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# A new genetic locus for antipsychotic-induced weight gain: A genome-wide study of first-episode psychosis patients using amisulpride (from the OPTiMiSE cohort)

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## Abstract

**Background:** Antipsychotic-induced weight gain is a common and debilitating side effect of antipsychotics. Although genome-wide association studies of antipsychotic-induced weight gain have been performed, few genome-wide loci have been discovered. Moreover, these genome-wide association studies have included a wide variety of antipsychotic compounds.

**Aims:** We aim to gain more insight in the genomic loci affecting antipsychotic-induced weight gain. Given the variable pharmacological properties of antipsychotics, we hypothesized that targeting a single antipsychotic compound would provide new clues about genomic loci affecting antipsychotic-induced weight gain.

**Methods:** All subjects included for this genome-wide association study ( $n=339$ ) were first-episode schizophrenia spectrum disorder patients treated with amisulpride and were minimally medicated (defined as antipsychotic use  $<2$  weeks in the previous year and/or  $<6$  weeks lifetime). Weight gain was defined as the increase in body mass index from before until approximately 1 month after amisulpride treatment.

**Results:** Our genome-wide association analyses for antipsychotic-induced weight gain yielded one genome-wide significant hit (rs78310016;  $\beta=1.05$ ;  $p=3.66 \times 10^{-08}$ ;  $n=206$ ) in a locus not previously associated with antipsychotic-induced weight gain or body mass index. Minor allele carriers had an odds ratio of 3.98 ( $p=1.0 \times 10^{-03}$ ) for clinically meaningful antipsychotic-induced weight gain ( $\geq 7\%$  of baseline weight). In silico analysis elucidated a chromatin interaction with *3-Hydroxy-3-Methylglutaryl-CoA Synthase 1*. In an attempt to replicate single-nucleotide polymorphisms previously associated with antipsychotic-induced weight gain, we found none were associated with amisulpride-induced weight gain.

**Conclusion:** Our findings suggest the involvement of rs78310016 and possibly *3-Hydroxy-3-Methylglutaryl-CoA Synthase 1* in antipsychotic-induced weight gain. In line with the unique binding profile of this atypical antipsychotic, our findings furthermore hint that biological mechanisms underlying amisulpride-induced weight gain differ from antipsychotic-induced weight gain by other atypical antipsychotics.

## Keywords

Pharmacogenetics, antipsychotics, body mass index, amisulpride-induced weight gain, schizophrenia, GWAS

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## Introduction

A very harmful side effect of antipsychotics is antipsychotic-induced weight gain (AiWG). A 3-year observational study reports clinically relevant AiWG ( $\geq 7\%$  of baseline weight) in up to 45% of participants on antipsychotics, resulting in a shift from normal weight to overweight in up to 15% of these patients (Bushe et al., 2012). Metabolic syndrome (MetS) often follows AiWG: the relative risk of developing MetS after antipsychotic treatment initiation compared to unmedicated schizophrenia patients is up to 2.57 (Mitchell et al., 2013). Schizophrenia patients on average have a 20% decreased life expectancy, with cardiovascular disease ranking as the leading cause of death (Newcomer, 2007). In addition, AiWG may hamper treatment efficacy as it reduces adherence (Müller and Kennedy, 2006). Furthermore, AiWG reduces quality of life by 12% (Allison et al., 2003).

Meta-analyses assessing the efficacy and safety of 15 antipsychotics in schizophrenia show superior efficacy and a relatively favorable safety profile for amisulpride (Huhn et al., 2019; Leucht et al., 2013). Study results on the amount of weight gain induced by amisulpride vary and it seems that amisulpride carries a lower weight gain risk at prolonged exposure than other antipsychotics. Previous meta-analyses that also incorporated long-term studies classify the compound as low risk or even weight neutral (Bak et al., 2014; Leucht et al., 2013; Rummel-Kluge et al., 2010). In contrast, a short-term study categorizes amisulpride as a mid-risk compound for AiWG with an average weight gain of 2.3 kg after 6 weeks of treatment (Nielsen et al., 2016). A recent meta-analysis confirms the categorization as a mid-risk compound (Huhn et al., 2019). This antipsychotic compound has a unique pharmacological profile with high potency for the D2 and D3 dopamine receptors, along with high binding affinities for two serotonin receptors: 5-HT2B and 5-HT7A (Abbas et al., 2009). Currently, the proposed mechanism for AiWG in amisulpride is through D2 antagonism, with two prime pathways possibly involved: tuberoinfundibular D2R inhibition via prolactin increase (Kapur and Marques, 2016; Reynolds and Kirk, 2010) and mesolimbic D2R blockade via disrupted reward processing (Nielsen et al., 2016; Volkow et al., 2011). Importantly, amisulpride differs from other commonly prescribed antipsychotics as it does not bind to histamine, muscarinic and other serotonin receptors (e.g. 5-HT1A, 5-HT2A and 5-HT2C), all of which have a role in AiWG (Amato, 2015; Buckley, 2007; Rasmussen et al., 2014). Of note, not only medication but also schizophrenia itself have been linked to metabolic features, such as levels of insulin-related peptides (Guest et al., 2010), insulin resistance (Pillinger et al., 2017; Tomasik et al., 2019), HbA1c (Cao et al., 2017) and leptin resistance (Martorell et al., 2019).

The amount of weight gain during antipsychotic treatment is associated with the type of antipsychotic, pre-treatment body mass index (BMI), sex, symptom reduction, and age (Gebhardt et al., 2009; Raben et al., 2017). Beside these variables, substantial interindividual differences in AiWG hint at the involvement of genetic mechanisms in AiWG. A monozygotic twin study confirms this notion by showing a greater similarity of AiWG profiles in monozygotic twins compared to same-sex siblings, resulting in a very high estimated heritability ( $h^2$ ) of 0.8 for AiWG (Theisen et al., 2005). Several studies have been conducted to discover and replicate genetic markers subtending

AiWG (Zhang et al., 2016). A few genetic loci have been associated with AiWG through genome-wide association studies (GWASs), with rs489693 nearby the melanocortin 4 receptor gene (*MC4R*) (Malhotra et al., 2012) and rs10977144 on the protein tyrosine phosphatase receptor type D gene (*PTPRD*) (Yu et al., 2016) exceeding the genome-wide significance threshold. Although results on *PTPRD* were not replicated in European and Afro-American populations, (Maciukiewicz et al., 2019), these findings hint that GWAS is a powerful approach to disentangle genetic polymorphisms underlying AiWG. Understanding the genetics of AiWG carries the potential to predict the risk of AiWG before treatment inception in the future, ultimately promoting compliance and quality of life.

Importantly, all previous AiWG GWASs have been performed in subjects using a range of atypical agents (e.g., quetiapine, risperidone, and aripiprazole) with most study populations comprising different patient subgroups (e.g., pediatric patients (Malhotra et al., 2012) and non-medication naïve patients (Brandl et al., 2016)). These agents, and amisulpride in particular, have specific binding profiles and differ with regard to their risk of inducing AiWG. The genetic mechanisms underlying AiWG may therefore not be equal for all these agents. Moreover, sustained use of prior antipsychotics may introduce bias in a GWAS of AiWG as substantial AiWG could have occurred before the first weight measurement. On a similar note, in pediatric patients, weight gain may be physiological as height and weight may increase physiologically (albeit possibly not to the same degree) during a clinical trial.

To circumvent these caveats of antipsychotic heterogeneity and patient subtype heterogeneity, here we targeted adult, first-episode, minimally medicated subjects suffering from psychosis. We reasoned that by targeting a single compound (amisulpride) in a homogeneous study population within one clinical trial, we had increased power compared to GWASs examining multiple antipsychotics as the genetic mechanisms underlying AiWG may differ between compounds. We report a genome-wide significant locus not previously associated with AiWG.

## Methods

### Study population

The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) study was a multicenter study consisting of three phases. The main objective of the OPTiMiSE study was optimization of treatment and management of schizophrenia by assessing effectiveness and safety, with remission as the primary outcome. Details on this study are outlined elsewhere (Leucht et al., 2015). The protocol was set up in line with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) guidelines and the study was registered as clinical trial (NCT01248195). All subjects included in the current GWAS were enrolled in Phase 1 of the OPTiMiSE study, were genotyped and met the requirement of having a height measurement plus two weight measurements (before and after completion of Phase 1). Subjects with suspected non-adherence, dropped informed consent, use of other antipsychotics during the study, or potential fraud were excluded. All ethnicities were allowed for this GWAS

and genetic outliers were only identified using GWAS quality control steps outlined below. Co-medication was allowed (with the exception of antipsychotics) and was analyzed based on the risk of inducing weight loss or gain (Supplementary Figure 5). Minimally medicated antipsychotic use was defined as prior antipsychotic use of less than 2 weeks in the previous year and/or less than 6 weeks lifetime. The current GWAS contained either absolute medication-naïve or minimally medicated first-episode schizophrenia and schizophreniform disorder patients aged 18–43 years old at the date of inclusion, meaning that subjects who had used antipsychotics for  $\geq 2$  weeks in the previous year and/or  $\geq 6$  weeks lifetime had been excluded. In the first phase of the study all participants were given a daily dose of amisulpride varying between 100 and 800 mg per day (mean=442 mg per day, standard deviation (SD)=118) for 14–49 days (mean duration of treatment=34.6 days, SD=5.3, median=34.5 days).

### Genotyping, imputation, and quality control

Genotyping was completed on 339 subjects (228 males and 111 females) for 945,212 single-nucleotide polymorphisms (SNPs) using the OmniExpressExome 8v1-4 A1 BeadChip (Illumina Inc., San Diego, CA, USA). Quality Control (QC) was conducted in PLINK 1.9 (Chang et al., 2015) before genotype imputation. We chose conservative QC cut-offs (e.g. PI-HAT $>0.1$ , minor allele frequencies (MAF)<sub>imputation</sub> $>5\%$ ) and included all possible covariates previously associated with AiWG (see below) for this relatively small GWAS to minimize the risk of finding false positive associations. Thus, during individual-level QC (Supplementary Figure 1), the following subjects were removed: related individuals (PI-HAT $>0.1$ ), subjects with genotype rate  $<95\%$ , subjects whose phenotypic sex did not match their genetic sex, and/or individuals with a heterozygosity rate  $>3$  SD from the mean. Principal component analysis was performed to identify population outliers on the first two genetic PCs ( $>3$  SD from the mean, Supplementary Figure 1). During SNP-level QC (Supplementary Figure 2), the following variants were excluded: those with MAF  $<1\%$ , a missing genotype rate  $>1\%$ , and/or a Hardy-Weinberg disequilibrium (HWE test  $p < 10^{-6}$ ). Prior to imputation, we removed strand-ambiguous AT/CG SNPs and SNPs with a non-matching minor allele frequency ( $\Delta\text{MAF} > 0.2$ ) compared to the Haplotype Reference Consortium (HRC) dataset (McCarthy et al., 2016). Imputation included autosomes only and was carried out on the Michigan Imputation Server with the HRC as a reference panel (mean imputation accuracy  $r^2=0.97$ ) (Das et al., 2016). Post-imputation QC removed SNPs with imputation accuracy of  $r^2 < 0.8$ , a MAF of  $<5\%$ , a MAF difference of  $>0.15$  compared to the HRC reference panel and strand-ambiguous AT/CG SNPs, leaving a total of 4,533,042 genotyped and imputed SNPs for statistical analysis (Supplementary Figure 2).

### Statistical analysis

All QC steps and association tests were conducted in PLINK 1.9 (Chang et al., 2015). After the QC steps described above, 206 subjects remained with the required genotype and phenotype information available (Supplementary Figure 1). BMI was calculated as (weight in kilograms)/(height in meters<sup>2</sup>). The outcome variable was BMI change per month: BMI adjusted for duration of study was chosen because of substantial variation in duration of

trial participation between subjects. We identified all potential confounders for our GWAS by performing an extensive PubMed search using the search terms: antipsychotic-induced weight gain [AND] predictors [OR] association. We found age, sex, BMI at inception, and clinical improvement to be significantly associated with AiWG (Gebhardt et al., 2009; Raben et al., 2017). Age distribution was as would be expected of a first-episode psychosis cohort (Supplementary Figure 3). We did not correct for amisulpride dose as amisulpride-induced weight gain was found not to be dose dependent (Nielsen et al., 2016; Pandit et al., 2019; Simon et al., 2009). Moreover, potentially weight influencing co-medication did not influence BMI change significantly and was therefore not corrected for (Supplementary Figure 5). Thus, our association test was a linear regression with 14 covariates: age (years), sex (male vs female), BMI at trial inception, change (%) in total Positive and Negative Scale Score (PANSS), and 10 principal components to correct for genetic ancestry. During the course of writing, a new study we conducted found specific phenotypic variables associated with amisulpride-induced weight gain (Pandit et al., 2019), so a sensitivity analysis was run with these variables as covariates, namely, a diagnosis of major depression disorder (MDD) and employment status. Because of incomplete information on MDD, 11 subjects were excluded. This sensitivity model thus contained 15 covariates in 195 subjects: age (years), sex (male vs female), BMI at inception, MDD diagnosis (yes or no), employment (yes or no), and 10 principal components.

The genome-wide significance threshold was set at the standard  $5 \times 10^{-8}$ . We ran standard additive linear models and for our genome-wide significant variant we also tested a dominant model as another sensitivity analysis, based on the literature (Malhotra et al., 2012). A recessive model could not be tested due to underrepresentation of homozygote minor allele subjects. For genome-wide hits, we also tested their clinical meaning by computing the odds ratio (OR) per allele for clinically meaningful AiWG (defined as  $>7\%$  weight gain) (Musil et al., 2015). The previously reported SNPs associated with AiWG by Malhotra et al. (2012), Yu et al. (2016) and Zhang et al. (2016) were then looked up in our dataset. In addition, our top SNP was looked up in the Malhotra et al. (2012) discovery cohort. Functional Mapping and Annotation (FUMA) was used for a gene-based test and to explore eQTL and chromatin interactions of loci reaching genome-wide significance (Watanabe et al., 2017). For our gene-based test in FUMA (performed by MAGMA), input SNPs were mapped to 18,257 protein coding genes and genome-wide significance was defined at a Bonferroni-corrected alpha of  $0.05/18257 = 2.739 \times 10^{-6}$ . Furthermore, we looked up associations of our top SNP in the GWAS catalog ([www.ebi.ac.uk/gwas/](http://www.ebi.ac.uk/gwas/)) and in a large BMI GWAS to increase the chances of pinpointing antipsychotic-induced weight gain-associated loci as opposed to non-medication induced weight gain-associated loci (Yengo et al., 2018). In addition to this, we looked up our top SNP in two other GWASs: type 2 diabetes (Xue et al., 2018) and anorexia nervosa (Watson et al., 2019). Finally, we calculated the variance explained by genome-wide significant hits by running two different models. One including solely the SNP ( $r^2 = \text{BMI change per month} \sim \text{SNP}$ ) and the other one taking into account the covariates ( $r^2 = (\text{BMI change per month} \sim \text{SNP} + \text{covariates} + \text{PCs}) - (\text{BMI change per month} \sim \text{covariates} + \text{PCs})$ ). Also, we checked the variance of BMI to determine the independence of the results.

**Table 1.** The baseline characteristics of the OPTiMiSE subset included in this study ( $n=206$ ).

Characteristics	N(%)/mean $\pm$ SD
Sex, number	Male $n=139$ (67.5%) Female $n=67$ (32.5%)
Age, mean (years)	26.4 $\pm$ 6.3
Duration of study, mean (days)	34.6 $\pm$ 5.3
Dose amisulpride, mean (mg/day)	442 $\pm$ 118
Baseline PANSS, mean	79.4 $\pm$ 19.9
PANSS score change (%), mean	-26.2 $\pm$ 19.9
PANSS score change, mean	-22.2 $\pm$ 18.4
Baseline BMI, mean	23.3 $\pm$ 4.1
BMI change per month, mean	0.89 $\pm$ 1.11
Weight gain per month (kg), mean	2.89 $\pm$ 3.53

BMI: body mass index; OPTiMiSE: Optimization of Treatment and Management of Schizophrenia in Europe; PANSS: Positive and Negative Scale Score.

## Results

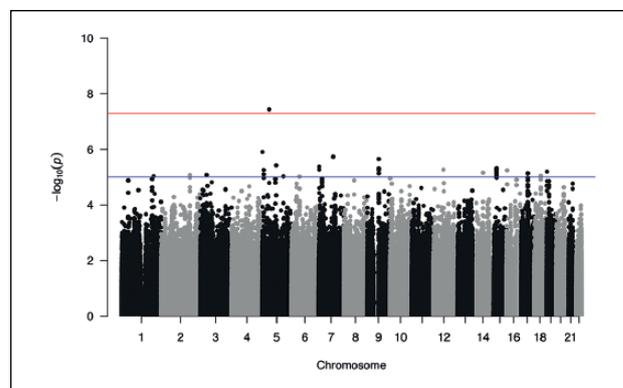
### Demographics

The baseline characteristics of our study population are shown in Table 1. As recently reported, several phenotypic variables (not including dose and sex) were found to be associated with amisulpride-induced weight gain, primarily employment status and a diagnosis of major depressive disorder (Pandit et al., 2019). The mean change in BMI per month throughout the trial was +0.89 kg/m<sup>2</sup> (SD=1.11), which led to clinically meaningful AiWG in 26.7% of the subjects. This weight gain brought the percentage of subjects meeting overweight (BMI >25 kg/m<sup>2</sup>) or obese (BMI >30 kg/m<sup>2</sup>) criteria from 27.2% to 32.5% during the trial.

### GWAS results

The Quantile-Quantile plot ( $\lambda=1.009$ , Supplementary Figure 4) suggested minimal inflation of test statistics. The additive primary GWAS model yielded seven SNPs at  $p < 5 \times 10^{-6}$  (Figure 1, Table 2). Among these SNPs, rs78310016 exceeded the genome-wide significance threshold ( $\beta=1.05$ ,  $p=3.66 \times 10^{-8}$ , Figure 2), with increased weight gain in minor allele G carriers (Figure 3). The variance ( $r^2$ ) in observed BMI change explained by allelic variation at this locus was 7–10% depending on the model, which was independent of baseline BMI (that had an  $r^2=0.5\%$ ). Running a dominant model on this variant did not increase the significance of our result ( $\beta=1.04$ ,  $p=2.83 \times 10^{-7}$ , Supplementary Table 2). In our sensitivity analysis that included covariates correcting for phenotypic variables associated with amisulpride-induced weight gain (Pandit et al., 2019), this same locus remained the most significant ( $\beta=1.03$ ,  $p=1.70 \times 10^{-7}$ , Supplementary Table 2).

G-allele carriers gained on average twice as much weight after 1 month of amisulpride treatment compared to non-carriers: 5.04 kg (SD=3.76,  $n=28$ ) versus 2.56 kg (SD=3.39,  $n=178$ ) ( $F_{ANOVA}=12.49$ ,  $p=5.06 \times 10^{-4}$ ; Figure 3). Moreover, G-allele carriers had an OR of 3.98 (95% confidence interval (CI)=1.75–9.06,  $p=1.0 \times 10^{-3}$ ) for clinically meaningful AiWG (>7%). The number of G-carriers ( $n=28$ ) going from normal BMI to



**Figure 1.** Manhattan plot of this genome-wide association study (GWAS) showing rs78310016 exceeding the GWAS significance threshold. On the y-axis log linear  $p$  values are listed (blue line= $1 \times 10^{-5}$ , indicating suggestive significance; red line= $5 \times 10^{-8}$ , indicating genome-wide significance) whereas position in base pair is reported on the x-axis. Supplementary Table 4 lists all single-nucleotide polymorphisms (SNPs)  $p < 1 \times 10^{-5}$ .

overweight ( $n=4$ ) was 14.3%. In the non G-carriers ( $n=178$ ) group it was  $n=9$  (5.1%). G-carriers had an OR of 3.13 (95% CI=0.89–10.96) for shifting from normal to overweight compared to non-carriers. No baseline characteristics group differences were observed between rs78310016 risk allele carriers (i.e., one or more G alleles) and non-carriers (Supplementary Table 5).

The genome-wide significant SNP rs78310016 is located in an intergenic region on chromosome 5 (Figure 2), 62 kb upstream from *Selenoprotein P1 (SEPP1)* and 228 kb upstream from *Growth Hormone Receptor (GHR)*. This SNP was not previously linked to other (metabolic) phenotypes. In-silico follow-up analysis using FUMA (Watanabe et al., 2017) highlighted a chromatin interaction with *HMGCS1* (Supplementary Figure 6). Strikingly, variants within *HMGCS1* were associated at nominal significance with amisulpride-induced weight gain (Supplementary Table 3). The MAGMA tissue expression analysis highlighted liver ( $p=0.038$ ) and small intestine ( $p=0.035$ ) as the main tissues implicated in AiWG (Supplementary Table 6), with all four top tissues pertaining to the gastrointestinal tract, an important target of dopamine. In our gene-based test none of the genes survived Bonferroni-correction for multiple testing, the most significant genes being *C15orf56* ( $p=4.864 \times 10^{-6}$ ), *TEAD3* ( $p=2.9127 \times 10^{-5}$ ), and *PALD1* ( $p=4.0596 \times 10^{-5}$ ).

### Replication effort of previously associated polymorphisms (Supplementary Table 7)

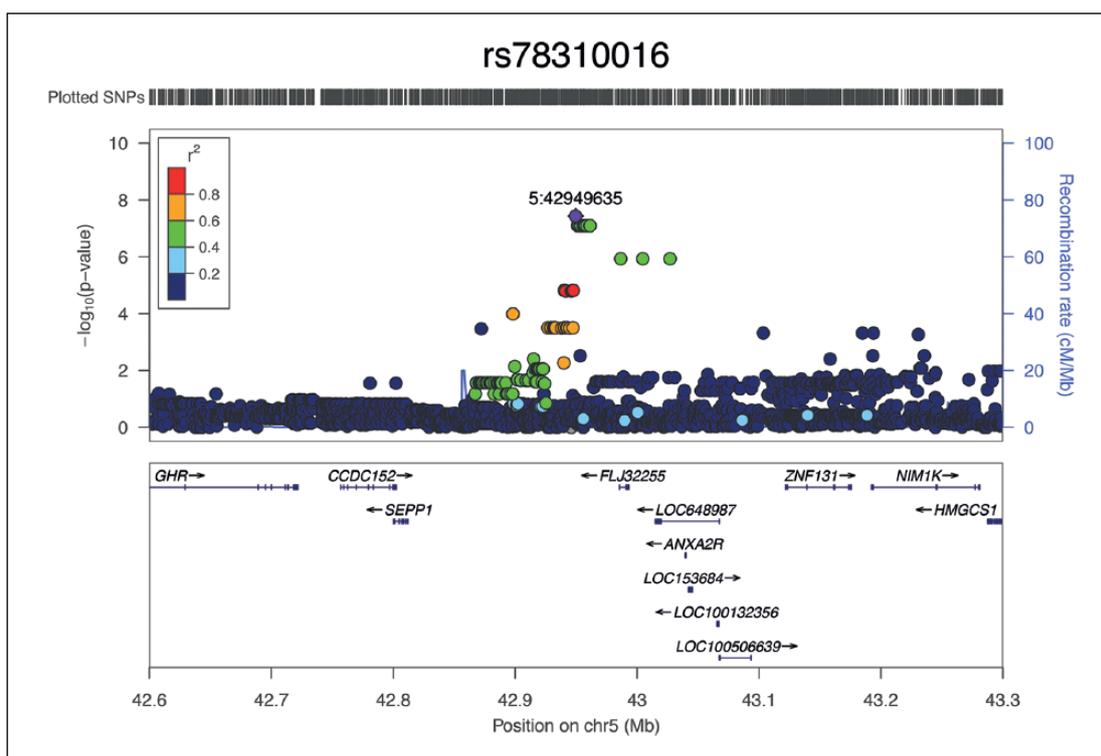
The previously found AiWG-associated SNP near *MC4R* (rs489693) (Malhotra et al., 2012) did not show any association ( $p > 0.05$ ) with amisulpride-induced weight gain, nor did any variants in weak or strong linkage disequilibrium (LD) ( $r^2 > 0.2$ ). Similarly, previously found rs10977144 (Yu et al., 2016) on *PTPRD* and its SNPs in LD ( $r^2 > 0.2$ ) did not show any association ( $p > 0.05$ ) in our dataset. In addition, our significant SNP rs78310016 was tested in the Malhotra et al. (2012) cohort, without any signs of association either ( $p > 0.05$ ). From our look-up endeavor, one nominally significant association with the same

**Table 2.** The most significantly associated SNPs with BMI (Body Mass Index) increase due to amisulpride treatment; depicted are those with a  $p$  value  $< 5 \times 10^{-05}$ ; the genome-wide significant SNP is shown in bold.

SNP	BP	Annotation	Nearest gene(s)	A1	MAF	CADD	$\beta^a$	$p$ value
<b>rs78310016</b>	<b>5:42949635</b>	<b>intergenic</b>	<b>CTD-2201E18.1</b>	<b>G</b>	<b>0.0726</b>	<b>3.566</b>	<b>1.052</b>	<b><math>3.656 \times 10^{-08}</math></b>
rs57818938	5:2278069	intergenic	Y_RNA	T	0.0611	0.920	0.9321	$1.254 \times 10^{-06}$
rs10278819	7:92057320	ncRNA_intronic	TMBIM7P	C	0.1023	8.766	0.8730	$1.846 \times 10^{-06}$
rs7024062	9:71745073	intronic	TJP2	A	0.1931	4.992	-0.5885	$2.217 \times 10^{-06}$
rs10070777	5:87424765	intergenic	TMEM161B	A	0.0743	13.98	0.8786	$3.824 \times 10^{-06}$
rs13230004	7:5345350	UTR3	SLC29A4	A	0.2724	0.357	0.5336	$4.244 \times 10^{-06}$
rs1048163	15:40543223	UTR3	PAK6 C15orf56	G	0.3383	2.795	0.4495	$4.864 \times 10^{-06}$

<sup>a</sup> $\beta$  is the regression coefficient of the linear regression analysis.

SNP: single-nucleotide polymorphism; BP: basepair; A1: Minor allele; MAF: minor allele frequencies; CADD: Combined Annotation Dependent Depletion (a measure for deleteriousness of SNPs).



**Figure 2.** Location of genome-wide significant rs78310016 in an intergenic region on chromosome 5 including single-nucleotide polymorphisms (SNPs) with minor allele frequencies (MAF)  $> 0.01$ , created in LocusZoom (Pruim et al., 2010).

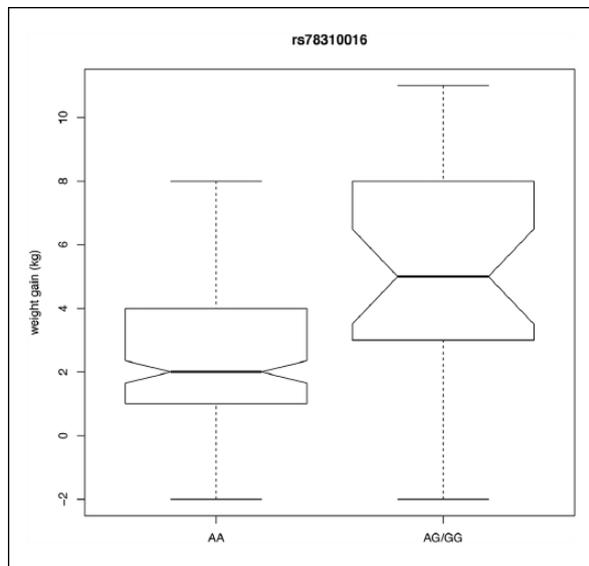
direction of effect arose: between amisulpride-induced weight gain and rs7131056 on the dopamine receptor D2 (*DRD2*) ( $\beta=0.2079$ ,  $p=0.04099$ , Supplementary Table 8).

## Discussion

In an effort to shed new light on genetic underpinnings of AiWG we conducted GWAS on a homogenous cohort of minimally medicated first episode, adult psychosis patients. We found one novel common variant associated with AiWG in our conservative GWAS model with 14 covariates. Functional follow-up analysis pointed to the involvement of *HMGCS1*. Of note, we are not aware of interactions between the dopamine system and *HMGCS1*. Liver and small intestine were highlighted as the main

tissues involved in amisulpride-induced weight gain. Strikingly, only one SNP previously associated with AiWG replicated at  $p < 0.05$  in our study population, whereas our significant SNP did not replicate in the previous AiWG GWASs, hinting that the genetic mechanisms underlying amisulpride-induced weight gain at least partly differ from those subtending weight-gain induced by other antipsychotics.

The genome-wide significantly associated SNP rs78310016 is located in an intergenic region on chromosome 5q13, in close vicinity to *SEPP1* and *GHR*. Both genes are involved in metabolism (Jørgensen et al., 2004) and have been linked to various metabolic phenotypes, such as diabetes mellitus, (Akbaba et al., 2018; Hellwege et al., 2014) weight and obesity, (Chen et al., 2017; Espinosa et al., 2019; Gao et al., 2011), and metabolic



**Figure 3.** Boxplot of weight gain in kilograms (kg) per rs78310016 genotype. As a result of underrepresentation of the GG genotype ( $n=1$ ), it was merged with the AG ( $n=27$ ) genotype. G-allele carriers ( $n=28$ ) gained on average 5.04 kg ( $SD=3.76$ ) and the non-carrier group ( $n=178$ ) 2.56 kg ( $SD=3.39$ ) ( $F_{ANOVA}=12.49$ ,  $p=5.06 \times 10^{-04}$ ).

syndrome (Gharipour et al., 2017). Interestingly, for rs78310016 we showed a chromatin interaction with *HMGCS1*. *HMGCS1* is a ubiquitously expressed gene, but of all tissues it is most highly expressed in brain and liver, which is in line with our tissue expression analysis. It encodes HMG-CoA synthase 1, which is also involved in metabolism as it regulates the biosynthesis of cholesterol (Vock et al., 2008). In further support of its role in amisulpride-induced weight gain is our observation that despite weak LD in the region, variants within *HMGCS1* are associated at nominal significance with amisulpride-induced weight gain (Supplementary Table 3).

Our GWAS and lookup results hint that the genetic mechanisms underlying AiWG differ between amisulpride and other antipsychotics. Various mechanisms have been proposed in AiWG involving different receptors, mostly suggesting an increase of appetite and a delay in satiety signaling (Deng, 2013). Although the blockade of 5HT<sub>2C</sub> by olanzapine and clozapine induces food craving and binge eating (Kluge et al., 2007), D<sub>2</sub> receptor (D<sub>2</sub>R)-mediated pathways likely play a more important role in agents with high D<sub>2</sub>R affinity, such as amisulpride. D<sub>2</sub>R blockade can cause weight gain by induced hormonal dysregulation via prolactin increase (Reynolds and Kirk, 2010) or increase food intake by disrupted reward processing (Nielsen et al., 2016; Volkow et al., 2011).

The strengths of our study include the collection of a homogeneous set of minimally medicated first-episode, adult patients using the same antipsychotic. In addition, phenotypic data were meticulously collected, allowing for correction of several important potentially confounding variables. Some limitations should, however, be borne in mind when interpreting our results. The sample size for this GWAS was in the middle ranges compared to previous AiWG GWASs, which used discovery sets of  $n=139$  (Malhotra et al., 2012),  $n=189$  (Brandl et al., 2016), and  $n=534$

(Yu et al., 2016). In addition, a replication cohort was lacking for the current analyses. Collecting another cohort with minimally medicated psychosis patients on amisulpride will likely require many years. Ideally, a well powered study targeting over a thousand first-episode patients who are treated with, for example, amisulpride and olanzapine will allow for mega-analyses and thereby increased accuracy.

In conclusion, we highlight a novel variant associated with AiWG and provide evidence for a role of *HMGCS1* in amisulpride-induced weight gain. We also find evidence for different underlying genetic mechanisms for amisulpride-induced weight gain compared to weight gain caused by other antipsychotics. Future well-powered AiWG GWASs are highly needed to allow for meta-analyses parsed by antipsychotic compound to further elucidate genetic mechanisms involved in AiWG in general and AiWG caused by specific agents. Larger cohorts may also disentangle the effect sizes of both single variants and polygenic risk scores, including whether the genetic make-up of AiWG may be a combination of polygenicity and single genetic variants of medium to large effect. Moreover, such large studies could provide us with more insight into genetic vulnerability of AiWG, including the degree of polygenicity. Such pharmacogenetic data combined with other characteristics (e.g. duration of illness and dietary factors) may be used in clinical practice for psychosis patients to more readily identify those most susceptible to AiWG and thus optimize tailor-made prevention and management programs for this burdensome adverse event.

### Author note

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## Supplemental material

Supplemental material for this article is available online.

## References

- Abbas AI, Hedlund PB, Huang X-P, et al. (2009) Amisulpride is a potent 5-HT7 antagonist: Relevance for antidepressant actions in vivo. *Psychopharmacology* 205: 119–128.
- Akbaba G, Akbaba E, Sahin C, et al. (2018) The relationship between gestational diabetes mellitus and selenoprotein-P plasma 1 (SEPP1) gene polymorphisms. *Gynecol Endocrinol* 34: 849–852.
- Allison DB, Mackell JA and McDonnell DD (2003) The impact of weight gain on quality of life among persons with schizophrenia. *Psychiatr Serv* 54: 565–567.
- Amato D (2015) Serotonin in antipsychotic drugs action. *Behav Brain Res* 277: 125–135.
- Bak M, Franssen A, Janssen J, et al. (2014) Almost all antipsychotics result in weight gain: A meta-analysis. *PLoS One* 9: e94112.
- Brandl EJ, Tiwari AK, Zai CC, et al. (2016) Genome-wide association study on antipsychotic-induced weight gain in the CATIE sample. *Pharmacogenomics* 16: 352–356.
- Buckley PF (2007) Receptor-binding profiles of antipsychotics: Clinical strategies when switching between agents. *J Clin Psychiatry* 68(Suppl. 6): 5–9.
- Bushe CJ, Slooff CJ, Haddad PM, et al. (2012) Weight change from 3-year observational data: Findings from the worldwide schizophrenia outpatient health outcomes database. *J Clin Psychiatry* 73: e749–e755.
- Cao H, Chen J, Meyer-Lindenberg A, et al. (2017) A polygenic score for schizophrenia predicts glycemic control. *Transl Psychiatry* 7: 1295.
- Chang CC, Chow CC, Tellier LC, et al. (2015) Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience* 4: 7.
- Chen M, Liu B, Wilkinson D, et al. (2017) Selenoprotein P is elevated in individuals with obesity, but is not independently associated with insulin resistance. *Obes Res Clin Pract* 11: 227–232.
- Das S, Forer L, Schönherr S, et al. (2016) Next-generation genotype imputation service and methods. *Nat Genet* 48: 1284–1287.
- Deng C (2013) Effects of antipsychotic medications on appetite, weight, and insulin resistance. *Endocrinol Metab Clin North Am* 42: 545–563.
- Espinosa E, Salame L, Marrero-Rodriguez D, et al. (2019) Expression of the growth hormone receptor isoforms and its correlation with the metabolic profile in morbidly obese subjects. *Endocrine* 63: 573–581.
- Gao L, Zheng Z, Cao L, et al. (2011) The growth hormone receptor (GHR) exon 3 polymorphism and its correlation with metabolic profiles in obese Chinese children. *Pediatric Diabetes* 12(4 Pt 2): 429–434.
- Gebhardt S, Haberhausen M, Heinzl-Gutenbrunner M, et al. (2009) Antipsychotic-induced body weight gain: Predictors and a systematic categorization of the long-term weight course. *J Psychiatr Res* 43: 620–626.
- Gharipour M, Sadeghi M, Salehi M, et al. (2017) Association of expression of selenoprotein P in mRNA and protein levels with metabolic syndrome in subjects with cardiovascular disease: Results of the Selenogene study. *J Gene Med*. Epub ahead of print 11 February 2017. DOI: 10.1002/jgm.2945.
- Guest PC, Wang L, Harris LW, et al. (2010) Increased levels of circulating insulin-related peptides in first-onset, antipsychotic naïve schizophrenia patients. *Mol Psychiatry* 15: 118–119.
- Hellwege JN, Palmer ND, Ziegler JT, et al. (2014) Genetic variants in selenoprotein P plasma 1 gene (SEPP1) are associated with fasting insulin and first phase insulin response in Hispanics. *Gene* 534: 33–39.
- Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. (2019) Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet*. Epub ahead of print 14 September 2019. DOI: 10.1016/S0140-6736(19)31135-3.
- Jørgensen JOL, Krag M, Jessen N, et al. (2004) Growth hormone and glucose homeostasis. *Horm Res* 62(Suppl. 3): 51–55.
- Kapur S and Marques TR (2016) Dopamine, striatum, antipsychotics, and questions about weight gain. *JAMA Psychiatry* 73: 107–108.
- Kluge M, Schuld A, Himmerich H, et al. (2007) Clozapine and olanzapine are associated with food craving and binge eating: Results from a randomized double-blind study. *J Clin Psychopharmacol* 27: 662–666.
- Leucht S, Cipriani A, Spineli L, et al. (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *Lancet* 382: 951–962.
- Leucht S, Winter-van Rossum I, Heres S, et al. (2015) The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: Rationale for its methodology and a review of the effectiveness of switching antipsychotics. *Schizophr Bull* 41: 549–558.
- Maciukiewicz M, Gorbovskaya I, Tiwari AK, et al. (2019) Genetic validation study of protein tyrosine phosphatase receptor type D (PTPRD) gene variants and risk for antipsychotic-induced weight gain. *J Neural Transm (Vienna)* 126: 27–33.
- Malhotra AK, Correll CU, Chowdhury NI, et al. (2012) Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. *Arch Gen Psychiatry* 69: 904–912.
- Martorell L, Muntané G, Porta-López S, et al. (2019) Increased levels of serum leptin in the early stages of psychosis. *J Psychiatr Res* 111: 24–29.
- McCarthy S, Das S, Kretzschmar W, et al. (2016) A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet* 48: 1279–1283.
- Mitchell AJ, Vancampfort D, De Herdt A, et al. (2013) Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull* 39: 295–305.
- Müller DJ and Kennedy JL (2006) Genetics of antipsychotic treatment emergent weight gain in schizophrenia. *Pharmacogenomics* 7: 863–887.
- Musil R, Obermeier M, Russ P, et al. (2015) Weight gain and antipsychotics: A drug safety review. *Expert Opin Drug Saf* 14: 73–96.
- Newcomer JW (2007) Metabolic considerations in the use of antipsychotic medications: A review of recent evidence. *J Clin Psychiatry* 68(Suppl. 1): 20–27.
- Nielsen MØ, Rostrup E, Wulff S, et al. (2016) Striatal reward activity and antipsychotic-associated weight change in patients with schizophrenia undergoing initial treatment. *JAMA Psychiatry* 73: 121–128.
- Pandit R, Cianci D, Ter Hark SE, et al. (2019) Phenotypic factors associated with amisulpride-induced weight gain in first-episode psychosis patients (from the OPTiMiSE cohort). *Acta Psychiatr Scand* 140: 283–290.
- Pillinger T, Beck K, Gobjila C, et al. (2017) Impaired glucose homeostasis in first-episode schizophrenia: A systematic review and meta-analysis. *JAMA Psychiatry* 74: 261–269.
- Pruim RJ, Welch RP, Sanna S, et al. (2010) LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics* 26: 2336–2337.
- Raben AT, Marshe VS, Chintoh A, et al. (2017) The complex relationship between antipsychotic-induced weight gain and therapeutic benefits: A systematic review and implications for treatment. *Front Neurosci* 11: 741.

- Rasmussen H, Ebdrup BH, Oranje B, et al. (2014) Neocortical serotonin2A receptor binding predicts quetiapine associated weight gain in antipsychotic-naïve first-episode schizophrenia patients. *Int J Neuropsychopharmacol* 17: 1729–1736.
- Reynolds GP and Kirk SL (2010) Metabolic side effects of antipsychotic drug treatment—pharmacological mechanisms. *Pharmacol Ther* 125: 169–179.
- Rummel-Kluge C, Komossa K, Schwarz S, et al. (2010) Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. *Schizophr Res* 123: 225–233.
- Simon V, van Winkel R and De Hert M (2009) Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry* 70: 1041–1050.
- Theisen FM, Gebhardt S, Haberhausen M, et al. (2005) Clozapine-induced weight gain: A study in monozygotic twins and same-sex sib pairs. *Psychiatr Genet* 15: 285–289.
- Tomasik J, Lago SG, Vázquez-Bourgon J, et al. (2019) Association of insulin resistance with schizophrenia polygenic risk score and response to antipsychotic treatment. *JAMA psychiatry* 76(8): 864–867.
- Vock C, Döring F and Nitz I (2008) Transcriptional regulation of HMG-CoA synthase and HMG-CoA reductase genes by human ACBP. *Cell Physiol Biochem* 22: 515–524.
- Volkow ND, Wang G-J and Baler RD (2011) Reward, dopamine and the control of food intake: Implications for obesity. *Trends Cogn Sci* 15: 37–46.
- Watanabe K, Taskesen E, van Bochoven A, et al. (2017) Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* 8: 1826.
- Watson HJ, Yilmaz Z, Thornton LM, et al. (2019) Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* 51: 1207–1214.
- Xue A, Wu Yang, Zhu Z, et al. (2018) Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat Commun* 9: 2941.
- Yengo L, Sidorenko J, Kemper KE, et al. (2018) Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. *Hum Mol Genet* 27: 3641–3649.
- Yu H, Wang L, Lv L, et al. (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 J-P, Lencz T, Zhang RX, et al. (2016) Pharmacogenetic associations of antipsychotic drug-related weight gain: A systematic review and meta-analysis. *Schizophr Bull* 42: 1418–1437.