Title: Association of CRTC1 polymorphisms with obesity markers in subjects from the general population with lifetime depression.

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S1 : Comparison between the different studies used to test the association between *CRTC1* polymorphisms and obesity markers:

	PsyCoLaus	Radiant study	NESDA/NTR
N (case-control)	1,434 - 1,920	2,338 - 810	
MDD diagnosis	DSM-IV, DIGS interview	ICD–10 and/or DSM–IV, SCAN interview	DSM-IV, Composite Interview Diagnostic Instrument
Investigated obesity marker	Fat mass BMI Waist circumference (all measured)	BMI (self-reported)	BMI (measured)
Investigated *CRTC1* SNPs	- *rs6510997C>T* - *rs7257846T>C*[&]	- *rs2075017T>C*[$] - *rs3746266A>G*	- *rs6510997C>T* - *rs3746266A>G*
Genotyping method	Affymetrix GeneChipR Human Mapping 500K array	Illumina HumanHap610-Quad BeadChips	Affymetrix-Perlegen 5.0, Illumina 370K, Illumina 660K, Illumina Omni 1M and Affymetrix 6.0

[&] *rs7257846T>C* is in very strong linkage disequilibrium with *rs3746266A>G* (r^2=0.93)

[$] *rs2075017T>C* is in complete linkage disequilibrium with *rs6510997C>T* (r^2=1)

Abbreviations: MDD: major depressive disorders, BMI: body mass index, DIGS: semi-structured Diagnostic Interview for Genetic Studies, CRTC1: CREB-regulated transcription coactivator 1, SNPs: single nucleotide polymorphism

S2: Characteristics of the PsyCoLaus population:

		MDD status			
	All participants	**Atypical depressed**	**Non atypical depressed**	**No MDD**	**p-value[g]**
Total No.	3362	424	1010	1920	
Women, % [95CI]	53.1	72.9 [68.6-77.1]	63.1 [60.1-66.1]	43.6 [41.7-45.8]	0.001[h]
Age, mean (SD), y	51.5 (8.5)	50.8 (8.2)	51.3 (8.5)	51.8 (8.5)	0.297[i]
SES[a], mean (SD)	3.4 (1.3)	3.3 (1.2)	3.4 (1.3)	3.4 (1.2)	0.015[i]
Married, % [95CI]	58.5	50.9 [46.2-55.7]	49.2 [46.1-52.3]	65.2 [63.1-67.3]	0.549[h]
Anxiety disorders[b], % [95CI]	19.7	33.9 [29.4-38.4]	27.8 [25.0-30.5]	12.4 [10.9-13.9]	0.021[h]
Smoking status, % [95CI]					
Former	32.7	29.7 [25.3-34.1]	32.8 [29.9-35.7]	33.3 [31.2-35.4]	0.257[h]
Current	27.7	30.9 [26.5-35.3]	30.9 [28.0-33.7]	25.2 [23.3-27.2]	0.998[h]
Alcohol intake[c], % [95CI]					
Low	57.9	61.6 [56.9-66.2]	57.8 [54.9-61.0]	57.0 [54.8-59.2]	0.201[h]
High	16.8	10.8 [7.9-13.8]	14.9 [12.7-17.0]	19.1 [17.3-20.8]	0.044[h]
Substance dependence[d], % [95CI]	5.9	5.9 [3.7-8.2]	6.6 [5.0-8.1]	5.6 [4.6-6.6]	0.643[h]
Physically active[e], % [95CI]	57.8	55.0 [49.8-60.2]	59.8 [56.5-63.0]	57.4 [55.0-59.8]	0.121[h]
Antidepressant use, % [95CI]	8.7	22.6 [18.6-26.6]	12.4 [10.3-14.4]	3.7 [2.9-4.5]	<0.001[h]
Age at MDD onset, mean (SD), y	NA	33.1 (13.5)	33.8 (12.6)	NA	0.467[i]
Time spent in episodes, mean (SD), wk	NA	230.3 (398.4)	160.2 (275.2)	NA	<0.001[i]
Appetite, % [95CI]	NA	41.5 [36.8-46.2]	5.1 [3.8-6.5]	NA	<0.001[h]
BMI, mean (SD)	25.6 (4.6)	26.5 (5.2)	24.8 (4.4)	25.8 (4.4)	<0.001[i]
MDE current, % [95CI]	7.5	28.1 [23.8-32.4]	13.1 [11.0-15.1]	NA	<0.001[h]

Abbreviation: MDD, major depressive disorder; MDE, major depressive episode; SES, socioeconomic status; BMI, body mass index; 95CI, 95% confidence interval; NA, not applicable.

a Hollingshead Four-Factor Index of Social Status (5 is the highest status).

b Generalized anxiety disorder, social phobia, panic disorder, or agoraphobia.

c Number of drinks per week (10-12g of ethanol/drink): low = 1-13 and high = 14 or more.

d Lifetime dependence on cocaine, heroin, stimulant, sedative, or hallucinogen.
e Physically active more than 20 minutes twice a week.
g comparison between atypical and non atypical depressives.
h Chi-square test.
i Wilcoxon-Mann-Whitney test.

S3: Association between *CRTC1 rs6510997C>T* polymorphism and fat mass, BMI and waist circumference in the PsyCoLaus sample, among sex-stratified and MDD subjects and controls adjusting for other co-variables:

		Fat mass		BMI		Waist circumference	
	n	Estimates (95% C.I.)	p-value	Estimates (95% C.I.)	p-value	Estimates (95% C.I.)	p-value
All subjects	3362	-0.71 (-1.3 to -0.11)	**0.02**	-0.27 (-0.58 to 0.05)	0.09	-0.61 (-1.53 to 0.32)	0.20
Males	1576	-0.01 (-0.54 to 0.53)	0.97				
Females	1786	-1.08 (-1.8 to -0.36)	**0.003**				
Subjects with MDD	1434	-1.34 (-2.07 to -0.6)	**<0.001**				
Controls	1920	-0.02 (-0.59 to 0.56)	0.96				

GLM model adjusted for age, sex (when appropriate), Socioeconomic status, Drug Dependence, High Alcohol consumption, Low Alcohol consumption, Former tabac consumer and Current tabac consumer

BMI: body mass index, C.I.: confidence interval, MDD: Major depressive disorder

S4: Association between *CRTC1 rs7257846C>T* polymorphism and fat mass, BMI and waist circumference in the total, depressive cases and controls of the PsyCoLaus study sample:

		Fat mass		BMI		Waist circumference	
	n	Estimates (95% C.I.)	p-value	Estimates (95% C.I.)	p-value	Estimates (95% C.I.)	p-value
Total population	3362	-0.65 (-1.31 - 0.02)	0.06	-0.32 (-0.66 - 0.02)	0.07	-0.91 (-1.91 - 0.09)	0.07
Male	1576	-0.18 (-0.75 - 0.39)	0.53	-0.30 (-0.72 - 0.12)	0.16	-0.89 (-2.04 - 0.27)	0.13
Female	1786	-1.06 (-1.85 - -0.28)	**0.008**	-0.37 (-0.88 - 0.13)	0.15	-1.13 (-2.40 - 0.14)	0.08
Pre-menopause	823	-0.66 (-1.86 - 0.55)	0.28	-0.40 (-1.07 - 0.27)	0.25	-1.47 (-3.17 - 0.23)	0.09
menopause	940	-1.29 (-2.36 - -0.21)	**0.02**	-0.43 (-1.18 - 0.31)	0.25	-0.89 (-2.76 - 0.97)	0.35
Controls	1920	-0.17 (-0.80 - 0.45)	0.59	-0.17 (-0.60 - 0.25)	0.42	-0.58 (-1.70 - 0.55)	0.32
Male	1083	0.15 (-0.54 - 0.84)	0.67	-0.10 (-0.61 - 0.41)	0.70	-0.28 (-1.66 - 1.11)	0.70
Female	837	-0.68 (-1.81 - 0.46)	0.24	-0.32 (-1.05 - 0.42)	0.40	-1.06 (-2.93 - 0.80)	0.26
Pre-menopause	366	-1.00 (-2.73 - 0.74)	0.26	-0.23 (-1.20 - 0.74)	0.64	-1.16 (-3.64 - 1.32)	0.36
menopause	463	-0.40 (-1.92 - 1.13)	0.61	-0.40 (-1.46 - 0.67)	0.47	-0.94 (-3.64 - 1.77)	0.50
Depressive cases	1434	-1.26 (-2.05 - -0.46)	**0.002**	-0.57 (-1.10 - -0.05)	**0.03**	-1.61 (-2.97 - -0.25)	**0.02**
Male	488	-0.87 (-1.90 - 0.16)	0.10	-0.71 (-1.44 - 0.03)	0.06	-2.12 (-4.25 - 0.01)	0.05
Female	946	-1.47 (-2.55 - -0.38)	**0.008**	-0.48 (-1.18 - 0.22)	0.18	-1.3 (-3.05 - 0.44)	0.14
Pre-menopause	457	-0.87 (-2.51 - 0.78)	0.30	-0.62 (-1.56 - 0.32)	0.20	-2.01 (-4.36 - 0.34)	0.09
menopause	475	-2.12 (-3.57 - -0.67)	**0.004**	-0.47 (-1.51 - 0.57)	0.38	-0.79 (-3.36 - 1.78)	0.55
Depressive cases							
Atypical depression	424	-1.90 (-3.44 - -0.36)	**0.02**	-0.67 (-1.73 - 0.40)	0.22	-2.33 (-5.07 - 0.41)	0.10
Non-atypical depression	1010	-1.09 (-2.01 - -0.18)	**0.02**	-0.62 (-1.20 - -0.04)	**0.04**	-1.48 (-2.99 - 0.03)	0.06
Depression, no medication	607	-0.71 (-1.85 - 0.43)	0.22	-0.44 (-1.19 - 0.31)	0.25	-1.62 (-3.60 - 0.37)	0.11
Depression, medication	827	-1.65 (-2.75 - -0.55)	**0.003**	-0.66 (-1.39 - 0.07)	0.08	-1.52 (-3.37 - 0.33)	0.11
Atypical Depression	264	-3.14 (-5.20 - -1.08)	**0.003**	-1.18 (-2.55 - 0.20)	0.09	-2.62 (-6.09 - 0.85)	0.14
Non-atypical depression	563	-1.07 (-2.35 - 0.20)	0.10	-0.52 (-1.36 - 0.32)	0.23	-1.21 (-3.35 - 0.93)	0.27

Models were for age and sex (when appropriate).

BMI: body mass index, C.I.: confidence interval

Summary of the psychiatric samples in the article by Choong et al (Choong et al., 2013):

Caucasian subjects treated with atypical antipsychotics (AP) and/or mood stabilizers (MS) lithium and valproate, were included in this study. Associations between *CRTC1* SNPs and BMI were first investigated in Sample 1, and positive results were replicated in samples 2 and 3.

Samples 1 and 3

Samples 1 (S1, n=152) and 3 (S3, n=118) are two retrospective studies, S1 was conducted in out-patient psychiatric centers of Geneva University Hospital from 2006 to 2008, while S3 was conducted in two out-patient psychiatric centers of Lausanne (Lausanne University Hospital (CHUV) and a private psychiatric center) from 2010 to 2011. Treatment for more than 3 months (S1) and 9 months (S3) with clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate (S1 and S3), and/or aripiprazole, amisulpride, and/or sertindole (S3) was indicated as inclusion criteria. At inclusion of both samples, body weight and height were measured for all patients, while their baseline weight before the initiation of the current treatment and/or at different times during treatment was collected from the medical file or was self-reported (baseline weight was self-reported in 76% of S1 and 78% of S3). In the subset of patients for whom both data were available, self-reported weight was in agreement with weight obtained from the medical files (n=29, r^2>0.9 for S1 and n=39, r^2>0.8 for S3). In addition to the baseline and the measured weight at inclusion, 54% and 29% of patients in S1 and S3, respectively, had at least one additional recorded weight from the medical files during the study duration which was also included in the statistical analysis. Finally, self-reported weights before the initiation of the first psychotropic treatment were also obtained for most of the patients (98% and 95% for S1 and S3, respectively). Both samples consisted of one single visit performed during the usual

clinical psychiatric follow-up. 51% of patients in S1 and 27% of S3 were diagnosed with mood disorder.

Sample 2

A follow-up study is ongoing since 2007 in all psychiatric wards of CHUV. 174 patients with newly prescribed aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and/or lithium, valproate were recruited. Sixty-six percent had already received other psychotropic treatments and were included in the study after having switched medication. No wash-out period was required. Weights and clinical variables were prospectively recorded at several time points during the first 12 months according to published recommended monitoring guidelines (i.e. before starting the current psychotropic drugs, then at months 1, 2, 3, 6, 9, and 12).(Association and American Psychiatric Association, 2005; Choong et al., 2008) At the baseline and the follow-up visits, the severity of disorders was rated using the Clinical Global Impression (CGI) rating scale, which is a commonly used measure of psychotic symptom severity.(Busner and Targum, 2007) This scale measured the severity of the disorder at each visit relative to the baseline state at the introduction of the newly studied psychotropic drug, rather than the onset of the disorder. 41% of patients in this sample were diagnosed with mood disorder.

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