

Supplementary Table S1: List of candidate genes, their chromosomal location and rationale for their inclusion.

Gene symbol	Description	Location	Rationale
BDNF	brain-derived neurotrophic factor	11p13	Reported pharmacogenetic associations ^{1,2}
NTRK2	neurotrophic tyrosine kinase, receptor, type 2	9q22.1	BDNF receptor
GSK3A	glycogen synthase kinase 3 alpha	19q13.2	Related to GSK3B
GSK3B	glycogen synthase kinase 3 beta	3q13.3	Reported pharmacogenetic associations ^{3,4}
AKT1	serine-threonine protein kinase 1	14q32.32	Involved in BDNF signaling
NR3C1	glucocorticoid receptor	5q31.3	Reported pharmacogenetic association ⁵
CRHR1	Corticotropin-releasing factor receptor 1	17q12-q22	Involved in depression pathogenesis ⁶
CREB1	Cyclic AMP response element binding protein	2q34	Reported pharmacogenetic association ⁷
SLC6A4	serotonin transporter	17q11.1	Reported pharmacogenetic associations ⁸
SLC6A2	norepinephrine transporter	16q12.2	Reported pharmacogenetic association ⁹
SLC6A3	dopamine transporter	5p15.3	Dopamine signaling
HTR1A	serotonin receptor 1A	5q11.2-q13	Reported pharmacogenetic association ²
HTR1B	serotonin receptor 1B	6q13	Serotonin signaling
HTR2A	serotonin receptor 2A	13q14-q21	Reported pharmacogenetic association ¹⁰
HTR2B	serotonin receptor 2B	2q36.3-q37.1	Serotonin signaling
HTR2C	serotonin receptor 2C	Xq24	Serotonin signaling
HTR3A	serotonin receptor 3A	11q23.1	Serotonin signaling
HTR3B	serotonin receptor 3B	11q23.1	Serotonin signaling
HTR4	serotonin receptor 4	5q31-q33	Serotonin signaling
HTR5A	serotonin receptor5A	7q36.1	Serotonin signaling
HTR7	serotonin receptor 7	10q21-q24	Serotonin signaling
ADRA1A	adrenergic alpha-1A receptor	8p21-p11.2	Norepinephrine signaling
ADRA1B	adrenergic alpha-1B receptor	5q23-q32	Norepinephrine signaling
ADRA2A	adrenergic alpha-2A receptor	10q24-q26	Norepinephrine signaling
ADRA2B	adrenergic alpha-2B receptor	2p13-q13	Norepinephrine signaling
ADRA2C	adrenergic alpha-2C receptor	4p16	Norepinephrine signaling
DRD1	dopamine receptor D1	5q35.1	Dopamine signaling
DRD2	dopamine receptor D2	11q23	Dopamine signaling
DRD3	dopamine receptor D3	3q13.3	Dopamine signaling

DRD4	dopamine receptor D4	11p15.5	Dopamine signaling
DRD5	dopamine receptor D5	4p16.1	Dopamine signaling
GRIK1	glutamate receptor, ionotropic, kainate 1	21q22.11	Glutamate signaling
GRIK2	glutamate receptor, ionotropic, kainate 2	6q16.3-q21	Reported pharmacogenetic association ¹¹
GRIK3	glutamate receptor, ionotropic, kainate 3	1p34-p33	Glutamate signaling
GRIK4	glutamate receptor, ionotropic, kainate 4	11q22.3	Reported pharmacogenetic association ¹²
GRIK5	glutamate receptor, ionotropic, kainate 5	19q13.2	Glutamate signaling
GRIA1	glutamate receptor, ionotropic, AMPA 1	5q31.1	Glutamate signaling
GRIA2	glutamate receptor, ionotropic, AMPA 2	4q32-q33	Glutamate signaling
GRIA3	glutamate receptor, ionotropic, AMPA 3	Xq25-q26	Reported pharmacogenetic association ¹¹
GRIA4	glutamate receptor, ionotropic, AMPA 4	11q22	Glutamate signaling
GRIN1	glutamate receptor, ionotropic, N-methyl D-aspartate 1	9q34.3	Glutamate signaling
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16p13.2	Glutamate signaling
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	12p12	Glutamate signaling
GRIN2C	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	17q.25	Glutamate signaling
GRIN2D	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	19q13.1-qter	Glutamate signaling
GRIN3A	glutamate receptor, ionotropic, N-methyl D-aspartate 3A	9q31.1	Glutamate signaling
GNB3	guanine nucleotide binding protein (G protein), beta polypeptide 3	12p.13	Reported pharmacogenetic association ¹³
FKBP5	FK506 binding protein 5	6p21.3-p21.2	Reported pharmacogenetic association ^{14,15}
TPH1	tryptophan hydroxylase 1	11p15.3-p14	Reported pharmacogenetic associations ²
TPH2	tryptophan hydroxylase 2	12q21.1	Serotonin synthesis
MAOA	monoamine oxidase A	Xp11.3	Monoamine signaling
COMT	catechol-O-methyltransferase	22q11.21	Monoamine signaling
AVPR1A	arginine vasopressin receptor 1A	12q14-q15	Related to AVPR1B
AVPR1B	arginine vasopressin receptor 1B	1q32	Involved in antidepressant effect ¹⁶
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	7q21.1	Reported pharmacogenetic association ¹⁷
P2RX7	purinergic receptor P2X, ligand-gated ion channel, 7	12q24	Associated with depression ^{18,19}
PCLO	piccolo (presynaptic cytomatrix protein)	7q11.23-q21.3	Associated with depression ²⁰
ANK3	ankyrin 3, node of Ranvier (ankyrin G)	10q21	Associated with bipolar affective disorder ^{21,22}
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	12p13.3	Associated with bipolar affective disorder ^{21,23}
ZNF804A	zinc finger protein 804A	2q32.1	Associated with schizophrenia ²⁴
LEP	leptin	7q31.3	Antidepressant effect of leptin ^{25,26}
LEPR	leptin receptor	1p31	Antidepressant effect of leptin ^{25,26}
PDE1A	phosphodiesterase 1A, calmodulin-dependent	2q32.1	Reported pharmacogenetic association ²⁷

PDE9A	phosphodiesterase 9A	21q22.3	Reported pharmacogenetic association ²⁷
PDE11A	phosphodiesterase 11A	2q31.2	Reported pharmacogenetic association ²⁷
PSMB4	proteasome (prosome, macropain) subunit, beta type, 4	1q21	Reported pharmacogenetic association ²⁸
TBX21	T-box 21	17q21.32	Reported pharmacogenetic association ²⁸
CD3E	CD3e molecule, epsilon (CD3-TCR complex)	11q23	Reported pharmacogenetic association ²⁸
PRKCH	protein kinase C, eta	14q22-q23	Reported pharmacogenetic association ²⁸
IL6	interleukin 6 (interferon, beta 2)	7p21	Involved in depression ²⁹
PSMD9	proteasome (prosome, macropain) 26S subunit, non-ATPase, 9	12q24.31-q24.32	Reported pharmacogenetic association ²⁸
STAT3	signal transducer and activator of transcription 3	17q21.31	Reported pharmacogenetic association ²⁸

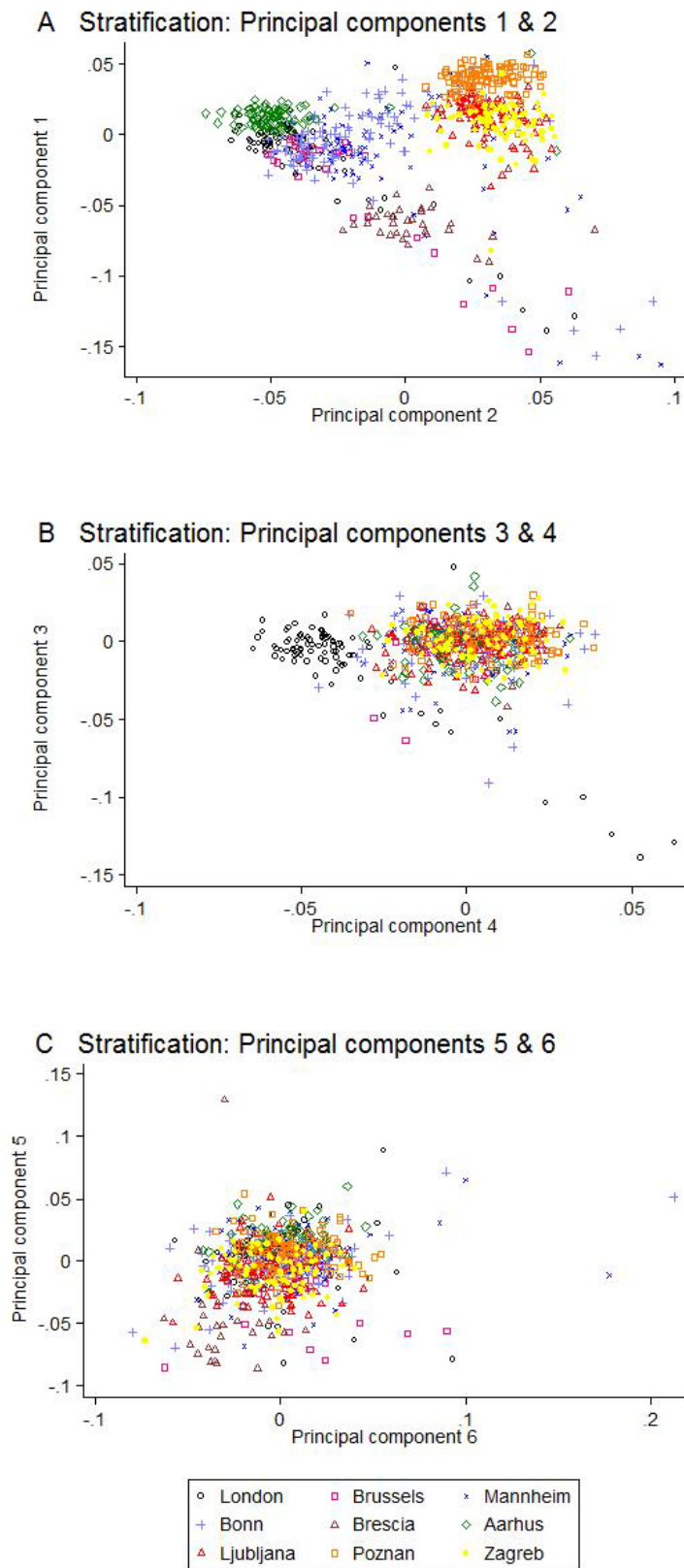
Supplementary Table S2: Strongest associated markers in each candidate gene in the whole sample analysis.

Chromosome	Gene	Markers per gene	Strongest associated marker	MAF	Alleles	Whole sample		Escitalopram		Nortriptyline		Gene x drug		HWE p-value
						<i>b</i>	<i>p</i>	<i>b</i>	<i>p</i>	<i>b</i>	<i>p</i>	<i>b</i>	<i>p</i>	
1	GRIK3	31	rs11801494	0.10	T/C	8.7	0.00132	8.4	0.02852	9.3	0.01593	1.4	0.79690	0.38870
1	LEPR	44	rs913199	0.45	T/G	4.5	0.00346	2.5	0.23710	7.1	0.00215	4.4	0.15940	0.49460
1	PSMB4	5	rs1887545	0.20	A/G	0.9	0.64780	1.0	0.72780	0.5	0.87680	-0.6	0.88100	0.05613
1	AVPR1B	11	rs28419084	0.08	T/C	4.3	0.14600	8.7	0.02513	-2.2	0.62170	-11.6	0.05068	0.61080
2	ADRA2B	5	rs749457	0.34	G/A	-1.4	0.40960	-2.1	0.37110	-0.2	0.93210	2.2	0.50190	0.67730
2	PDE11A	108	rs7594290	0.06	T/C	6.6	0.04947	5.9	0.18340	7.1	0.16630	0.8	0.90010	0.49410
2	PDE1A	79	rs17649232	0.08	C/T	-5.8	0.04603	-4.7	0.26520	-6.5	0.11390	-1.5	0.80390	0.21730
2	ZNF804A	31	rs1021043	0.38	G/A	-3.7	0.02331	-5.0	0.02221	-1.9	0.43510	2.9	0.37850	0.63250
2	CREB1	7	rs2551949	0.21	G/A	1.5	0.44010	0.4	0.87940	2.8	0.35750	2.4	0.54390	0.82340
2	HTR2B	4	rs13394402	0.16	T/G	3.8	0.06276	4.5	0.09844	3.3	0.28970	-0.8	0.85230	0.01888
3	SLC6A1	43	rs9682960	0.13	C/T	5.0	0.03117	7.2	0.02488	3.2	0.34620	-3.9	0.40830	0.73760
3	DRD3	23	rs7631540	0.45	T/C	2.8	0.08330	2.7	0.21530	3.2	0.19970	0.2	0.94520	0.32370
3	GSK3B	24	rs11919783	0.10	A/G	-6.1	0.01846	-10.1	0.00482	-1.5	0.69360	8.4	0.10350	1.00000
4	ADRA2C	5	rs12506413	0.19	T/C	-3.0	0.13760	-1.3	0.62310	-6.1	0.04878	-4.7	0.25090	0.53810
4	DRD5	4	rs1878943	0.17	T/C	-2.5	0.23870	-1.8	0.53760	-3.1	0.31480	-1.5	0.72320	0.89330
4	GRIA2	9	rs4691394	0.14	A/G	2.7	0.23020	4.2	0.17190	1.3	0.69400	-3.4	0.44670	0.20720
5	SLC6A3	27	rs11133767	0.34	T/C	-3.9	0.02023	-5.1	0.02583	-3.0	0.23440	1.9	0.56880	0.93270
5	HTR1A	2	rs1364043	0.22	G/T	-2.5	0.17980	-6.4	0.01261	2.1	0.44280	8.6	0.02093	0.44770
5	NR3C1	21	rs2963156	0.23	T/C	3.3	0.08692	3.4	0.20950	3.3	0.22990	0.1	0.98330	0.45550
5	HTR4	41	rs1345697	0.49	C/T	2.5	0.11040	0.5	0.80710	5.1	0.03376	4.9	0.12190	0.65170
5	GRIA1	99	rs9324752	0.31	G/A	4.0	0.02963	4.5	0.07040	4.0	0.15390	-0.8	0.82950	0.00016
5	ADRA1B	22	rs6892282	0.44	T/G	4.1	0.00999	3.8	0.06668	4.2	0.09307	0.1	0.97440	0.81940
5	DRD1	23	rs266004	0.49	T/G	-2.4	0.11940	-1.6	0.45510	-3.3	0.14480	-2.1	0.48690	0.32800
6	FKBP5	23	rs6931945	0.35	A/G	-2.6	0.09076	-4.0	0.05179	-1.2	0.62760	3.2	0.30740	0.00115
6	HTR1B	13	rs1936158	0.37	T/G	2.6	0.10130	5.7	0.00962	-1.0	0.69170	-6.4	0.04840	0.68740
6	GRIK2	166	rs2782900	0.31	C/T	3.5	0.03780	4.3	0.05071	2.1	0.41230	-2.1	0.54540	0.60140
7	IL6	17	rs7801617	0.11	A/G	4.6	0.07486	10.7	0.00213	-2.4	0.52950	-13.8	0.00689	0.44170
7	PCLO	82	rs16887353	0.10	G/A	4.4	0.09487	1.8	0.59490	7.5	0.07195	5.5	0.30380	0.68500
7	ABCB1	65	rs7793196	0.16	G/A	-4.1	0.04629	-4.0	0.15110	-4.7	0.12890	-1.0	0.80280	0.02717

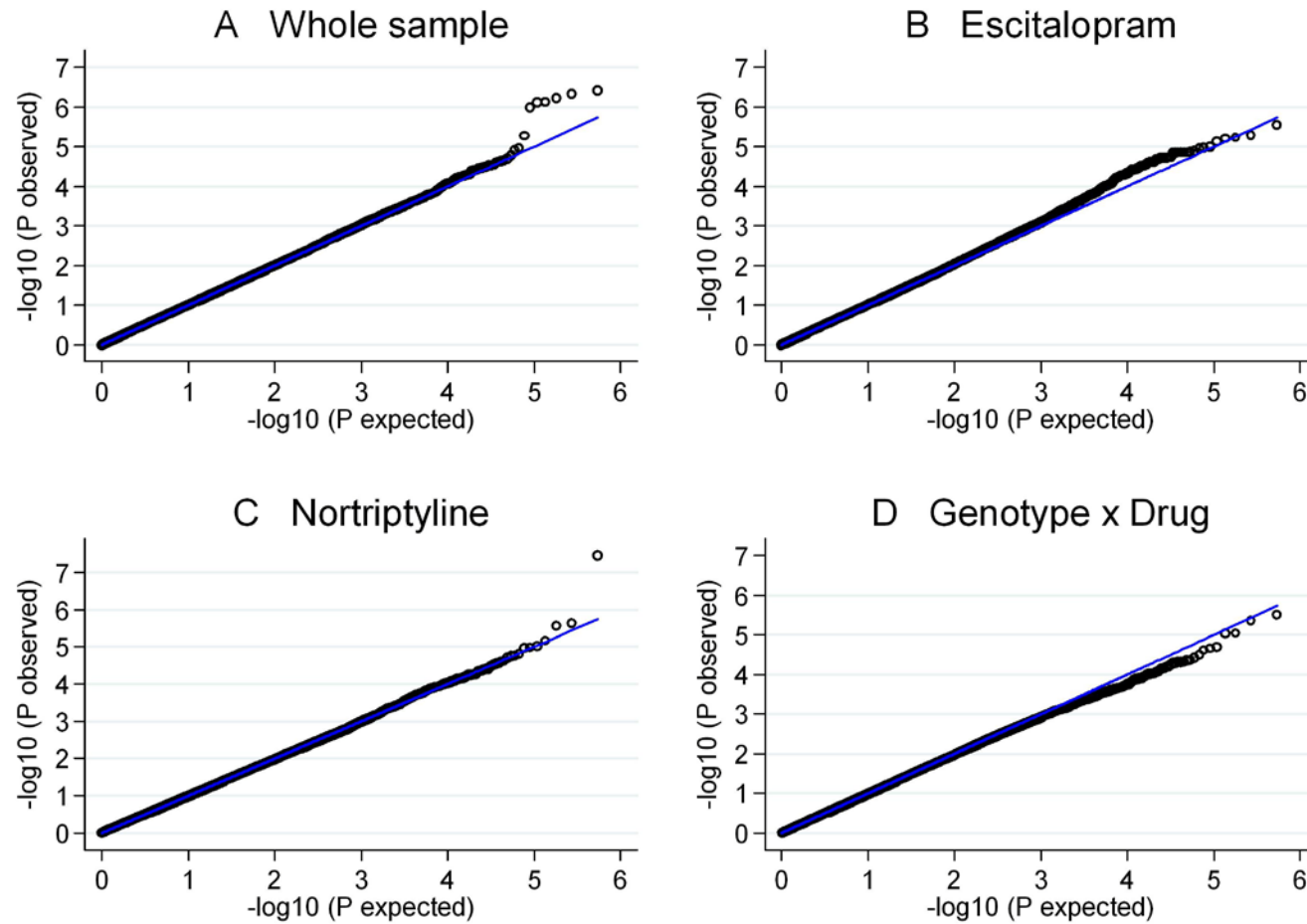
7	LEP	12	rs1466146	0.12	A/G	-4.8	0.04779	-4.6	0.16480	-4.8	0.18130	0.0	0.99800	1.00000
7	HTR5A	18	rs2241859	0.30	T/G	-2.3	0.19730	-2.5	0.28760	-1.8	0.49300	0.4	0.90600	0.17770
8	ADRA1A	69	rs13261597	0.06	G/A	-10.8	0.00095	-10.7	0.01200	-11.0	0.03286	-0.4	0.94710	1.00000
9	NTRK2	82	rs17087753	0.09	C/T	-5.7	0.02693	-9.4	0.00320	0.5	0.90730	9.8	0.07868	0.03973
9	GRIN3A	62	rs10081707	0.37	A/G	3.1	0.05674	4.4	0.04554	1.0	0.67890	-3.4	0.30050	0.57090
9	GRIN1	3	rs10870198	0.35	G/A	4.0	0.01774	3.8	0.09270	4.8	0.06084	1.1	0.75100	0.28600
10	ANK3	121	rs12782806	0.14	C/T	-4.9	0.02728	-3.8	0.22060	-5.7	0.08501	-1.7	0.69950	0.43950
10	HTR7	23	rs7920627	0.03	C/T	-13.0	0.00288	-9.0	0.12910	-17.7	0.00645	-8.5	0.32990	0.54750
10	ADRA2A	10	rs7908645	0.29	G/T	-3.7	0.03899	-1.6	0.49720	-6.0	0.02619	-4.3	0.22710	0.19860
11	DRD4	6	rs11246226	0.50	A/C	1.7	0.28830	-0.1	0.97950	3.4	0.14950	3.3	0.30240	0.32870
11	TPH1	8	rs17794760	0.18	A/G	-3.4	0.09158	-4.3	0.10340	-2.1	0.50240	2.3	0.57990	0.43670
11	BDNF	14	rs2203877	0.48	C/T	2.4	0.11960	2.8	0.16850	1.7	0.49470	-1.2	0.70600	0.36660
11	GRIA4	57	rs11226845	0.08	C/T	-10.2	0.00077	-9.8	0.02901	-10.1	0.01658	-0.6	0.91520	0.41740
11	DRD2	29	rs2734849	0.46	A/G	-2.3	0.16680	-3.4	0.12990	-0.7	0.77300	2.7	0.40960	0.04880
11	HTR3B	11	rs1176744	0.32	C/A	-3.9	0.02208	-4.2	0.06997	-3.7	0.15210	0.3	0.92700	0.43950
11	HTR3A	24	rs17543669	0.04	C/T	-6.6	0.09174	2.5	0.67320	-13.0	0.01280	-15.1	0.05617	0.31700
11	CD3E	6	rs4938506	0.24	A/G	-1.9	0.31450	-1.9	0.44930	-1.6	0.56350	0.1	0.98500	0.75980
11	GRIK4	107	rs3781817	0.47	C/T	3.9	0.01590	3.7	0.08905	4.2	0.08441	0.8	0.80130	0.32610
12	CACNA1C	193	rs10848645	0.44	G/A	5.5	0.00033	4.1	0.05172	7.5	0.00104	3.0	0.32560	0.10910
12	GNB3	16	rs1129649	0.35	C/T	4.7	0.00400	2.9	0.19190	6.7	0.00601	3.5	0.28080	0.45650
12	GRIN2B	176	rs1805494	0.04	T/C	-8.6	0.03030	-14.2	0.01046	-2.5	0.65930	11.1	0.16300	0.63050
12	AVPR1A	13	rs10219543	0.40	T/A	-2.7	0.09047	-1.6	0.47640	-4.7	0.05527	-3.3	0.31750	0.75390
12	TPH2	34	rs5019656	0.09	T/C	6.7	0.01219	5.9	0.11140	7.6	0.05265	1.9	0.72170	0.10330
12	P2RX7	26	rs12815078	0.10	G/A	5.6	0.03098	6.2	0.07919	4.6	0.23760	-1.5	0.77870	0.27830
12	PSMD9	6	rs2230681	0.13	T/C	5.0	0.03008	4.0	0.18480	6.4	0.07940	2.8	0.55320	1.00000
13	HTR2A	51	rs1923884	0.14	T/C	-4.0	0.07760	-0.5	0.87600	-9.4	0.00926	-8.8	0.05546	0.76010
14	PRKCH	80	rs4902049	0.21	G/A	5.6	0.00348	4.3	0.09209	7.5	0.01171	3.1	0.42430	0.82340
14	AKT1	4	rs4983559	0.42	G/A	-0.4	0.82140	1.9	0.37240	-3.8	0.12190	-5.8	0.06971	0.75820
16	GRIN2A	147	rs4782265	0.19	A/G	-4.7	0.01736	-4.2	0.11910	-5.4	0.06471	-0.8	0.84580	0.38770
16	SLC6A2	40	rs36023	0.38	A/G	-5.5	0.00053	-6.4	0.00240	-4.7	0.05844	2.1	0.51780	0.42680
17	SLC6A4	14	rs2066713	0.38	A/G	1.9	0.23840	2.3	0.28020	1.1	0.64240	-1.1	0.72800	0.34020
17	STAT3	11	rs8072785	0.09	T/C	-6.1	0.02654	-3.0	0.43630	-8.9	0.02410	-5.4	0.32640	0.81430
17	CRHR1	19	rs17763104	0.12	A/G	-5.0	0.04258	-8.1	0.01148	-0.8	0.84120	7.7	0.12050	1.00000
17	TBX21	5	rs7502875	0.24	C/A	3.7	0.03777	7.3	0.00371	0.4	0.86260	-6.9	0.05402	0.14960

17	GRIN2C	6	rs690418	0.21	T/C	2.6	0.17240	4.4	0.08819	0.4	0.88130	-4.1	0.29430	0.82150
19	GRIK5	5	rs4803523	0.20	T/C	-2.9	0.14510	-4.6	0.08134	-0.8	0.80310	3.9	0.33490	0.48200
19	GSK3A	1	rs11878620	0.07	A/G	2.3	0.44290	8.0	0.05652	-3.0	0.47000	-11.5	0.05122	0.58230
19	GRIN2D	9	rs276721	0.13	C/T	-4.4	0.04534	-7.6	0.00823	-1.1	0.73860	6.3	0.15410	0.00524
21	GRIK1	117	rs363512	0.06	A/G	8.5	0.01032	0.7	0.87370	17.8	0.00023	16.5	0.01264	1.00000
21	PDE9A	58	rs13048733	0.09	T/C	-8.2	0.00291	-8.0	0.03081	-8.6	0.03735	-0.7	0.90460	0.34690
22	COMT	31	rs2239395	0.04	G/T	7.4	0.05834	9.0	0.08673	5.7	0.32580	-3.8	0.63060	0.32870
X	MAOA	10	rs3027409	0.03	G/T	6.3	0.19610	9.8	0.12080	0.3	0.96660	.	.	1.00000
X	HTR2C	16	rs11167436	0.16	A/C	4.3	0.07653	4.4	0.19250	4.2	0.24200	.	.	0.29090
X	GRIA3	60	rs5910001	0.21	T/C	-4.4	0.03106	-7.8	0.00673	-0.5	0.86330	.	.	0.02154

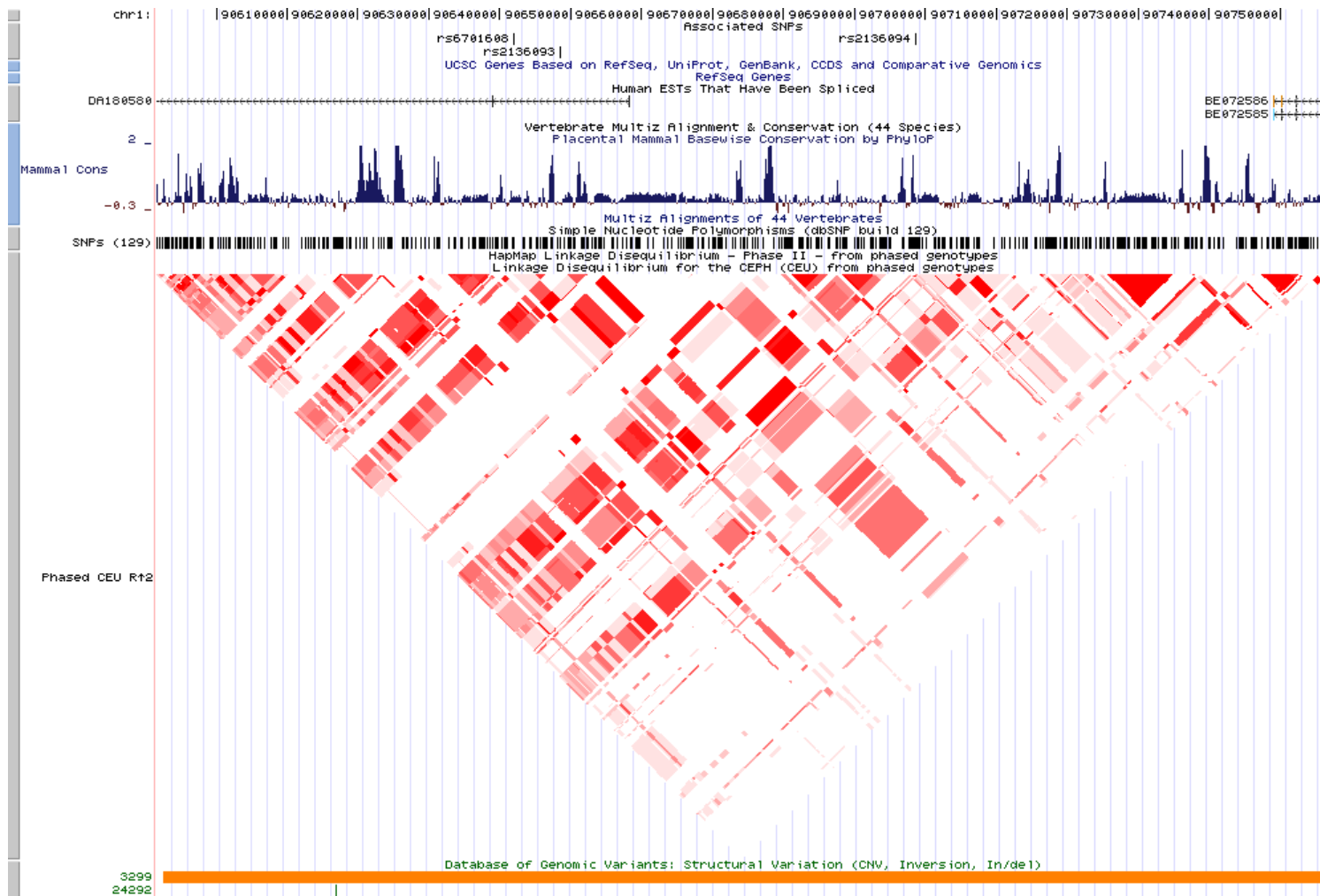
Supplementary Figure S1: Population structure. Plots show individual loadings on principal components according to centre of recruitment.



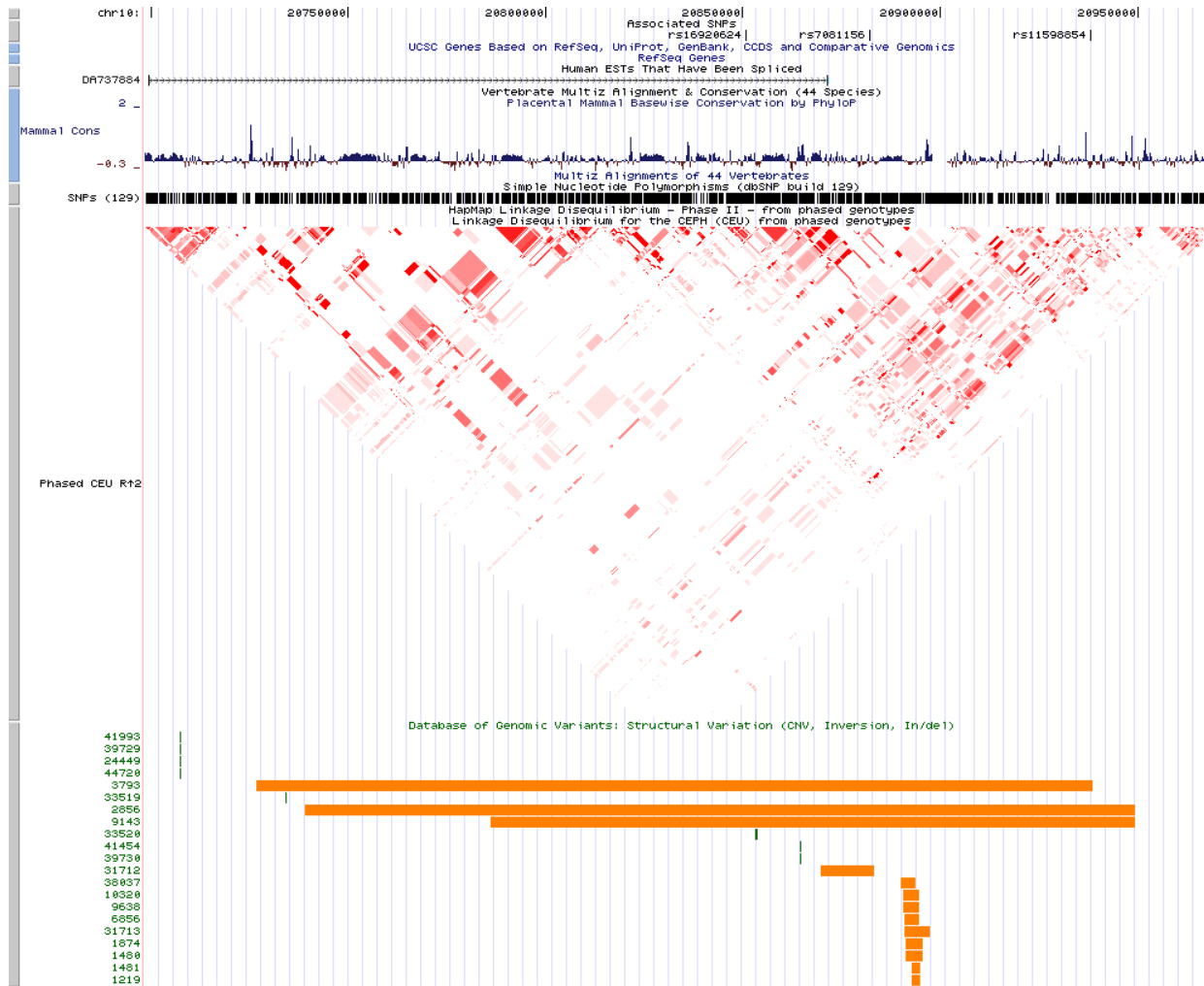
Supplementary Figure S2: Quantile-quantile plots for the genome-wide pharmacogenetic analyzes.



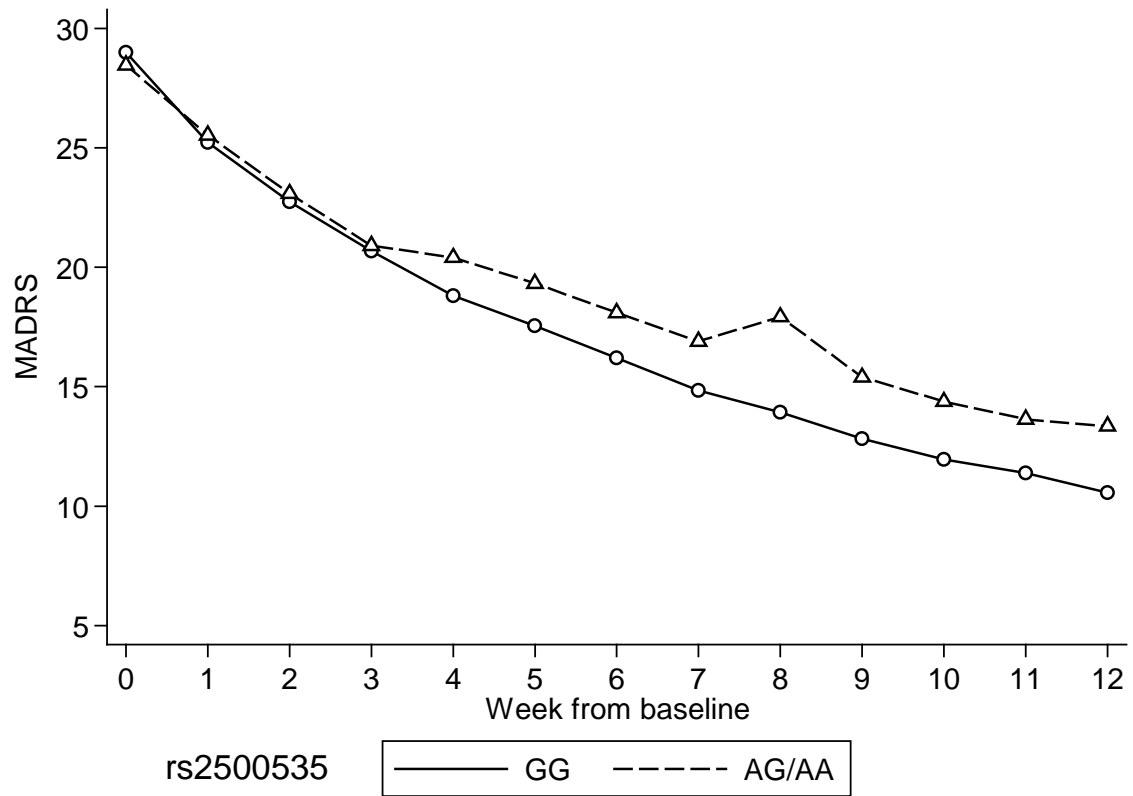
Supplementary Figure S4: The associated markers within a copy number on chromosome 1 in genomic context. Associated SNPs are marked in the top part of the Figure under the genomic position line. Under them are human expressed sequence tags (ESTs). Triangular LD plot is based on the Caucasian HapMap Phase II CEU sample. The Figure was produced using the UCSC genome browser (<http://genome.ucsc.edu/cgi-bin/hgTracks>).



Supplementary Figure S5: The associated markers within a copy number on chromosome 10 in genomic context. Associated SNPs are marked in the top part of the Figure under the genomic position line. Under them are human expressed sequence tags (ESTs). Triangular LD plot is based on the Caucasian HapMap Phase II CEU sample. The Figure was produced using the UCSC genome browser (<http://genome.ucsc.edu/cgi-bin/hgTracks>).



Supplementary Figure S8: Marker rs2500535 in the *UST* gene and response to nortriptyline over the twelve weeks of treatment. As there was only one AA homozygote, this individual was combined with the 36 heterozygotes.



Supplementary References:

- 1 Gratacos M, Soria V, Urretavizcaya M, Gonzalez JR, Crespo JM, Bayes M *et al.* A brain-derived neurotrophic factor (BDNF) haplotype is associated with antidepressant treatment outcome in mood disorders. *Pharmacogenomics J* 2008; **8**: 101-112.
- 2 Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry* 2008;
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- 4 Tsai SJ, Liou YJ, Hong CJ, Yu YW, Chen TJ. Glycogen synthase kinase-3beta gene is associated with antidepressant treatment response in Chinese major depressive disorder. *Pharmacogenomics J* 2008; **8**: 384-390.
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