 | 2.90E-08 | 0.28 | | | |
| | rs240702 | 2.50E-21 | 0.75 | | | | rs240702 | 6.80E-07 | 0.32 | rs240702 | 9.40E-09 | -0.17 | rs240702 | 1.30E-24 | 0.63 | rs240702 | 5.00E-08 | 0.27 | | | |
| | rs153106 | 5.00E-21 | 0.75 | | | | rs153106 | 7.20E-07 | 0.32 | rs153106 | 1.00E-08 | -0.18 | rs153106 | 2.00E-25 | 0.65 | rs153106 | 3.60E-08 | 0.27 | | | |
| | rs7202948 | 4.50E-20 | 0.72 | | | | rs7202948 | 0.000001 | 0.31 | rs7202948 | 1.70E-08 | -0.17 | rs7202948 | 9.40E-25 | 0.63 | rs7202948 | 1.90E-08 | 0.28 | | | |

| TISSUE | *CDC37P1* | | | *EIF3C* | | | *EIF3CL* | | | *SH2B1* | | | *SULT1A2* | | | *TUFM* | | | *IL27* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β |
| Adipose - Visceral (Omentum) | rs3888190 | 1.10E-11 | 0.67 | | | | | | | rs3888190 | 0.0000012 | -0.15 | rs3888190 | 8.50E-11 | 0.51 | rs12928404 | 0.0000052 | 0.21 | | | |
| | rs62037371 | 1.10E-11 | 0.67 | | | | | | | rs62037371 | 0.0000012 | -0.15 | rs62037371 | 8.50E-11 | 0.51 | | | | | | |
| | rs8055138 | 1.10E-11 | 0.67 | | | | | | | rs8055138 | 0.0000014 | -0.15 | rs8055138 | 9.90E-11 | 0.51 | | | | | | |
| | rs7498555 | 6.30E-07 | 0.54 | | | | | | | rs8061590 | 0.0000041 | -0.14 | rs7498555 | 1.70E-10 | 0.53 | | | | | | |
| | rs8061590 | 4.30E-11 | 0.66 | | | | | | | rs7498665 | 0.0000012 | -0.15 | rs8061590 | 3.60E-10 | 0.5 | | | | | | |
| | rs62037369 | 6.60E-07 | 0.53 | | | | | | | rs8055982 | 0.0000012 | -0.15 | rs62037369 | 6.70E-11 | 0.54 | | | | | | |
| | rs7498665 | 1.10E-11 | 0.67 | | | | | | | rs7198606 | 0.0000012 | -0.15 | rs7498665 | 8.50E-11 | 0.51 | | | | | | |
| | rs8055982 | 1.10E-11 | 0.67 | | | | | | | rs62037367 | 0.0000012 | -0.15 | rs8055982 | 8.50E-11 | 0.51 | | | | | | |
| | rs7198606 | 1.10E-11 | 0.67 | | | | | | | rs4788102 | 0.0000015 | -0.14 | rs7198606 | 8.50E-11 | 0.51 | | | | | | |
| | rs62037367 | 1.10E-11 | 0.67 | | | | | | | rs11861174 | 0.0000012 | -0.15 | rs62037367 | 8.50E-11 | 0.51 | | | | | | |
| | rs4788102 | 8.10E-11 | 0.65 | | | | | | | rs62037365 | 0.0000012 | -0.15 | rs4788102 | 1.00E-10 | 0.51 | | | | | | |
| | rs11861174 | 1.10E-11 | 0.67 | | | | | | | rs62037364 | 0.0000019 | -0.14 | rs11861174 | 8.50E-11 | 0.51 | | | | | | |
| | rs12446589 | 1.10E-07 | 0.57 | | | | | | | rs4788101 | 0.0000012 | -0.15 | rs12446589 | 5.40E-11 | 0.54 | | | | | | |
| | rs62037365 | 1.10E-11 | 0.67 | | | | | | | rs7205323 | 0.0000012 | -0.15 | rs62037365 | 8.50E-11 | 0.51 | | | | | | |
| | rs62037364 | 1.60E-11 | 0.67 | | | | | | | rs80275162 | 0.0000012 | -0.15 | rs62037364 | 1.10E-10 | 0.51 | | | | | | |
| | rs4788101 | 1.10E-11 | 0.67 | | | | | | | rs9972693 | 0.0000012 | -0.15 | rs4788101 | 8.50E-11 | 0.51 | | | | | | |
| | rs7205323 | 1.20E-11 | 0.67 | | | | | | | rs7187776 | 0.0000012 | -0.15 | rs7205323 | 8.40E-11 | 0.51 | | | | | | |
| | rs80275162 | 5.90E-10 | 0.63 | | | | | | | rs4788099 | 0.0000012 | -0.15 | rs80275162 | 2.00E-11 | 0.53 | | | | | | |
| | rs9972693 | 1.10E-11 | 0.67 | | | | | | | rs61737565 | 0.0000012 | -0.15 | rs9972693 | 8.50E-11 | 0.51 | | | | | | |
| | rs7187776 | 2.30E-09 | 0.6 | | | | | | | rs28403629 | 0.0000012 | -0.15 | rs7187776 | 8.00E-11 | 0.51 | | | | | | |
| | rs4788099 | 1.10E-11 | 0.67 | | | | | | | rs3088215 | 0.0000012 | -0.15 | rs4788099 | 8.50E-11 | 0.51 | | | | | | |
| | rs61737565 | 1.10E-11 | 0.67 | | | | | | | rs55830740 | 0.0000012 | -0.15 | rs61737565 | 8.50E-11 | 0.51 | | | | | | |
| | rs28403629 | 1.10E-11 | 0.67 | | | | | | | rs55719896 | 0.0000012 | -0.15 | rs28403629 | 8.50E-11 | 0.51 | | | | | | |
| | rs3088215 | 1.10E-11 | 0.67 | | | | | | | rs56404918 | 0.0000012 | -0.15 | rs3088215 | 8.50E-11 | 0.51 | | | | | | |
| | rs12325113 | 6.60E-07 | 0.53 | | | | | | | rs12444171 | 0.0000012 | -0.15 | rs12325113 | 7.00E-11 | 0.54 | | | | | | |
| | rs55830740 | 1.10E-11 | 0.67 | | | | | | | rs62036657 | 0.0000012 | -0.15 | rs55830740 | 8.50E-11 | 0.51 | | | | | | |
| | rs55719896 | 1.10E-11 | 0.67 | | | | | | | rs62036626 | 0.0000012 | -0.15 | rs55719896 | 8.50E-11 | 0.51 | | | | | | |
| | rs56404918 | 1.10E-11 | 0.67 | | | | | | | rs56358680 | 0.0000012 | -0.15 | rs56404918 | 8.50E-11 | 0.51 | | | | | | |
| | rs12444171 | 1.10E-11 | 0.67 | | | | | | | rs55991577 | 0.0000012 | -0.15 | rs12444171 | 8.50E-11 | 0.51 | | | | | | |
| | rs62036657 | 1.10E-11 | 0.67 | | | | | | | rs62036624 | 0.0000012 | -0.15 | rs62036657 | 8.50E-11 | 0.51 | | | | | | |
| | rs62036626 | 1.10E-11 | 0.67 | | | | | | | rs8062405 | 9.60E-07 | -0.15 | rs62036626 | 8.50E-11 | 0.51 | | | | | | |
| | rs56358680 | 1.10E-11 | 0.67 | | | | | | | rs62036621 | 0.0000012 | -0.15 | rs56358680 | 8.50E-11 | 0.51 | | | | | | |
| | rs55991577 | 1.10E-11 | 0.67 | | | | | | | rs62036620 | 0.0000012 | -0.15 | rs55991577 | 8.50E-11 | 0.51 | | | | | | |
| | rs12443881 | 3.80E-07 | 0.55 | | | | | | | rs4788095 | 0.0000013 | -0.14 | rs12443881 | 3.50E-11 | 0.55 | | | | | | |
| | rs72793812 | 5.20E-07 | 0.54 | | | | | | | rs62036617 | 0.0000014 | -0.14 | rs72793812 | 4.20E-11 | 0.54 | | | | | | |
| | rs62036624 | 1.80E-11 | 0.67 | | | | | | | rs1987472 | 0.0000014 | -0.14 | rs62036624 | 8.50E-11 | 0.51 | | | | | | |
| | rs72793811 | 6.80E-07 | 0.54 | | | | | | | rs2008514 | 0.0000015 | -0.14 | rs72793811 | 4.30E-11 | 0.54 | | | | | | |
| | rs8062405 | 2.10E-11 | 0.67 | | | | | | | rs62037363 | 0.0000012 | -0.15 | rs8062405 | 7.40E-11 | 0.51 | | | | | | |
| | rs62036622 | 7.10E-07 | 0.54 | | | | | | | rs56040780 | 0.0000012 | -0.15 | rs62036622 | 3.60E-11 | 0.55 | | | | | | |
| | rs4451951 | 1.30E-11 | 0.65 | | | | | | | rs8049439 | 0.0000011 | -0.15 | rs4451951 | 4.10E-11 | 0.5 | | | | | | |
| | rs62036621 | 7.20E-12 | 0.68 | | | | | | | rs11864107 | 0.0000012 | -0.15 | rs62036621 | 8.00E-11 | 0.51 | | | | | | |
| | rs62036620 | 7.00E-12 | 0.68 | | | | | | | rs7193733 | 0.0000012 | -0.15 | rs62036620 | 8.00E-11 | 0.51 | | | | | | |
| | rs4788095 | 5.30E-12 | 0.68 | | | | | | | rs9972768 | 0.0000012 | -0.15 | rs4788095 | 7.80E-11 | 0.51 | | | | | | |
| | rs62036617 | 2.90E-12 | 0.68 | | | | | | | rs78613234 | 0.0000012 | -0.15 | rs62036617 | 7.90E-11 | 0.51 | | | | | | |
| | rs62036616 | 6.90E-07 | 0.54 | | | | | | | rs72793809 | 0.0000012 | -0.15 | rs62036616 | 4.40E-11 | 0.54 | | | | | | |
| | rs1987472 | 2.30E-12 | 0.68 | | | | | | | rs11860513 | 0.0000011 | -0.14 | rs1987472 | 8.20E-11 | 0.51 | | | | | | |
| | rs2008514 | 2.20E-12 | 0.68 | | | | | | | rs11864750 | 0.0000022 | -0.14 | rs2008514 | 8.20E-11 | 0.51 | | | | | | |
| | rs7359397 | 6.60E-07 | 0.53 | | | | | | | rs11150609 | 0.0000012 | -0.15 | rs7359397 | 6.70E-11 | 0.54 | | | | | | |
| | rs62037363 | 8.00E-12 | 0.68 | | | | | | | rs56186137 | 0.0000014 | -0.14 | rs62037363 | 8.10E-11 | 0.51 | | | | | | |
| | rs56040780 | 1.10E-11 | 0.67 | | | | | | | rs7191618 | 3.20E-08 | -0.16 | rs56040780 | 8.40E-11 | 0.51 | | | | | | |
| | rs8049439 | 1.30E-09 | 0.61 | | | | | | | rs4788083 | 4.30E-08 | -0.16 | rs8049439 | 2.40E-11 | 0.52 | | | | | | |
| | rs11864107 | 1.10E-11 | 0.67 | | | | | | | rs4788084 | 4.20E-08 | -0.16 | rs11864107 | 8.50E-11 | 0.51 | | | | | | |
| | rs7193733 | 8.00E-12 | 0.68 | | | | | | | rs62034326 | 4.20E-08 | -0.16 | rs7193733 | 4.50E-11 | 0.52 | | | | | | |
| | rs12448902 | 2.10E-07 | 0.56 | | | | | | | rs62034324 | 2.80E-08 | -0.16 | rs12448902 | 3.70E-11 | 0.54 | | | | | | |
| | rs7187333 | 2.20E-07 | 0.55 | | | | | | | rs28772958 | 4.30E-08 | -0.16 | rs7187333 | 3.00E-11 | 0.54 | | | | | | |
| | rs9972768 | 1.10E-11 | 0.67 | | | | | | | rs4788085 | 4.30E-08 | -0.16 | rs9972768 | 8.50E-11 | 0.51 | | | | | | |
| | rs78613234 | 1.60E-11 | 0.67 | | | | | | | rs28698667 | 4.20E-08 | -0.16 | rs78613234 | 8.50E-11 | 0.51 | | | | | | |
| | rs72793809 | 6.20E-12 | 0.68 | | | | | | | rs62034319 | 4.50E-08 | -0.16 | rs72793809 | 7.90E-11 | 0.51 | | | | | | |
| | rs11860513 | 2.30E-12 | 0.68 | | | | | | | rs240702 | 4.70E-08 | -0.16 | rs11860513 | 7.70E-11 | 0.5 | | | | | | |
| | rs62036614 | 6.70E-07 | 0.53 | | | | | | | rs153106 | 1.70E-07 | -0.15 | rs62036614 | 3.30E-11 | 0.55 | | | | | | |
| | rs12928404 | 3.80E-09 | 0.57 | | | | | | | rs7202948 | 8.00E-08 | -0.16 | rs12928404 | 5.50E-11 | 0.49 | | | | | | |
| | rs11864750 | 5.60E-12 | 0.67 | | | | | | | | | | rs11864750 | 3.70E-11 | 0.51 | | | | | | |
| | rs11150609 | 1.10E-11 | 0.67 | | | | | | | | | | rs11150609 | 8.50E-11 | 0.51 | | | | | | |
| | rs62036658 | 0.0000015 | 0.53 | | | | | | | | | | rs62036658 | 9.70E-11 | 0.55 | | | | | | |
| | rs56186137 | 2.30E-12 | 0.68 | | | | | | | | | | rs56186137 | 8.20E-11 | 0.51 | | | | | | |
| | rs7191618 | 2.00E-09 | 0.6 | | | | | | | | | | rs7191618 | 4.00E-16 | 0.61 | | | | | | |
| | rs4788083 | 4.40E-09 | 0.58 | | | | | | | | | | rs4788083 | 1.40E-16 | 0.61 | | | | | | |
| | rs4788084 | 3.10E-10 | 0.62 | | | | | | | | | | rs4788084 | 6.40E-17 | 0.62 | | | | | | |
| | rs62034326 | 3.10E-10 | 0.62 | | | | | | | | | | rs62034326 | 6.60E-17 | 0.62 | | | | | | |
| | rs62034324 | 8.50E-10 | 0.61 | | | | | | | | | | rs62034324 | 3.10E-17 | 0.63 | | | | | | |
| | rs28772958 | 4.40E-09 | 0.58 | | | | | | | | | | rs28772958 | 1.40E-16 | 0.61 | | | | | | |
| | rs4788085 | 4.40E-09 | 0.58 | | | | | | | | | | rs4788085 | 1.40E-16 | 0.61 | | | | | | |
| | rs28698667 | 3.10E-10 | 0.62 | | | | | | | | | | rs28698667 | 6.50E-17 | 0.62 | | | | | | |
| | rs62034319 | 2.60E-09 | 0.58 | | | | | | | | | | rs62034319 | 2.50E-17 | 0.62 | | | | | | |
| | rs240702 | 4.20E-09 | 0.58 | | | | | | | | | | rs240702 | 4.00E-17 | 0.62 | | | | | | |
| | rs153106 | 6.60E-10 | 0.61 | | | | | | | | | | rs153106 | 2.70E-17 | 0.62 | | | | | | |
| | rs7202948 | 2.70E-09 | 0.6 | | | | | | | | | | rs7202948 | 3.00E-16 | 0.62 | | | | | | |

| TISSUE | CDC37P1 | | | EIF3C | | | EIF3CL | | | SH2B1 | | | SULT1A2 | | | TUFM | | | IL27 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β |
| Liver | | | | | | | | | | | | | | | | | | | rs3888190 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62037371 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs8055138 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7498555 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs8061590 | 3.00E-08 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs62037369 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs7498665 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs8055982 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7198606 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62037367 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs4788102 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs11861174 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs12446589 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs62037365 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62037364 | 2.40E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs4788101 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7205323 | 4.30E-08 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs80275162 | 1.40E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs9972693 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7187776 | 0.0000027 | 0.33 |
| | | | | | | | | | | | | | | | | | | | rs4788099 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs61737565 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs28403629 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs3088215 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs12325113 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs55830740 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs55719896 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs56404918 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs12444171 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036657 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036626 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs56358680 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs55991577 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs12443881 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs72793812 | 5.60E-07 | 0.37 |
| | | | | | | | | | | | | | | | | | | | rs62036624 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs72793811 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs8062405 | 5.10E-08 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs62036622 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs4451951 | 2.00E-08 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs62036621 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036620 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs4788095 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036617 | 2.60E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036616 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs1987472 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs2008514 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7359397 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs62037363 | 4.20E-08 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs56040780 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs8049439 | 0.0000027 | 0.33 |
| | | | | | | | | | | | | | | | | | | | rs11864107 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7193733 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs12448902 | 3.90E-07 | 0.37 |
| | | | | | | | | | | | | | | | | | | | rs7187333 | 5.50E-07 | 0.37 |
| | | | | | | | | | | | | | | | | | | | rs9972768 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs78613234 | 2.70E-08 | 0.35 |
| | | | | | | | | | | | | | | | | | | | rs72793809 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs11860513 | 2.60E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036614 | 3.60E-07 | 0.38 |
| | | | | | | | | | | | | | | | | | | | rs11864750 | 8.40E-08 | 0.37 |
| | | | | | | | | | | | | | | | | | | | rs11150609 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs62036658 | 5.30E-07 | 0.37 |
| | | | | | | | | | | | | | | | | | | | rs56186137 | 2.70E-08 | 0.39 |
| | | | | | | | | | | | | | | | | | | | rs7191618 | 5.20E-11 | 0.45 |
| | | | | | | | | | | | | | | | | | | | rs4788083 | 5.20E-11 | 0.45 |
| | | | | | | | | | | | | | | | | | | | rs4788084 | 6.30E-10 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs62034326 | 6.30E-10 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs62034324 | 7.30E-09 | 0.41 |
| | | | | | | | | | | | | | | | | | | | rs28772958 | 5.20E-11 | 0.45 |
| | | | | | | | | | | | | | | | | | | | rs4788085 | 5.20E-11 | 0.45 |
| | | | | | | | | | | | | | | | | | | | rs28698667 | 6.30E-10 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs62034319 | 6.30E-10 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs240702 | 6.50E-10 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs153106 | 1.20E-09 | 0.42 |
| | | | | | | | | | | | | | | | | | | | rs7202948 | 1.20E-10 | 0.44 |

**S4 Fig. eQTL data of rs3888190 and its proxies (r2≥0.8)** Cis-association data of significant SNPs influence on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations (Illumina OMNI 5M SNP Array)(4)

| TISSUE | DHX33 | | | RPAIN | | | NUP88 | | | RABEP1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β | SNP | P-value | β |
| Adipose - Subcutaneous | rs3026101 | 0.0000069 | -0.17 | rs1000940 | 1.40E-08 | -0.24 | | | | | | |
| | rs58351927 | 0.0000061 | -0.17 | rs3026101 | 4.70E-09 | -0.25 | | | | | | |
| | rs12600578 | 0.0000061 | -0.17 | rs16954604 | 2.80E-08 | -0.23 | | | | | | |
| | rs1806263 | 0.00001 | -0.17 | rs58351927 | 1.80E-08 | -0.24 | | | | | | |
| | rs1806246 | 0.0000051 | -0.18 | rs12600578 | 1.80E-08 | -0.24 | | | | | | |
| | | | | rs1806263 | 3.90E-08 | -0.23 | | | | | | |
| | | | | rs1806246 | 1.60E-08 | -0.24 | | | | | | |
| Adrenal Gland | | | | | | | | | | | | |
| Brain | | | | | | | rs3026101 | 0.0000031 | 0.51 | | | |
| Pituitary | | | | | | | | | | rs1000940 | 4.50E-07 | -0.7 |
| | | | | | | | | | | rs3026101 | 1.00E-07 | -0.73 |
| | | | | | | | | | | rs16954604 | 1.00E-07 | -0.73 |
| | | | | | | | | | | rs58351927 | 1.00E-07 | -0.73 |
| | | | | | | | | | | rs12600578 | 1.00E-07 | -0.73 |
| | | | | | | | | | | rs1806263 | 9.60E-08 | -0.74 |
| | | | | | | | | | | rs1806246 | 9.70E-08 | -0.74 |
| Thyroid | rs1000940 | 0.0000028 | -0.22 | | | | | | | rs1000940 | 2.00E-16 | -0.41 |
| | rs3026101 | 0.000005 | -0.22 | | | | | | | rs3026101 | 1.50E-16 | -0.41 |
| | rs16954604 | 0.0000027 | -0.22 | | | | | | | rs16954604 | 3.00E-16 | -0.4 |
| | rs58351927 | 0.0000027 | -0.22 | | | | | | | rs58351927 | 3.00E-16 | -0.4 |
| | rs12600578 | 0.0000027 | -0.22 | | | | | | | rs12600578 | 3.00E-16 | -0.4 |
| | rs1806263 | 0.0000057 | -0.22 | | | | | | | rs1806263 | 4.50E-16 | -0.4 |
| | rs1806246 | 0.0000036 | -0.22 | | | | | | | rs1806246 | 9.20E-17 | -0.41 |

**S5 Fig. eQTL data of rs1000940 and its proxies r2≥0.8** Cis-association data of significant SNPs influence on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations (Illumina OMNI 5M SNP Array)(4)

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