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

Running Title: GWAS of amisulpride-induced weight gain

Sophie E. ter Hark[1], Stéphane Jamain[2,3,4], Dick Schijven[1], Bochao D. Lin[1], Mark K. Bakker[1], Anne Boland-Auge[5], Jean-François Deleuze[5], Réjane Troudet[2,3,4], Anil K. Malhotra[6], Sinan Guloksuz[7,8], Christiaan H. Vinkers[9,10], Bjørn H. Ebdrup[11,12], René S. Kahn[13,14], Marion Leboyer[2,3,4,15], Jurjen J. Luykx*[1,13,16]

1. Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, 3584 CG, The Netherlands.
2. Inserm U955, Psychiatrie Translationnelle, F-94000, Créteil, France
3. Université Paris Est, Faculté de Médecine, F-94000, Créteil, France
4. Fondation FondaMental, F-94000, Créteil, France
5. Centre National de Recherche en Génomique Humaine (CNRGH), Institut de Biologie François Jacob, CEA, Université Paris-Saclay, F-91000, Evry, France
6. The Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY USA

7. Department of Psychiatry and Neuropsychology, School for Mental Health Neuroscience Maastricht University Medical Center, Maastricht, The Netherlands
8. Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA
9. Department of Psychiatry, Amsterdam UMC (location VUmc), Amsterdam, The Netherlands
10. Department of Anatomy and Neurosciences, Amsterdam UMC (location VUmc), Amsterdam, The Netherlands
11. Centre for Neuropsychiatric Schizophrenia Research (CNSR), Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, Copenhagen University Hospital, DK-2600 Glostrup, Denmark
12. Department of Clinical Medicine, Faculty of Health and Medical Sciences University of Copenhagen, Copenhagen, Denmark
13. Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands.
14. Department of Psychiatry, Icahn School of Medicine, Mount Sinai, New York, USA
15. AP-HP, DHU Pe-PSY, Pôle de Psychiatrie et d'addictologie des Hôpitaux universitaires Henri Mondor, F-94000, Créteil, France
16. GGNet Mental Health, Apeldoorn, The Netherlands

*corresponding author:

Jurjen J. Luykx

Departments of Translational Neuroscience and Psychiatry

University Medical Center Utrecht

Universiteitsweg 100, 3584 CG Utrecht

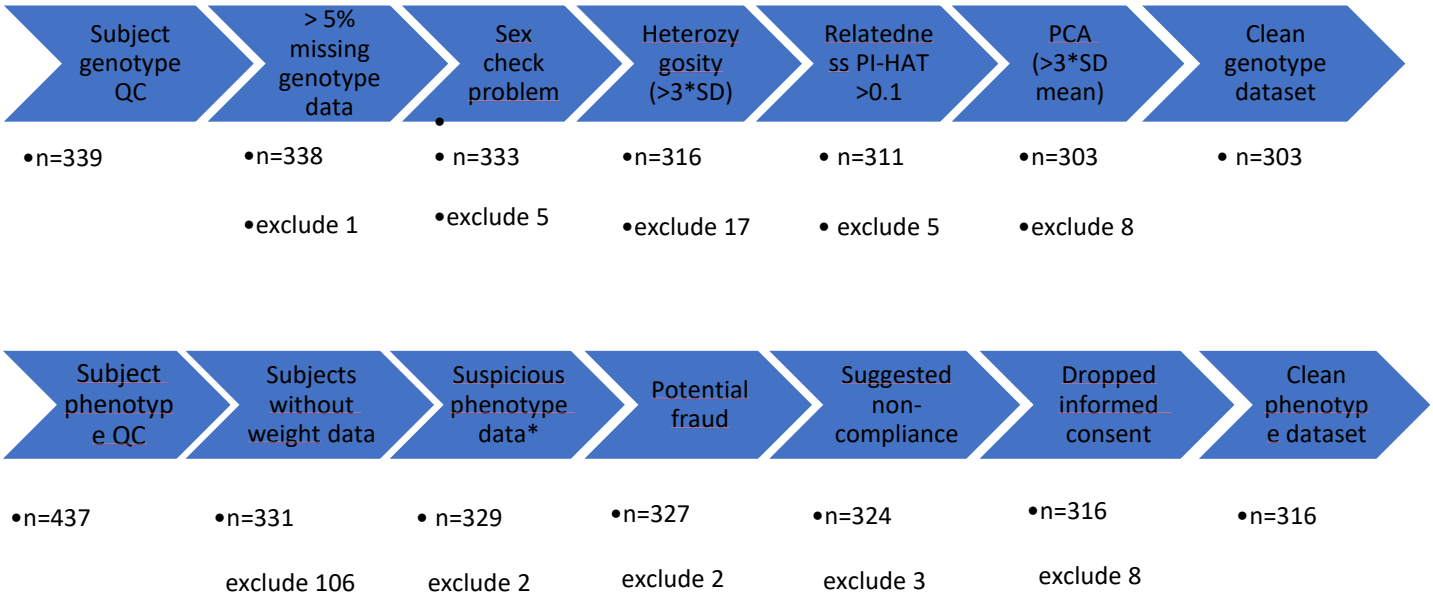
The Netherlands

E-mail: j.luykx@umcutrecht.nl

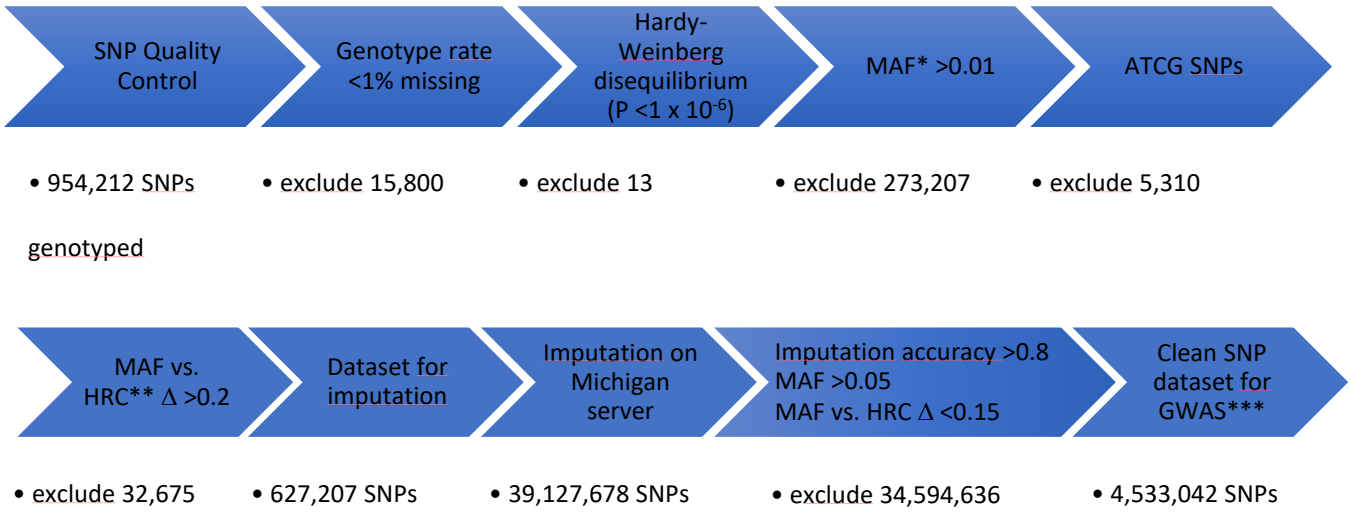
Telephone: +31 (0)88 75 68638

Fax: +31 (0)88 75 68638

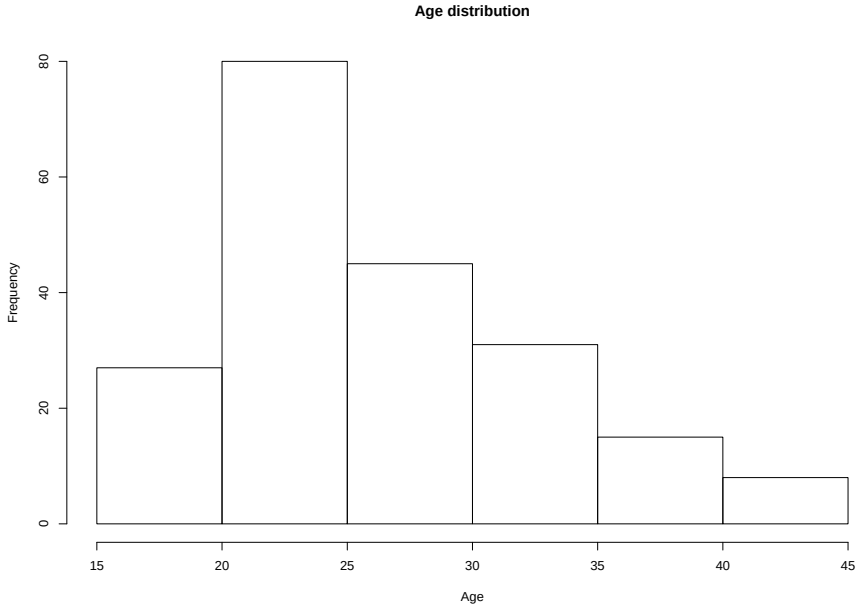
Supplementary figure 1. *Subject-level Quality Control (QC) steps: genotype and phenotype QC steps. Merging both cleaned datasets (genotype and phenotype) into one led to the current study population (n=206). *Suspicious phenotype data is classified as either BMI change >5 (n=1) or height <1.40 meters (n=1).*



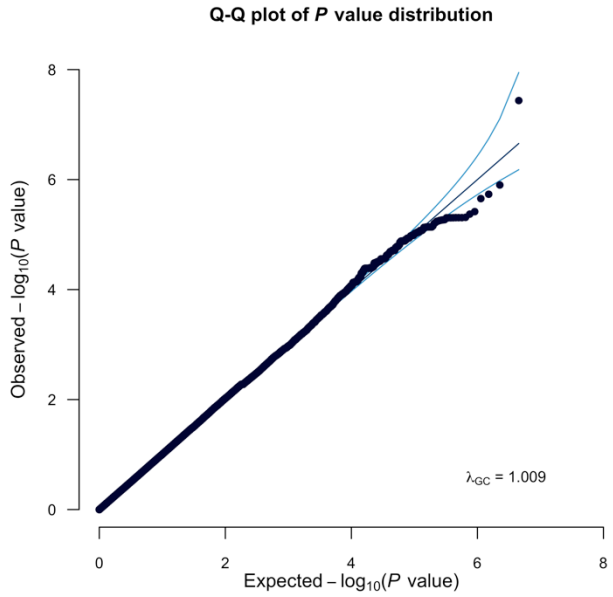
Supplementary figure 2. *SNP Quality Control (QC). *Minor allele frequency **Haplotype reference consortium.***Genome-wide association study*



Supplementary figure 3. *Age distribution in this GWAS, mean age=26.4 years (SD=6.3). The Y-axis showing frequency and age (years) on the x-axis.*



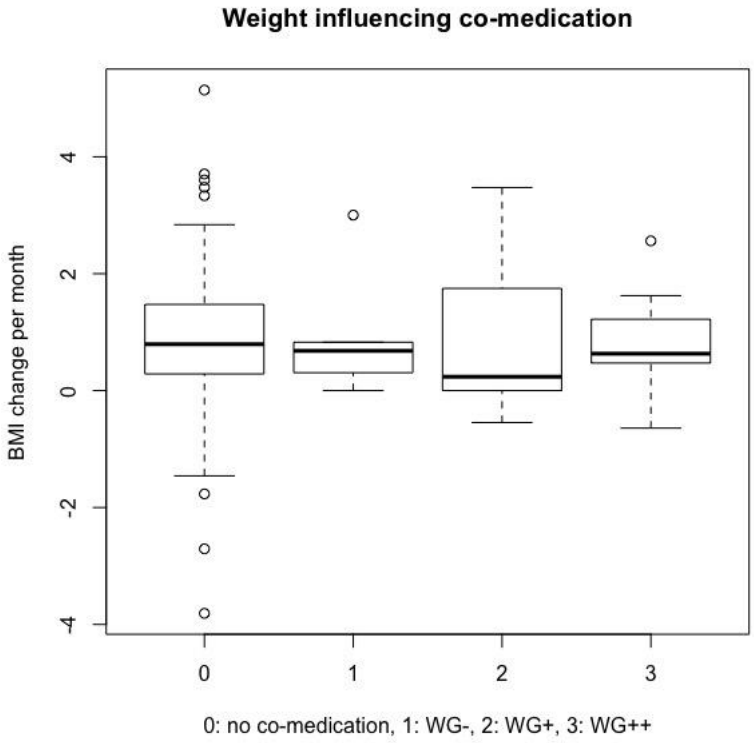
Supplementary figure 4. *The QQ (Quantile-Quantile) plot of the OPTiMiSE GWAS (n=206), suggesting minimal inflation of the test statistic.*



Supplementary table 1. *Ethnic origin of subjects.*

Race	Number of participants	Percentage (%)
European(EUR)	184	89,3%
African (AFR)	9	4,4%
Ad Mixed American (AMR)	6	2,9%
South Asian (SAS)	3	1,5%
East Asian (EAS)	2	0,9%
Unknown	2	0,9%

Supplementary figure 5. *The effect of potentially weight influencing co-medication (this did not include antipsychotics as antipsychotic co-medication was not allowed) on BMI change per month in OPTiMiSE. WG-: co-medication commonly associated with weight loss (methylphenidate or dextroamphetamine), WG+: co-medication commonly associated with weight gain (mirtazapine, carbamazepine, amitriptyline, clomipramine or SSRIs), WG++: co-medication commonly associated with substantial weight gain (lithium or valproate). Mean±SD BMI changes per month: group 0 (no co-medication): mean=0.90±1.13 (n=176), group 1 (WG-): mean=0.96±1.18 (n=5), group 2 (WG+): mean=0.95±1.61 (n=7) group 3 (WG++): mean=0.71±0.73 (n=18). (F_{ANOVA}=0.165, P=0.92)*



Supplementary table 2. *Sensitivity analyses*

	GWAS Model	Number of subjects	Top SNP	β [a]	P-value
1	A dominant GWAS model	206	rs78310016	1.04	2.817×10^{-07}
2	An additive GWAS model correcting for phenotypic variables associated with amisulpride-induced weight gain (MDD diagnosis, employment status)	195	rs78310016	1.033	1.696×10^{-07}

[a] β is the regression coefficient of the linear regression analysis

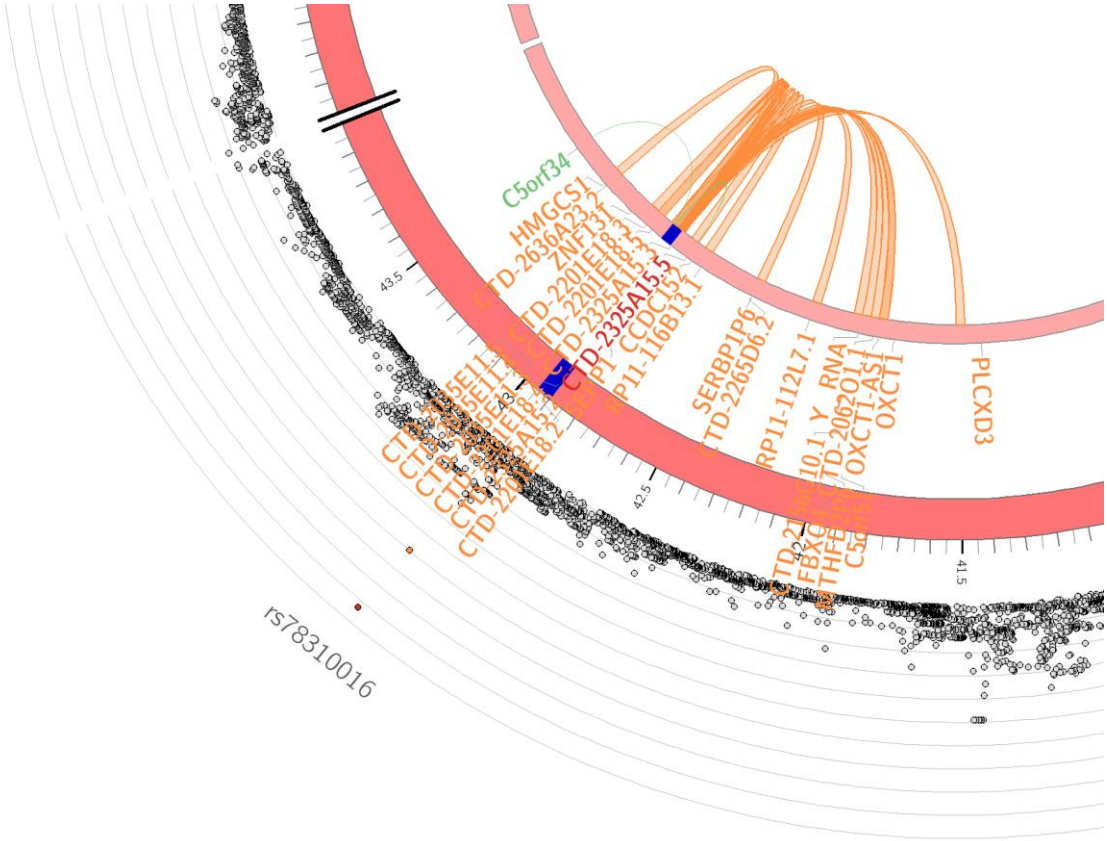
Supplementary table 3. *Top 3 SNPs on HMGCS1 associated with AiWG (MAF >0.01). Nominally significant associations (P <0.05) in are in bold.*

SNP	Location (GChr37)	A1	β [a]	STAT [b]	P-value
rs9292869	5:43292808	G	0.8105	2.641	**0.008962**
rs6894240	5:43291532	T	0.0120	2.328	**0.02097**
rs10069507	5:43301801	A	0.0203	1.854	0.06531

[a] β is the regression coefficient of the linear regression analysis

[b] STAT is the coefficient t-statistic

Supplementary figure 6. *Circos plot showing eQTL interactions (green) and chromatin interactions (orange) of rs78310016 (created in FUMA (Watanabe et al. 2017)).*



Supplementary table 4. *(Independent)* SNPs associated with amisulpride-induced weight gain at $P < 1 \times 10^{-05}$.

SNP	BP	A1	β	P
rs927899	1:201428553	C	0.7423	9.334×10^{-06}
rs2129108	2:179674929	A	0.7948	8.466×10^{-06}
rs9836481	3:41189723	A	0.9768	8.359×10^{-06}
rs57818938	5:2278069	T	0.9321	1.254×10^{-06}
rs41501	5:9663859	A	0.5127	7.933×10^{-06}
rs28800	5:9666545	A	0.5223	5.541×10^{-06}
rs78310016	5:42949635	G	1.052	3.656×10^{-08}
rs10070777	5:87424765	A	0.8786	3.824×10^{-06}
rs28716841	5:132733467	C	0.8716	9.452×10^{-06}
rs1107257	6:52229298	C	0.4668	9.623×10^{-06}
rs11979775	7:5342413	C	0.5007	5.351×10^{-06}
rs13230004	7:5345350	A	0.5336	4.244×10^{-06}
rs7024062	9:71745073	A	-0.5885	2.217×10^{-06}
rs112045010	12:64725714	C	0.9056	5.404×10^{-06}
rs17834779	14:63122799	A	0.4471	6.936×10^{-06}
rs1048164	15:40543104	A	0.4365	8.966×10^{-06}
rs76356591	16:4187065	T	0.5878	5.662×10^{-06}
rs17546654	17:42995095	A	0.5526	7.292×10^{-06}
rs8092589	18:43229254	A	0.4724	9.061×10^{-06}
rs10426669	19:4564781	G	0.7649	6.304×10^{-06}

Supplementary table 5*. Group difference in baseline characteristics between rs78310016 risk alleles carriers (i.e. 1 or more G alleles) and non-carriers.*

Characteristic	**Mean risk allele carriers**	**Mean risk allele non-carriers**	**Group difference (test performed)**
Age (years)	28.55	26.00	t=1.896, P=0.0664 (independent t-test)
Average daily dose (mg/day)	437.1	442.6	t=-0.1597, P=0.874 (independent t-test)
Days of study participation (days)	33.89	34.66	t=-0.7648, P=0.4491 (independent t-test)
PANSS change (%)	-24.72	-26.42	t=0.4044, P=0.6883 (independent t-test)
Sex (male/female)	18/10	121/57	X^2=0.29119, P=0.865 (Pearson's Chi-squared Yates)

Supplementary table 6. *Top 5 tissues from the MAGMA tissue expression analysis. Nominally significant associations (P <0.05) in are in bold.*

Tissue	Number of genes	β [a]	SE [b]	P-value
Small intestine	15884	0.0175	0.00966	**0.035**
Liver	15884	0.0120	0.00674	**0.038**
Stomach	15884	0.0203	0.01420	0.076
Colon	15884	0.0212	0.0165	0.100
Bladder	15884	0.0125	0.0150	0.202

[a] β is the regression coefficient of the linear regression analysis

[b] SE is the standard error

Supplementary table 7. *Look-up of previously significantly associated SNPs with AiWG in GWASs.*

Gene	Location (GChr37)	Outcome	Study information	Original AiWG association	OPTiMiSe
MC4R (Malhotra et al. 2012)	rs489693A (18:57882787)	BMI change after 6 or 12 weeks of treatment	<u>Discovery cohort (n=139)</u>: • quetiapine • risperidone • aripiprazole	P=2.8 x 10^{-7}	β^{a}=-0.033 STAT ^{b}=0.307 P=0.759 (NS)
			<u>First replication cohort (n=73):</u> • clozapine	P=1.40 x 10^{-4}	
			<u>Second replication cohort (n=40):</u> • quetiapine • risperidone • aripiprazole	P=0.007	
			<u>Third replication cohort (n=92)</u>: • haloperidol, • amisulpride • quetiapine • ziprasidone	P=0.042	

PTPRD(Yu et al. 2016)	rs10977144T (9:8474233)	BMI change after 8 weeks of treatment	<u>Discovery cohort (n=534)</u>: • risperidone • quetiapine • clozapine • aripiprazole • ziprasidone	P=9.26 x 10^{-9}	β^{a}=-0.270 STAT[b]= -1.277 P=0.203 (NS)
			<u>Replication cohort (n=236)</u> • risperidone • quetiapine	P=4.30 x 10^{-3}	

[a] β is the regression coefficient of the linear regression analysis

[b] STAT is the coefficient t-statistic

Supplementary table 8. *Look-up of previously significantly associated SNPs from (Zhang et al. 2016).*

Nominally significant associations (P <0.05) in are in bold.

Gene	SNP	Location (GChr37)	Region	Major allele/minor allele	Proxy SNP (r^2)	OPTiMiSE (n=206)
ADRA2A	rs1800544	10:112836503		C/G	rs2484515G (1.0)	β[a]= 0.1052, P=0.3516
ADRB3	rs4994	8:37966280	(Missense)	T/C	rs2071493C (1.0)	β=0.1946, P=0.2942
BDNF	rs6265	11:27658369	(Missense)	G/A	rs4923464T (1.0)	β=-0.03956, P=0.7602
DRD2	rs1799732	11:113475529	Intron	C/-	rs11214613A (1.0)	β=0.2779, P=0.08309
DRD2	rs6275A	11:113283477	Exon (synon)	A/G		β=0.0406, P=0.7074
DRD2	**rs7131056A**	**11:113329774**		**C/A**		**β=0.2079, P=0.04099**
GNB3	rs5443T	12:6954875	Exon (synon)	C/T		β=-0.02676, P=0.8048
HTR2C	rs3813929	X: 113871991	Exon 5	G/C		NA[b]
HTR2C	rs518147	X:113818582	5'UTR	G/C		NA[b]

INSIG2	rs17047764	2:118868582		G/C	rs3849327C (1.0)	β=0.1282, P=0.3112
MC4R	rs489693A	18:57882787		C/A		β=-0.03292, P=0.759
SNAP25	rs1051312C	20:10287088	3'UTR	T/C		β=0.169, P=0.1554

[a] β is the regression coefficient of the linear regression analysis

[b] NA not available

References

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.* doi: 10.1001/archgenpsychiatry.2012.191

Watanabe K, Taskesen E, van Bochoven A, Posthuma D (2017) Functional mapping and annotation of genetic associations with FUMA. *Nat Commun 8:1826.* doi: 10.1038/s41467-017-01261-5

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.* doi: 10.1093/schbul/sbv179

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*. doi: 10.1093/schbul/sbw058