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Table S1 Characteristics of genetic variants included in the study

Variant†	Location & nucleotide change	Amino acid change	Previous associations
***GCLC* gene**			
rs17883901	NM_001498.4: 138bp before the start of transcription site chr6-53410037-G-A	NA	This variant is related to cellular redox imbalances and modulates the risk of renal disease in patients with type 1 diabetes.[1] This variant has been associated with blood GSH and lead levels.[2]
(GAG)n repeats	5´UTR (10 bp upstream of the AUG start codon). Alleles may present 4, 7, 8, 9 or 10 repeats.	NA	This variant affects gene expression through translation.[3] High-risk alleles with 8 or 9 GAG repeats (vs. 7) were observed in 36% of the patients, but only 3% of the healthy controls in some samples.[4]
rs761142	chr6-53392108-A-C Intron 1: NM_001498.4:c.151-4783T>G	NA	This polymorphism could influence MeHg concentrations in pregnant mothers and their children, affecting early development.[5] It has been associated with lower *GCLC* mRNA expression and sulfamethoxazole-induced hypersensitivity in HIV/AIDS patients.[6] It also protects against type 2 diabetes.[7] Roadmap Epigenomics data shows that SNV rs761142 is associated with weak transcriptional activity and histone mark H3K79me2 in various cancer types.[8]
***GSTP1* gene**			
rs1695	chr11-67352689-A-G NM_000852.4:c.313A>G	p.Ile105Val	This polymorphism reduces enzymatic activity and the consequent detoxification of genotoxic compounds; it has been associated with several kinds of cancer.[9] It causes a metabolically less active variant of the enzyme,[10] and might influence chronic myeloid leukemia development and therapy response.[11] This variant was not associated with the risk of SZ in a Han Chinese population.[12]
CNVs of *GSTT1* and *GSTM1* genes			
0 to 4 copies. Loss or gains	Non-functional or null genotypes	NA	No evidence of enzyme activity encoded by the *GSTM1* and/or *GSTT1* genes is found in approximately 20-50% of people due to deletion of both alleles. DNA of null genotype cells is more likely to be subject to damage caused by carcinogens.[13,14] Germline copy number changes of the *GSTP1* gene have been described, but are extremely rare.[15]

† NCBI database of genetic variation, dbSNP.
NA = not applicable.

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Table S2 Genotype and allele frequencies of *GCLC* and glutathione S-transferases gene variants in patients with psychotic disorders (n=75)

Genetic variant (dbSNP)	Genotype/allele	n	Observed frequency	95%CI	Expected frequency†	χ^2-value, p-value and (adjusted p-value)
***GCLC* gene**						
(GAG)n repeats in 5´UTR	7/7	12	0.170	0.096-0.270	0.120	1.103
	7/8	14	0.190	0.118-0.302	0.070	1.000 (1.000)
	7/9	11	0.150	0.086-0.255	0.380	
	8/8	0	0.000	0.000-0.061	0.010	
	8/9	0	0.000	0.000-0.061	0.110	
	9/9	35	0.490	0.374-0.599	0.320	
	7	49	0.340	0.268-0.421	-	
	8	14	0.097	0.058-0.158	-	
	9	81	0.562	0.481-0.641	-	
rs761142	AA	5	0.100	0.027-0.160	0.100	0.446
	AC	35	0.440	0.386-0.614	0.440	1.000 (1.000)
	CC	30	0.460	0.319-0.545	0.460	
	A	45	0.321	0.250-0.403	-	
	C	95	0.679	0.597-0.750	-	
rs17883901	AA	0	0.000	0.000-0.062	0.000	1.908
	AG	8	0.110	0.057-0.212	0.110	1.000 (1.000)
	GG	62	0.890	0.788-0.943	0.890	
	A	8	0.057	0.028-0.110	-	
	G	132	0.943	0.890-0.972	-	
***GST*s gene**						
*GSTP1*_rs1695	AA	15	0.330	0.208-0.471	0.320	0.187
	AG	22	0.480	0.341-0.619	0.490	1.000 (1.000)
	GG	9	0.200	0.104-0.334	0.190	
	A	52	0.565	0.463-0.662	-	
	G	40	0.434	0.338-0.537	-	
GSTM1 del	1/1	38	0.809	0.672-0.898	0.671	22.174
	1/del	1	0.021	<0.001-0.121	0.296	**0.0005 (0.004)**
	del//del	8	0.170	0.086-0.304	0.033	
	1	77	0.819	0.728-0.885	-	
	del	17	0.181	0.115-0.272	-	
GSTM1 dup	1/1	26	0.553	0.412-0.686	0.368	0.224
	1/dup	5	0.106	0.042-0.230	0.477	1.000 (1.000)
	dup/dup	16	0.340	0.221-0.483	0.155	
	1	57	0.606	0.505-0.699	-	
	dup	37	0.394	0.301-0.495	-	

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Genetic variant (dbSNP)	Genotype/allele	n	Observed frequency	95%CI	Expected frequency†	χ^2-value, p-value and (adjusted p-value)
GSTT1 del	1/1	13	0.260	0.158-0.397	0.176	0.080
	1/del	16	0.320	0.207-0.459	0.487	1.000 (1.000)
	del//del	21	0.420	0.294-0.558	0.336	
	1	42	0.420	0.328-0.518	-	
	del	58	0.580	0.482-0.672	-	
GSTT1 dup	1/1	47	0.940	0.832-0.986	0.884	1.758
	1/dup	0	0.000	0.000-0.085	0.113	1.000 (1.000)
	dup/dup	3	0.060	0.014-0.168	0.004	
	1	94	0.940	0.872-0.974	-	
	dup	6	0.060	0.025-0.127	-	

† Calculated by Hardy–Weinberg law.
del = deletion; dup = duplication; GSTs = Glutathione S-transferases; UTR = untranslated region.

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Table S3 Genotype and allele frequencies of *GCLC* and Glutathione S-transferase genes variants in Mexican mestizo healthy controls (n=40)

Genetic variant (dbSNP)	Genotype/allele	n	Observed frequency	95%CI	Expected frequency†	χ^2-value, p-value and (adjusted p-value)
***GCLC* gene**						
(GAG)n repeats in 5´UTR	7/7	13	0.325	0.200 - 0.481	0.200	1.353
	7/8	8	0.200	0.102 - 0.350	0.090	1.000 (1.000)
	7/9	2	0.050	0.005 - 0.174	0.410	
	8/8	0	0.000	0.000 - 0.104	0.010	
	8/9	0	0.000	0.000 - 0.104	0.090	
	9/9	17	0.425	0.285 - 0.578	0.200	
	7	36	0.450	0.346 - 0.559	-	
	8	8	0.100	0.049 - 0.187	-	
	9	36	0.450	0.346 - 0.559	-	
rs761142	AA	12	0.300	0.180 - 0.455	0.280	0.128
	AC	18	0.450	0.307 - 0.602	0.500	1.000 (1.000)
	CC	10	0.250	0.140 - 0.404	0.230	
	A	42	0.525	0.417 - 0.631	-	
	C	38	0.475	0.369 - 0.583	-	
rs17883901	AA	0	0.000	0.000 - 0.104	0.000	1.740
	AG	3	0.075	0.019 - 0.206	0.070	1.000 (1.000)
	GG	37	0.925	0.794 - 0.981	0.930	
	A	3	0.038	0.008 - 0.109	-	
	G	77	0.963	0.891 - 0.992	-	
***GSTs* gene**						
GSTP1 rs1695	AA	36	0.923	0.790 - 0.981	0.852	1.688
	AG	0	0.000	0.000 - 0.107	0.142	1.000 (1.000)
	GG	3	0.077	0.019 - 0.210	0.006	
	A	72	0.923	0.839 - 0.967	-	
	G	6	0.077	0.032 - 0.160	-	
GSTM1 del	1/1	24	0.615	0.356 - 0.625	0.411	0.406
	1/del	2	0.051	0.003 - 0.145	0.460	1.000 (1.000)
	del//del	13	0.333	0.161 - 0.404	0.129	
	1	50	0.641	0.530 - 0.739	-	
	del	28	0.359	0.261 - 0.470	-	
GSTM1 dup	1/1	9	0.237	0.010 - 0.322	0.156	0.117
	1/dup	12	0.316	0.148 - 0.389	0.478	1.000 (1.000)
	dup/dup	17	0.447	0.234 - 0.496	0.366	
	1	30	0.395	0.292 - 0.507	-	
	dup	46	0.605	0.493 - 0.708	-	

Genetic variant (dbSNP)	Genotype/allele	n	Observed frequency	95%CI	Expected frequency†	χ^2-value, p-value and (adjusted p-value)
GSTT1 del	1/1	38	1.000	0.890 - 1.000	1.000	ND
	1/del	0	0.000	0.000 - 0.109	0.000	
	del//del	0	0.000	0.000 - 0.109	0.000	
	1	76	1.000	0.942 - 1.000	-	
	del	0	0.000	0.000 - 0.058	-	
GSTT1 dup	1/1	6	0.160	0.071 - 0.308	0.190	0.245
	1/dup	21	0.550	0.397 - 0.699	0.490	1.000 (1.000)
	dup/dup	11	0.290	0.169 - 0.449	0.320	
	1	33	0.434	0.329 - 0.546	-	
	dup	43	0.566	0.453 - 0.671	-	

† Calculated by Hardy–Weinberg law.
del = deletion; dup = duplication; GSTs = Glutathione S-transferases; ND = not determined, since only one genotype was observed; UTR = untranslated region.

Table 4 GSH levels and GPx activity analyzed by genotype in healthy controls

Variant	Genotype	GSH levels (µM) (mean±SD)	t / F value	p[a] and (adjusted p-value)	GPx activity[†] (mean±SD)	χ^2-value, W-value	p[b] and (adjusted p-value)
***GCLC* gene**							
(GAG)n	7/7	6.16 ± 1.74	0.990	0.409 (0.622)	149.40 ± 38.91	0.074	0.995 (0.995)
	7/8	5.46 ± 0.78			155.30 ± 63.46		
	7/9	4.45 ± 0.76			177.20 ± 100.03		
	9/9	5.48 ± 1.46			149.08 ± 34.96		
rs761142	AA	5.90 ± 1.49	0.900	0.415 (0.622)	171.20 ± 45.43	4.976	0.083 (0.249)
	AC	5.96 ± 1.63			148.70 ± 33.28		
	CC	5.23 ± 0.91			134.24 ± 56.00		
rs17883901	AG	5.95 ± 1.44	0.244	0.826 (0.826)	157.60 ± 13.60	66.500	0.599 (0.719)
	GG	5.74 ± 1.46			151.36 ± 46.26		
***GSTs* gene**							
*GSTP1*_rs1695	AA	5.74 ± 1.52	1.744	0.190 (0.622)	172.20 ± 29.86	1.932	0.380 (0.570)
	AG	5.36 ± 1.39			149.50 ± 39.92		
	GG	6.32 ± 1.26			150.69 ± 58.67		
GSTT1 CNV	0	4.73 ± 0.40	1.127	0.352 (0.622)	95.71 ± 20.518	7.808	0.050 (0.249)
	1	-			-		
	2	6.10 ± 1.52			159.60 ± 22.10		
	3	5.75 ± 0.42			173.30 ± 40.49		
	4	5.39 ± 1.55			144.20 ± 1.67		
GSTM1 CNV	0	5.45 ± 1.30	0.579	0.566 (0.679)	151.04 ± 39.46	2.584	0.275 (0.550)
	1	5.89 ± 1.62			164.00 ± 47.86		
	2	6.13 ± 1.65			129.42 ± 32.98		
	4	---			-		

[a] Parametric and [b] non-parametric test probability values.
CNV = copy number variations; GSTs = Glutathione S-transferases; UTR = untranslated region.
[†] GPx activity is expressed as µmol GSH/500µg protein/30 min.

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Table S5 Tukey tests for GSH levels in patients with psychotic disorders for every pair of *GCLC*_(GAG)n genotypes and genotypes of *GSTM1*_CNVs

Gene/variant	Comparison of genotypes	95% family-wise CI	p-value
*GCLC*_(GAG)n			
	7/7 vs 7/8	-1.969-1.770	1.000
	7/7 vs 7/9	0.488-4.372	**0.008**
	7/7 vs 9/9	-0.964-2.282	0.707
	7/8 vs 7/9	0.709-4.351	**0.002**
	7/8 vs 9/9	-0.717-2.234	0.530
	7/9 vs 9/9	-3.338 to -0.204	**0.021**
*GSTM1*_CNV			
	0 vs 1	0.533-0.773	0.960
	0 vs 2	-0.222-1.277	0.250
	0 vs 4	0.819-3.652	**0.0007**
	1 vs 2	-0.358-1.173	0.492
	1 vs 4	0.691-3.540	**0.001**
	2 vs 4	0.236-3.180	**0.017**

Bold type indicates statistically significant values.

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Table S6 Pairwise Wilcoxon rank sum test for GPx activity in patients for every pair of *GCLC*_rs761142 genotypes and CNVs of *GSTM1*

Gene/variant	Genotypes	p-value†
*GCLC*_rs761142	AA vs AC	0.110
	AA vs CC	0.210
	AC vs CC	0.100
	AA vs AC	0.110
*GSTM1*_CNV	0 vs 1	0.759
	0 vs 2	**0.043**
	0 vs 4	**0.045**
	1 vs 2	**0.031**
	1 vs 4	**0.046**
	2 vs 4	**0.045**

Bold type indicates statistically significant values.
† Probability adjusted by Benjamini-Hochberg.

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Table S7 Comparison of genotype frequencies by groups

Variant	Genotype	Control	Patient	OR	95%CI	p-value and (adjusted p-value)
***GCLC* gene**						
(GAG)n	7/7	13	12	1.000	-	
	7/8	8	14	1.895	0.588-6.112	0.381[a] (0.572)
	7/9	2	11	5.958	1.090-32.573	**0.039[b]** (0.156)
	9/9	17	35	2.230	0.841-5.915	0.136[a] (0.272)
rs761142	AA	12	5	1.000	-	
	AC	18	35	4.667	1.422-15.311	**0.008[a]** (0.048)
	CC	10	30	7.200	2.032-25.514	**0.001[a]** (0.012)
rs17883901	AG	3	8	1.000	-	
	GG	37	62	0.541	0.743-0.509	0.743[b] (0.999)
***GSTs* gene**						
*GSTP1*_rs1695	AA	6	15	1.000	-	
	AG	21	22	0.419	0.137-1.284	0.123[a] (0.272)
	GG	11	9	0.101	0.090-1.193	0.859[a] (1.000)
GSTT1 CNV	2	20	17	1.000	-	
	Ht & Hm del	3	9	3.529	0.821-15.165	0.104[b] (0.272)
	Ht & Hm dup	15	21	1.647	0.653-4.157	0.289[a] (0.495)
GSTM1 CNV	0	17	21	1.000	-	
	1	12	16	1.079	0.403-2.889	1.000[b] (1.000)
	2	9	10	0.899	0.298-2.714	1.000[b] (1.000)
	4	0	3	NA	NA	NA

Bold type indicates statistically significant values.
CNV = copy number variant; del = deletion; dup = duplication; GSTs = Glutathione-S-transferases; Hm = homozygote; Ht = heterozygote; OR = odds ratio; p = probability value by [a] χ^2 and [b]Fisher's tests.

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Table S8 Comparison of the frequencies of the multilocus genotypes in both groups

Gene	Multilocus genotype (GAG repeats & rs761142)	Healthy controls	Patients	OR	95%CI	p-value
GCLC	7/7-7/8 & AA	8	1	1	-	-
	7/7-7/8 & AC-CC	13	23	6.571	1.535-63.388	**0.004 (0.060)**
	7/9-9/9 & AA	4	4	3.200	0.645-49.760	0.079 (0.079)
	7/9-9/9 & AC-CC	15	40	10.000	2.371-92.471	**0.0003 (0.0009)**

Bold type indicates statistically significant values.
OR = odds ratio; p = probability value by Fisher's test.

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Table S9 Stepwise logarithmic model with multilocus genotypes

Variable	OR	CI	Z-value	p-value†
Intercept	-	-	-0.020	0.984
GSH levels‡	0.692	0.565-0.833	-3.692	**0.0002**
GPx activity‡	1.009	1.004-1.014	3.409	**0.0006**
Male sex	0.587	0.297-1.122	-1.605	0.108
7/7.7/8-AC.CC	732.559	0.000-NA	0.023	0.982
7/9.9/9-AA	391.092	0.000-NA	0.021	0.983
7/9.9/9-AC.CC	1188.404	0.000-NA	0.025	0.980

Bold type indicates statistically significant values.
OR = odds ratio.
† Probit logarithmic model probability.
‡ Increments of 1 unit.

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Table S10 Tukey test for GSH levels and clinical diagnosis of patients

Clinical diagnoses	95%CI	p-value
IIP-BD	-0.350-4.527	0.118
SD-BD	-2.628-1.547	0.903
SZ-BD	-1.442-2.310	0.928
SD-IIP	-4.716-0.541	**0.008**
SZ-IIP	-3.531-0.221	0.103
SZ-SD	-0.416-2.365	0.261

Bold type indicates statistically significant values.
BD = bipolar disorder; IIP = interictal psychosis; SD = schizoaffective disorder; SZ = schizophrenia.

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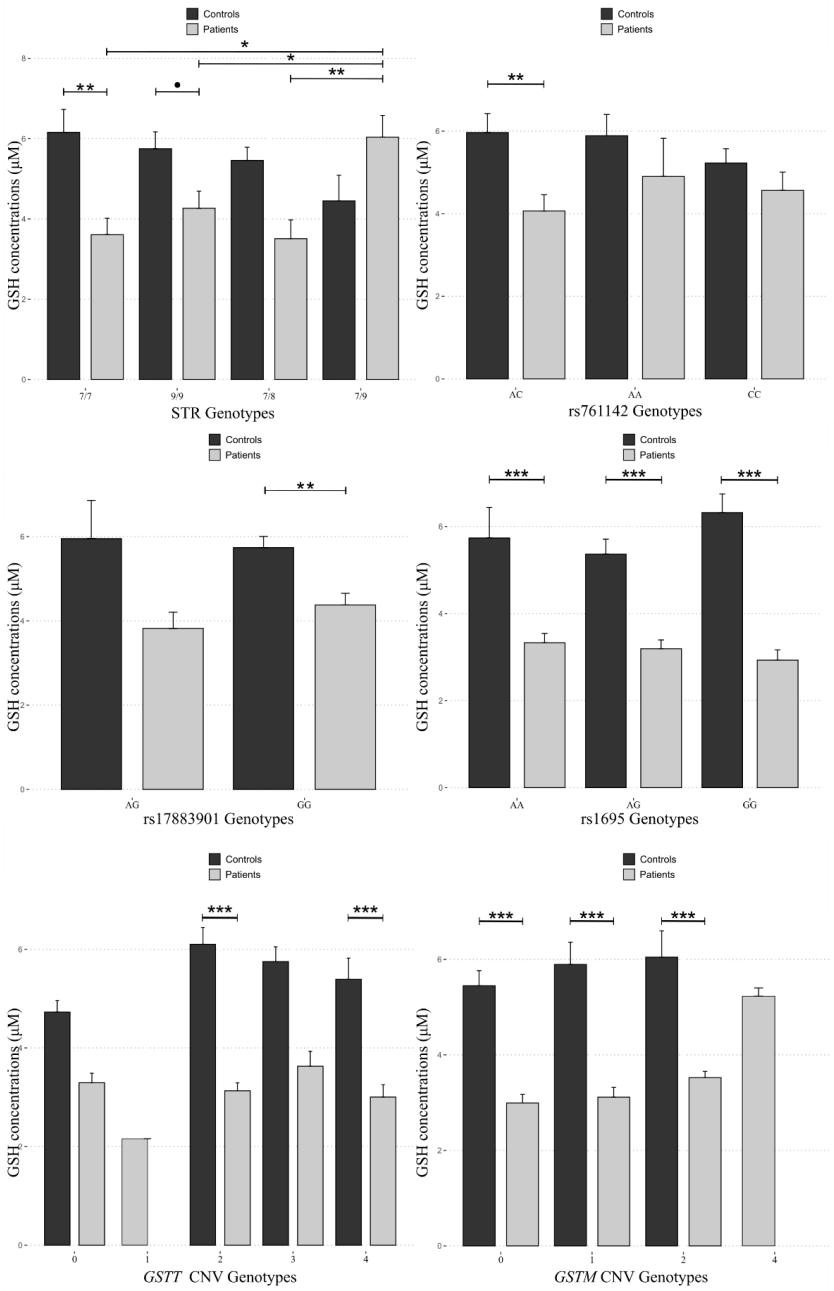
Table S11 Genetic variants, clozapine concentrations, adjusted dose-corrected plasma concentrations and metabolic ratio in patients with psychotic disorders

Variant	Genotype	CLZ (µmol/L) (mean±SD)	χ^2 and W value	p[a] and (adjusted p-value)	CLZ dose corrected (ng ml^{-1}/mg kg^{-1}) (mean±SD)	χ^2 and W value	p[b] and (adjusted p-value)	Metabolic ratio	χ^2 and W value	p[b] and (adjusted p-value)
***GCLC* gene**										
(GAG)n	7/7	186.03 ± 150.475	1.694	0.638	77.24 ± 37.291	2.671	0.445	2.662 ± 1.085	3.317	0.345 (0.183)
	7/8	98.42 ± 53.617		(0.766)	63.89 ± 40.299		(0.705)	2.310 ± 1.365		
	7/9	124.587 ± 129.167			72.551 ± 70.019			1.830 ± 0.818		
	9/9	181.198 ± 218.701			63.62 ± 58.321			1.932 ± 1.087		
rs761142	AA	71.620 ± 29.254	1.185	0.533	44.22 ± 25.672	4.853	0.088	1.988 ± 0.552	2.865	0.238 (0.357)
	AC	167.290 ± 179.292		(0.766)	82.80 ± 58.124		(0.528)	2.428 ± 1.195		
	CC	163.793 ± 180.064			57.534 ± 47.145			1.848 ± 0.951		
rs17883901	AG	367.660 ± 411.054	106.000	0.308	86.28 ± 36.411	109	0.258	2.865 ± 0.266	129	0.061 (0.183)
	GG	148.699 ± 151.243		(0.766)	68.711 ± 54.311		(0.705)	2.109 ± 1.108		
***GSTs* gene**										
*GSTP1*_rs1695	AA	149.660 ± 130.448	2.660	0.264	53.039 ± 29.712	1.323	0.516	2.292 ± 1.381	0.461	0.794 (0.862)
	AG	212.50 ± 274.955		(0.766)	74.986 ± 57.301		(0.705)	1.898 ± 0.926		
	GG	75.953 ± 66.396			54.89 ± 43.810			1.953 ± 1.272		
*GSTT1*_CNV	0	153.047 ± 174.007	1.442	0.837	64.04 ± 46.844	6.948	0.705	1.771 ± 1.255	6.633	0.157 (0.314)
	1	143.100		(0.837)	144.5		(0.705)	4.733		
	2	105.000 ± 76.284			64.009 ± 39.730			2.081 ± 0.810		
	3	341.550 ± 376.187			117.86 ± 81.130			3.006 ± 1.389		
	4	159.100 ± 223.153			41.038 ± 20.606			1.930 ± 1.377		
*GSTM1*_CNV	0	95.05 ± 60.316	2.573	0.462	50.862 ± 30.851	1.400	0.7054	2.065 ± 1.300	0.747	0.862 (0.862)
	1	160.416 ± 141.516		(0.766)	75.56 ± 51.391		(0.705)	2.257 ± 1.448		
	2	254.240 ± 344.595			70.23 ± 61.284			1.999 ± 0.767		
	4	214.660 ± 131.599			97.03 ± 106.619			2.711 ± 1.305		

[a] Analysis of variance and Student's *t* test and [b] Kruskal-Wallis and Mann-Whitney-Wilkoxon tests probability values.
† Differences against the rest of genotypes. Metabolic ratio = [clozapine levels]/[n-desmethyl-clozapine].

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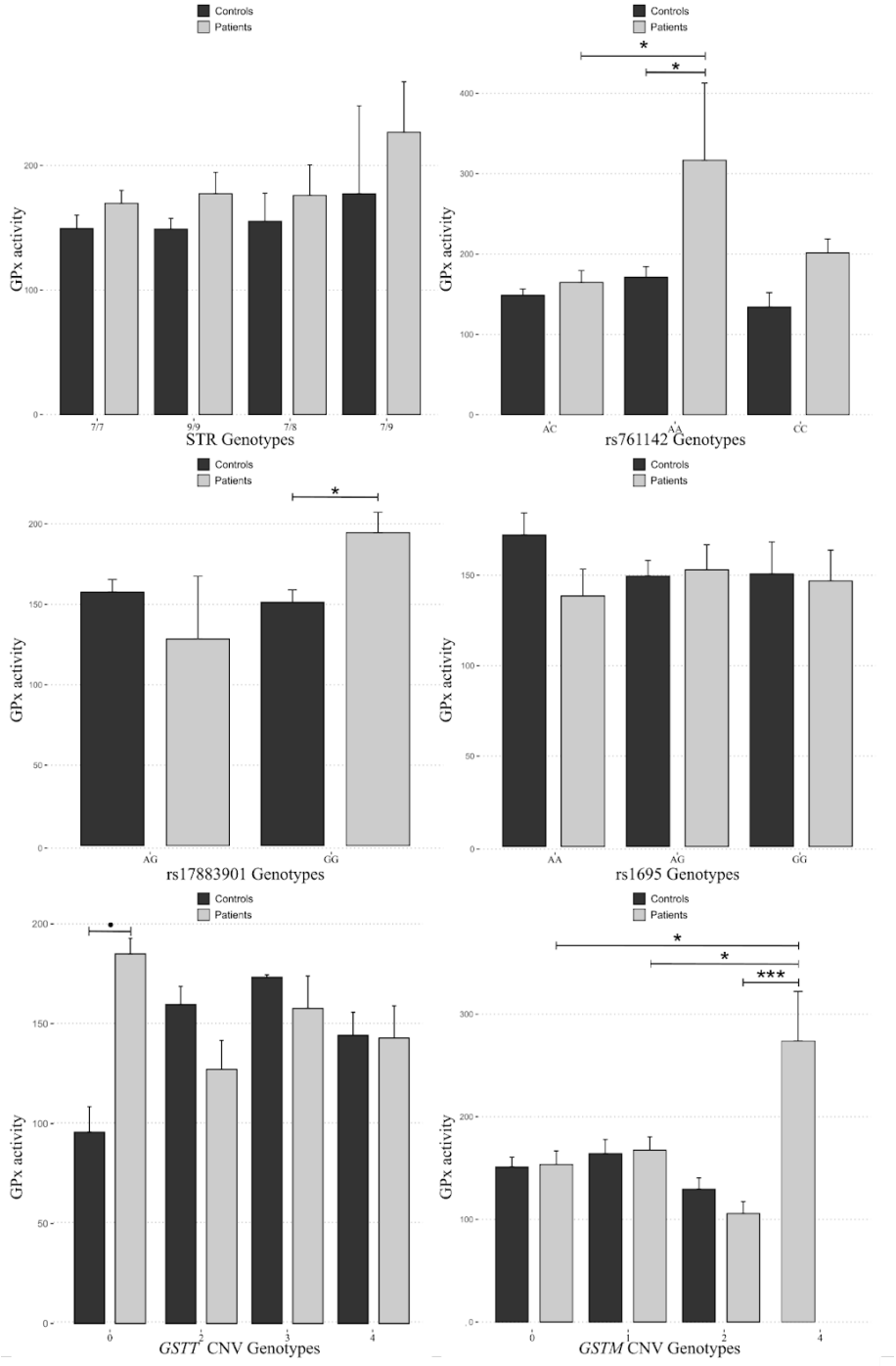
Figure S1 Two-way analysis of variance test comparing GSH levels in patients and controls by genotypes observed in the variants studied. A) GAG repeats in 5'UTR of *GCLC*. B) *GCLC*-rs761142. C) *GCLC*-rs17883901. D) *GSTP1*-rs1695. E) CNV of *GSTT1*. F) CNV of *GSTM1*.



Vertical bars: standard error.
• $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

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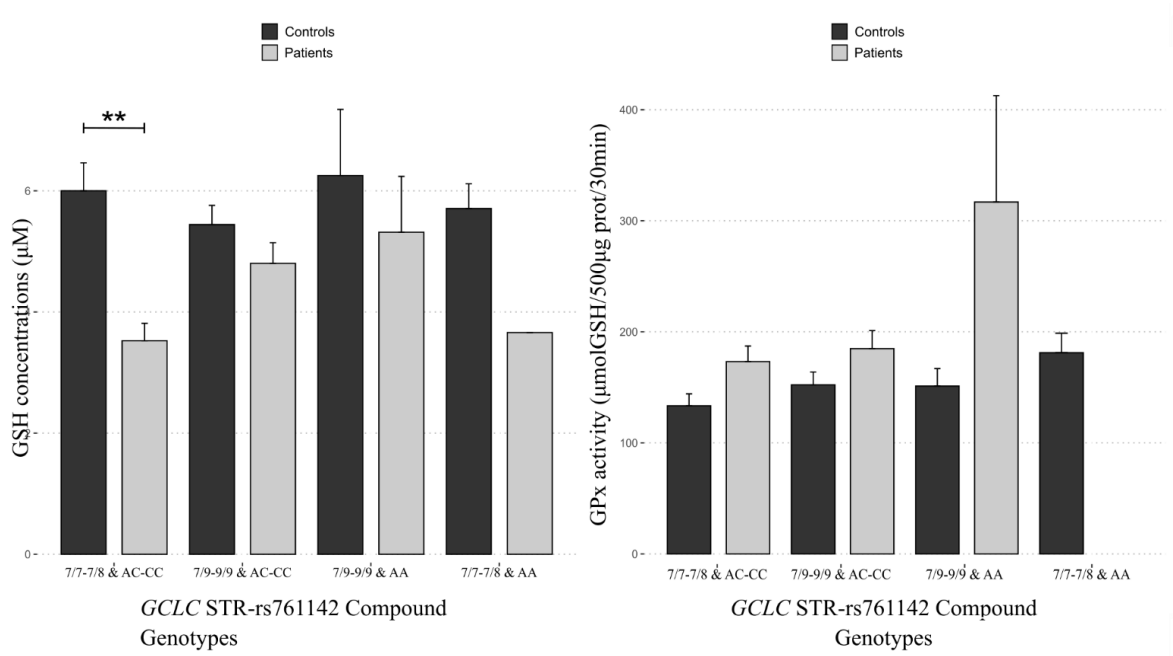
Figure S2 Two-way ANOVA of GPx activity comparisons by group (patients and healthy controls) and genotype of the variants studied. A) GAG repeats in 5'UTR of *GCLC*. B) *GCLC*-rs761142. C) *GCLC*-rs17883901. D) *GSTP1*-rs1695. E) CNV of *GSTT1*. F) CNV of *GSTM1*.



Vertical bars: standard error.
• $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
GPx activity is expressed as µmol GSH/500µg protein/30 min.

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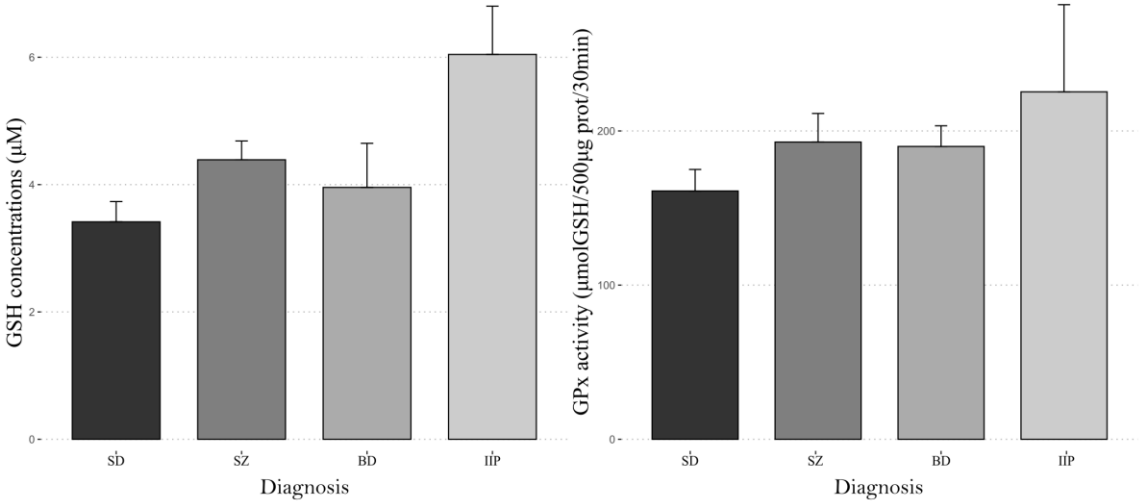
Figure S3 Comparisons of A) GSH and B) GPx values by group (patients and healthy controls) and compound (multilocus) genotypes of the GAG repeats in 5´UTR and rs761142 of *GCLC* using two-way ANOVA.



** $p < 0.01$.

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Figure S4 A) GSH concentrations and B) GPx activity by the different diagnostics.



BD = bipolar disorder; IIP = interictal psychosis; SD = schizoaffective disorder; SZ = schizophrenia.
GPx activity is expressed as µmol GSH/500µg protein/30 min. GSH concentrations between IIP and SD patients, p=0.014, ANOVA test.