Supplemental Information, Figures and Tables

Supplemental Material and Methods

Subjects

Brain tissue was obtained from the Quebec Suicide Brain Bank (QSBB; Douglas Mental Health Institute, Verdun, Québec). All subjects were Caucasians of French–Canadian descent, a population with a well-identified founder effect(1). All individuals were male and group-matched for age, pH and post-mortem intervals (PMI) (see SITable1). There was no difference across groups for age (Suicide: 38.8±11.4; CTRL: 40.9±14.3; $t_{(1, 60)}$= -0.59, p>0.1), pH (Suicide: 6.6±0.3; CTRL: 6.5±0.3; $t_{(1, 60)}$= 0.46, p>0.1), and PMI (Suicide: 31.3±14.2; CTRL: 32.6±15.1; $t_{(1, 60)}$= -0.31; p>0.1). Inclusion criteria also included sudden death without prolonged agonal state. Brain tissue samples (dentate gyrus) from the left hemisphere were obtained from sixty-two subjects (46 suicide and 16 CTRL) and carefully dissected at 4˚C after having been flash-frozen in isopentene at -80˚C. Dissection of the HPC was performed by histopathologists using reference neuroanatomical maps(2, 3). The project was approved by the Research Ethics Board at the Douglas University Mental Health Institute and signed informed consent was obtained from next of kin. Part of the sample investigated in this report has been used in a recently published study investigating the epigenetic effects of early-life adversity(4). However, the sample investigated in the current study is substantially larger.

Psychological Autopsies

Information on psychopathology, socio-demographic variables and development was obtained by way of psychological autopsies performed by trained clinicians with the informants best acquainted with the deceased, as described elsewhere(5). The process employed by our group in the collection of information used in psychological autopsies has been extensively investigated and found to produce valid information, especially in the context of observable behaviors and major life events(5-11). Both cases and controls were characterized by the same psychological autopsy methods, therefore avoiding the occurrence of systematic biases.

Psychopathology

Diagnoses were obtained using DSM-IV(12) criteria by means of SCID-I interviews(13) adapted for psychological autopsies. Psychopathology did not have a significant effect on methylation differences, with the exception of substance disorders. We adjusted for the effects of substance disorders in our analyses (see Statistical and Bioinformatic Analyses).

Methylated DNA Immunoprecipitation (meDIP), Labelling and Hybridization

MeDIP

Methylated DNA was extracted following an adaptation of a methylated DNA immunoprecipitation (meDIP) method developed previously(14). Briefly, 6pg of green fluorescent protein (GFP) and methylated luciferase (mLUC) plasmids was combined with 3 ug of genomic DNA and sonicated in order to create 300 to 800 bp fragments. A

representative fraction of genomic DNA (input) was immediately isolated. The remaining DNA was incubated with sepharose beads (GE Healthcare) and 5' methylcytosine antibody (Calbiochem) overnight. The preparation was then spun on a SpinX column (Corning Inc) and the flow-through was recovered as the unmethylated DNA fraction. The remaining DNA was thoroughly washed and the methylated DNA fraction was recovered. Input, unmethylated and methylated fractions were then purified by phenol-chloroform and precipitated in ethanol. Enrichment in either methylated or unmethylated DNA was assessed by PCR using primers targeting external (GFP, mLUC) and internal controls (B-Actin, H19) for input, unbound and bound fractions.

Labelling

Input and methylated DNA fractions were amplified using the GenomePlex Complete Whole Genome Amplification (WGA) Kit (Sigma) and purified using the GenElute PCR Clean-Up Kit (Sigma) following manufacturer's instructions. DNA concentration and quality was assessed on a NanoDrop ND-1000 UV-VIS Spectrophotometer (NanoDrop Technologies, Rockland, DE, USA). Input and methylated fractions were labeled to Cyanine 3-dUTP (Cy3) and Cyanine 5-dUTP (Cy5) using the Agilent Genomic Enzymatic Labeling Kit and then cleaned up using microcon Y-30 filters (Millipore). DNA yield and labeling specificity was assessed on Nanodrop. All samples reached the minimum Cy3 and Cy5 specific activity thresholds of 35 to 55pg and 25 to 40pg of DNA, respectively, and quantity ranges of 7 to 10µg of DNA.

Hybridization

Hybridization, washing steps, scanning and data extraction were performed following manufacturer's instructions (Agilent). Every subject was hybridized on a separate microarray. For all samples, dye swaps were performed in order to control for dye integration bias. Hybridization was performed for 40 hours at 60˚C in rotating chambers. All microarrays were washed with acetonitrile, stabilization, and drying solution in order to avoid ozone degradation of Cy5. Following washing steps, microarrays were scanned using an Agilent High-Resolution C Scanner (Agilent) at a resolution of 3µm under XDR mode. Data were extracted using Feature Extraction software (Agilent). For each sample, quality control (QC) reports were used in order to assess hybridization quality. Hybridization was assessed based on the following criteria: background noise <10, signal intensity >50, reproducibility <0.2 and derivative LR spread <0.3.

Microarray Analysis

Microarray design

A custom-designed 400K promoter tiling array was used for this study (Agilent). The array was designed using Agilent's array design platform eArray. Probes were selected to tile all known gene promoters, i.e. intervals roughly 2000 bp upstream to 400 bp downstream of the transcription start sites of genes described in Ensembl (version 55) at 100 bp-spacing.

MeDIP microarray normalization

Extracted microarray intensities were processed and analyzed using the R software environment for statistical computing(15). Log-ratios of the bound (Cy5) and input (Cy3)

microarray channel intensities were computed for each microarray, and then microarrays were normalized to one another using quantile-normalization(16) under the assumption that all samples have identical overall methylation levels.

Statistical and Bioinformatic Analyses

Methylation levels were estimated from normalized probe intensities by applying a Bayesian deconvolution algorithm(17). Promoter methylation levels were obtained taking the median estimated methylation level across each promoter. Promoters were defined as the region 2000 to -400bp of the transcription start sites of each gene.

Differential methylation between groups of samples was determined in several stages to ensure both statistical significance and biological relevance. In the first stage, linear models implemented in the 'limma' package(18) of Bioconductor(19) were used to combine the two dye labeling schemes from the dye swaps and to compute a modified t-statistic for each probe. Models were adjusted for selected covariables based on a combination of domain knowledge and variance analysis of the microarray data. Eigen-R2 (20) was used to estimate the amount of variance in the microarray data explained by each variable. The estimate for each variable is similar to taking the average of the correlations between the variable and the intensities of each probe on the microarray. Correlation averages are vulnerable to technical artifacts such as stochastic noise of probes in regions with little or no methylation so Eigen-R2 uses principal component analysis to reduce the contribution of these and other problematic probes. Following Eigen-R2 analysis, we adjusted for significant covariates, including history of adversity (5.4%), PMI (2.1%), substance comorbidity (1.7%) and age (1.7%).

An individual probe was called differentially methylated if the p-value of its t-statistic was at most 0.01 (uncorrected for multiple testing) and the associated difference of means between the groups was at least 0.5. Given that the DNA samples were sonicated prior to hybridization, we assumed that probes within 500bp should approximately agree. Therefore, we partitioned the genome into regions of 1000bp and calculated the significance of enrichment for high or low t-statistics of probes within each region (containing at least 1 probe). Significance was determined using the Wilcoxon rank-sum test comparing t-statistics of the probes within the region against those of all the probes on the microarray and then adjusted to obtain false discovery rates for each region. A probe was then called differentially methylated if it satisfied both of the following:

- it was called differentially methylated (i.e. the significance of its t-statistic was at most 0.01 and the difference of means between the groups was at least 0.5), and
- it belonged to a region whose false discovery rate(21) was at most 0.1.

A promoter was called differentially methylated if it contained a probe called differentially methylated.

Methylation and expression differences were summarized across all genes within1Mb partitions of the genome in order to estimate correlation between expression and methylation differences genome-wide. Methylation summaries were obtained by first computing a z-score for each promoter (2000 to +400bp with respect to the transcription start site) to indicate the enrichment of differentially methylated probes within the

promoter. The z-score summarizes the modified t-statistics of the probes in the promoter obtained from the differential analysis using limma Stouffer's method(22): $\sum_{i=1}^{k} t_i/\sqrt{k}$ where k is the number of probes in the promoter. Strictly speaking, Stouffer's method requires z-scores but t-statistics are a reasonable approximation when they come from t-tests involving a large number of samples (in our case 40). We then computed a z-score for each 1Mb region from Wilcoxon rank-sum statistics obtained by comparing z-scores of promoters within the region to those across the entire genome.

Expression microarray data

Microarray gene expression profiles were previously generated by our group(23). Gene expression arrays were available for several but not all of the individuals included in the methylation array study. Specifically, we have expression profiles for 9 controls and 13 suicides individuals of those included in this study. No significant difference in age (suicide: 30.9 ± 2.3, CTRL: 37.4 ± 4.2; t= 1.5, p= 0.15), pH (suicide: 6.6 ± 0.1, CTRL: 6.7 ± 0.1; t= 1.0, p= 0.32) and PMI (suicide: 23.2 ± 1.9, CTRL: 27.8 ± 3.2; t= -1.3, p= 0.21) were found between groups. Expression data was normalized as previously described(23), and expression differences were obtained using linear models implemented in the 'limma' package(18) of Bioconductor(19) yielding a modified t-statistic for each probeset. As with the methylation microarray analysis, models were adjusted for history of adversity, PMI, substance comorbidity, and age. Expression differences were summarized across 1Mb partitions of the genome by computing z-scores from Wilcoxon rank-sum statistics obtained by comparing promoter differential t-statistics within the region to those across the entire genome.

Fluorescence-Assisted Cell Sorting (FACS) of Neuronal and Non-Neuronal Nuclei

Nuclei were isolated from hippocampal tissue as described previously(24). Briefly, 150mg of tissue was thawed and dounced for one minute. Nuclei were then extracted by ultracentrifugation on a sucrose gradient (80%) for 2.5h at 24 000 RPM. Pelleted nuclei were resuspended and incubated with monoclonal human anti-NeuN (1:4000; Abcam), fluorescent Alexa488-labeled goat anti-mouse (1:4000; Invitrogen), blocking solution (10% BSA in normal goat serum) and 1X PBS for 1 hour at 4˚C on a rotating wheel. Nuclei were then filtered and sorted on a FACSVantage SE system (BD Bioscience, San Jose CA). Sorting specificity was assessed using an Olympus BX51 microscope with motorized stage under a 40X 0.75 NA UPlan FL N objective using both pre-sorted and sorted fractions (data not shown). Neuronal and non-neuronal nuclei were coverslipped with Vectashield containing DAPI (1:4 with DAPI-free Vectashield) (Vector Lab). Sorted nuclei were pelleted by centrifugation in a sucrose solution (20%) for 15 minutes at 3 000 RPM. For subsequent DNA extraction, nuclei were first lysed at 56˚C for 10 minutes in a solution containing EDTA (50mM), proteinase QIAgen protease (1 unit) and 10% Sodium Dodecyl Sulfate (SDS). DNA was then purified using the DNAeasy extraction kit (QIAgen). Concentration and quality of DNA was assessed on Nanodrop.

DNA Bisulfite treatment and Epityper

Neuronal and non-neuronal DNA fractions extracted from FACS-sorted nuclei were treated with sodium bisulfite (Na-BIS) using the Epitech Bisulfite kit (QIA). BIS DNA was then sent to the Innovation Center of Genome Quebec, where Epityper(25) was performed. Results were analyzed by two way-mixed model ANOVA with groups as a

fixed factor and CpGs as a repeated measure followed by LSD post-hoc tests. Level of significance was fixed at 0.05.

Supplementary Results

CHRNB2 A region of 451 bp, including 28 CpGs, was assessed in the promoter of CHRNB2 gene (chr1:154,539,946 to 154,540,386). Of this region, the first 312 bp (19 CpGs) are located in the promoter while the last 139 bp (9 CpGs) span the first exon. In the neuronal fraction, mixed-model ANOVA revealed a significant hypermethylation in suicides compared to CTRLs ($F_{(1,136)}$=5.36, $p<0.05$; Figure S1B). Post hoc analyses revealed a significant hypermethylation in suicides compared to CTRLs at CpGs sites 1 ($p<0.05$), 2 ($p<0.005$) and 10,11 ($p<0.05$) (Figure S1A). In the non-neuronal fraction, mixed-model ANOVA revealed a significant overall hypomethylation in suicides compared to CTRLs ($F_{(1,188)}$= 4.10, $p<0.05$; Figure S1D), post-hoc analysis showing a significant hypomethylation in suicides compared to CTRLs at CpG site 2 ($p<0.0005$) (Figure S1C).
CHRNB2 gene expression analyses suggested a trend toward a significant down-regulation of CHRNB2 expression in the brain of suicide completers compared to CTRLs ($F_{(1,47)}$ = 2.53, p=0.06; Figure S4A), and therefore, a possible effect of CHRNB2 promoter methylation in the neuronal cell fraction on gene expression. However, there was no significant correlation between expression and methylation (neuronal and non neuronal) data.

GRM7 A region of 179 bp located 367 bp upstream from the TSS including 12 CpGs was assessed in the promoter of the GRM7 gene (chr3:6,902,436 to 6,902,613). A trend toward hypermethylation in suicides was found in the neuronal fraction (mixed-model ANOVA $F_{(1,131)}$= 2.34, p=0.064; Figure S2B), while a significant hypomethylation was found in the non-neuronal fraction of suicides compared to CTRL (mixed-model ANOVA $F_{(1,203)}$=2.81, $p<0.05$; Figure S2D). Post-hoc analyses in the neuronal fraction revealed no site specific difference (Figure S2A) while in the non-neuronal fraction it showed significant hypomethylation at CpGs sites 5 ($p<0.0005$) and 12 ($p<0.05$) in suicides compared to CTRLs (Figure S2C).
Our data revealed a significant decrease in GRM7 expression in the hippocampus of suicide completers compared to CTRLs ($F(1,49)=10.81$, $p<0.005$; Figure S4B), suggesting a possible relationship between changes in promoter DNA methylation patterns in the neuronal cell fraction and GRM7 expression in suicide completers. We found no significant correlation between expression and methylation (neuronal and non neuronal) data.

DBH A region of 329 bp containing 17 CpGs located 24 bp downstream from the TSS within the first exon was assessed in DBH gene (chr9:136,501,510 to 136,501,877)). In the neuronal fraction, we found a trend toward a significant hypermethylation in suicides compared to CTRLs (mixed-model ANOVA $F_{(1,101)}$=2.27, p=0.067; Figure S3B), with post-hoc analyses showing a trend for a significant hypermethylation in suicides compared to CTRLs at CpG sites 5,6 (p=0.076), and 14 (p=0.073) (Figure S3A). No

mean or site-specific methylation difference was found between suicides and CTRLs in the non-neuronal fraction (Figure S3C-D).
Our analysis revealed no significant changes in gene expression between suicides and CTRLs (Figure S4C).

TABLE S1. Sample information

	Suicide	Control
Sexe (M/F)	46/0	16/0
Age	38.8±11.4	40.9±14.3
pH	6.6±0.3	6.5±0.3
PMI	31.3±14.2	32.6±15.1
RIN	6.23±0.6	6.48±0.6
Cause of death	Hanging: 63% (n=29) Drowning: 2% (n=1) Shooting: 2% (n=1) Intoxication: 26% (n=12) Jumping: 4% (n=2) Cutting: 2% (n=1)	Accidental death:100% (n =16)
DSM-IV	Major Depression: 56% (n=26) Substance Dependence: 15% (n=7) Bipolar Disorder: 13% (n=6) Psychotic Disorders: 7% (n=3) NIL: 9% (n=4)	NIL:100% (n=16)
Medication	15% (n=7)	0% (n=0)

Mean±SD

TABLE S2. List of genes differentially methylated rank by corrected p-value (q-value).

Hypermethylated Probes in Suicides						
CHRM	CH_3 Level	q-value	LFC	Gene Name	TSS	Group
7	1,00	3,2E-03	1,10	MUC3A	638	suicide
17	0,95	3,7E-03	1,48	KCNJ12	466	suicide
17	0,95	3,7E-03	1,29	KCNJ12	444	suicide
17	0,96	3,7E-03	1,05	KCNJ12	379	suicide
14	1,00	3,7E-03	1,32	SYNE2	NA	suicide
10	0,62	4,3E-03	0,92	SYNPO2L	298	suicide
1	0,88	4,6E-03	1,19	RPS6KA1	800	suicide
1	0,88	4,6E-03	0,74	RPS6KA1	253	suicide
1	0,90	5,3E-03	1,08	HIST2H2AB	1113	suicide
1	0,90	5,3E-03	0,95	HIST2H2AB	1074	suicide
2	0,28	5,4E-03	1,14	MIR10B	-96	suicide
19	0,91	5,4E-03	0,97	JUNB	468	suicide
11	NA	5,7E-03	0,91	SNX32	1060	suicide
15	0,98	5,8E-03	1,03	SNORD115-14	319	suicide
8	0,90	6,3E-03	0,98	C8orf45	-50	suicide
8	0,96	6,3E-03	0,94	C8orf45	97	suicide
8	0,96	6,3E-03	0,92	C8orf45	23	suicide
1	0,70	6,6E-03	1,39	SLC6A17	297	suicide
17	0,93	6,9E-03	1,10	CNP	1029	suicide
2	0,91	6,9E-03	1,14	ASB3	114	suicide
2	0,91	6,9E-03	0,81	ASB3	132	suicide
2	0,61	7,1E-03	1,09	PRPF40A	-268	suicide
2	0,41	7,1E-03	0,84	PRPF40A	-487	suicide
13	0,98	7,3E-03	0,83	F10	748	suicide
1	0,66	7,6E-03	1,36	S100A6	666	suicide
1	0,13	7,7E-03	1,16	DEDD	358	suicide
13	0,98	8,2E-03	1,32	HTR2A	2021	suicide
19	0,51	9,2E-03	1,36	TFPT	46	suicide
17	0,20	9,8E-03	0,93	FTSJ3	51	suicide
17	0,78	1,1E-02	1,04	CACNG4	857	suicide
4	0,99	1,1E-02	1,10	SCARNA22	821	suicide
19	0,95	1,1E-02	1,17	SNORA68	1053	suicide
19	0,88	1,1E-02	0,92	SNORA68	926	suicide
3	0,70	1,1E-02	1,01	CYB561D2	-265	suicide
1	0,90	1,1E-02	0,88	PMF1	731	suicide
1	0,83	1,1E-02	0,88	ARTN	NA	suicide
16	0,34	1,2E-02	0,87	ALDOA	-389	suicide
15	0,96	1,2E-02	1,14	SNORD115-41	-896	suicide
16	0,62	1,3E-02	0,82	FHOD1	612	suicide
13	1,00	1,3E-02	0,85	SLC15A1	977	suicide
6	0,49	1,3E-02	1,38	NR2E1	955	suicide
12	0,76	1,6E-02	0,98	SNORD59B	457	suicide
12	0,57	1,6E-02	0,83	SNORD59B	-56	suicide
3	0,63	1,6E-02	1,00	GRM7	953	suicide
19	0,57	1,6E-02	1,25	BCL2L12	-54	suicide
1	0,73	1,6E-02	0,85	GPR3	982	suicide

10	0,30	1,6E-02	1,07	NCRNA00081	-157	suicide
10	0,61	1,7E-02	1,01	ELOVL3	444	suicide
1	0,90	1,7E-02	1,07	DEDD	1188	suicide
8	0,88	1,7E-02	0,91	FAM49B	974	suicide
20	0,87	1,8E-02	1,35	SS18L1	-110	suicide
11	0,61	1,8E-02	0,95	SNORD31	-150	suicide
15	0,85	1,8E-02	1,08	HDC	-144	suicide
19	0,40	1,8E-02	1,05	TRIP10	270	suicide
17	0,76	1,9E-02	0,88	SENP3	980	suicide
14	0,85	1,9E-02	1,05	C14orf119	325	suicide
14	0,56	1,9E-02	1,11	METT11D1	516	suicide
6	0,88	1,9E-02	1,25	VTA1	1057	suicide
21	0,99	1,9E-02	1,28	UMODL1	1132	suicide
8	1,00	2,0E-02	1,13	FAM49B	1171	suicide
10	1,00	2,0E-02	1,13	C10orf57	-67	suicide
7	0,92	2,0E-02	1,15	TSPAN33	1183	suicide
14	0,66	2,0E-02	0,97	AKT1	443	suicide
8	0,49	2,0E-02	0,84	MOS	715	suicide
7	0,42	2,0E-02	0,81	ARMC10	-494	suicide
X	0,73	2,0E-02	0,77	NGFRAP1	775	suicide
12	0,47	2,1E-02	0,61	EMG1	77	suicide
11	NA	2,1E-02	0,93	OR2D3	-171	suicide
2	0,98	2,1E-02	1,11	LIMS2	621	suicide
6	0,67	2,1E-02	1,39	ME1	555	suicide
2	0,65	2,1E-02	1,36	NEUROD1	635	suicide
6	0,67	2,1E-02	1,05	ME1	572	suicide
6	0,72	2,1E-02	1,09	ME1	492	suicide
14	0,26	2,1E-02	1,05	ATG2B	-926	suicide
11	0,75	2,1E-02	1,58	ZNF259	945	suicide
22	0,87	2,1E-02	0,89	CTA-299D3.8	835	suicide
12	0,39	2,2E-02	1,14	DYRK2	1132	suicide
6	0,83	2,2E-02	1,07	TTBK1	-93	suicide
21	0,67	2,3E-02	0,99	GABPA	563	suicide
11	0,99	2,3E-02	1,23	NDUFS8	949	suicide
1	0,98	2,3E-02	1,04	MIR555	1255	suicide
1	0,98	2,3E-02	1,08	MIR555	1254	suicide
14	0,52	2,3E-02	1,12	SFRS5	-86	suicide
1	1,00	2,3E-02	1,28	G0S2	NA	suicide
1	0,94	2,4E-02	1,10	ARHGEF2	150	suicide
12	0,86	2,5E-02	1,08	MSI1	NA	suicide
9	0,97	2,6E-02	1,13	NPDC1	-767	suicide
12	1,00	2,6E-02	1,20	ARHGAP9	-555	suicide
17	0,93	2,6E-02	1,20	C17orf84	826	suicide
11	0,91	2,6E-02	1,13	NRGN	600	suicide
14	0,31	2,6E-02	1,03	NEK9	276	suicide
17	0,57	2,6E-02	0,86	FLOT2	544	suicide
2	0,39	2,6E-02	1,01	HOXD13	896	suicide
12	0,93	2,7E-02	0,83	IFNG	4408	suicide

12	0,95	2,7E-02	0,91	IFNG	4394	suicide
1	0,94	2,7E-02	1,17	GUK1	644	suicide
22	0,90	2,7E-02	1,10	LGALS2	-89	suicide
16	0,90	2,7E-02	1,24	NAT15	-262	suicide
19	0,95	2,8E-02	0,91	KLK12	125	suicide
19	0,70	2,9E-02	1,20	BBC3	535	suicide
12	0,93	2,9E-02	1,42	ACCN2	1175	suicide
20	1,00	2,9E-02	1,10	SNORD119	1066	suicide
7	0,35	3,0E-02	1,32	PTPRZ1	521	suicide
1	0,27	3,1E-02	0,86	TAF5L	-518	suicide
5	0,65	3,1E-02	1,00	CDX1	567	suicide
14	1,00	3,1E-02	1,20	SYNE2	-86	suicide
20	0,76	3,1E-02	1,16	PHACTR3	774	suicide
20	0,93	3,1E-02	1,09	PHACTR3	853	suicide
X	0,29	3,2E-02	0,84	PQBP1	-72	suicide
11	0,96	3,2E-02	1,11	BSCL2	-636	suicide
19	0,91	3,3E-02	1,11	SNORD37	992	suicide
11	1,00	3,4E-02	1,01	OR2AG2	847	suicide
11	0,76	3,4E-02	1,10	PRCP	196	suicide
21	0,97	3,4E-02	1,30	USP25	926	suicide
1	0,71	3,5E-02	1,15	CHRNB2	681	suicide
1	1,00	3,5E-02	1,06	AC096643.1	602	suicide
14	0,89	3,5E-02	0,93	C14orf34	NA	suicide
7	0,75	3,5E-02	1,04	CCDC136	161	suicide
8	0,55	3,6E-02	1,18	NEIL2	714	suicide
3	0,69	3,6E-02	0,95	MIR425	-788	suicide
10	0,51	3,6E-02	1,02	ZCCHC24	523	suicide
2	0,31	3,6E-02	1,19	SLC25A12	548	suicide
11	0,66	3,7E-02	0,98	APLP2	927	suicide
20	0,72	3,7E-02	1,36	E2F1	405	suicide
12	0,60	3,7E-02	0,91	NUAK1	518	suicide
12	0,60	3,7E-02	1,05	NUAK1	511	suicide
2	0,84	3,7E-02	1,09	LOC150935	1118	suicide
22	0,90	3,8E-02	1,07	ARVCF	-1576	suicide
17	0,91	3,8E-02	1,45	BCAS3	-364	suicide
3	0,24	3,8E-02	0,95	DLEC1	113	suicide
3	0,34	3,8E-02	0,99	DLEC1	-54	suicide
3	0,58	3,8E-02	0,84	FBXO45	-844	suicide
1	1,00	3,8E-02	1,25	SYTL1	-549	suicide
13	0,76	3,9E-02	1,17	POMP	1229	suicide
13	0,80	3,9E-02	0,90	POMP	896	suicide
6	NA	3,9E-02	1,16	GJA1	630	suicide
6	NA	3,9E-02	0,95	GJA1	465	suicide
6	NA	3,9E-02	1,01	GJA1	604	suicide
16	0,59	3,9E-02	1,18	C16orf45	357	suicide
14	0,88	4,0E-02	1,39	ZFYVE21	664	suicide
18	0,87	4,0E-02	1,01	RAB31	1218	suicide
18	0,90	4,0E-02	1,08	RAB31	1183	suicide

5	0,29	4,0E-02	0,97	MRPL22	73	suicide
12	0,99	4,0E-02	0,97	KRT75	352	suicide
9	0,63	4,1E-02	1,49	C8G	149	suicide
5	0,85	4,1E-02	1,04	SNORA47	28	suicide
15	0,86	4,1E-02	1,21	SNORD115-23	920	suicide
15	0,86	4,1E-02	1,07	SNORD115-22	-833	suicide
15	0,77	4,2E-02	0,88	SNORD115-7	-49	suicide
14	0,45	4,2E-02	1,16	SFRS5	622	suicide
17	0,83	4,2E-02	0,76	C17orf107	1034	suicide
3	1,00	4,3E-02	1,24	U73167.7	-534	suicide
8	0,70	4,3E-02	1,15	PTDSS1	-798	suicide
8	0,70	4,3E-02	1,26	PTDSS1	-778	suicide
X	0,62	4,3E-02	1,20	TFDP3	682	suicide
10	0,37	4,4E-02	0,87	GFRA1	358	suicide
19	0,84	4,4E-02	1,03	CYP2B7P1	NA	suicide
17	0,63	4,5E-02	0,91	SMCR8	-545	suicide
1	0,63	4,5E-02	0,88	ILDR2	1179	suicide
7	1,00	4,5E-02	1,02	WIPF3	969	suicide
X	0,97	4,5E-02	1,49	KLHL34	1002	suicide
X	0,91	4,5E-02	1,32	KLHL34	921	suicide
X	1,00	4,5E-02	1,05	KLHL34	1068	suicide
12	0,13	4,5E-02	1,36	MCRS1	205	suicide
12	0,13	4,5E-02	0,89	MCRS1	152	suicide
2	0,10	4,7E-02	1,04	PLCL1	457	suicide
19	1,00	4,7E-02	1,19	MUC16	793	suicide
19	0,82	4,7E-02	1,18	MED29	-1052	suicide
9	0,80	4,7E-02	1,22	MSMP	1101	suicide
15	0,87	4,7E-02	1,17	PKM2	467	suicide
X	0,53	4,7E-02	0,97	RBM3	482	suicide
8	0,95	4,8E-02	0,93	C8orf74	993	suicide
18	0,41	5,0E-02	0,96	C18orf54	432	suicide
13	0,45	5,0E-02	1,22	EDNRB	125	suicide
1	0,77	5,2E-02	0,74	RNASEL	1142	suicide
20	0,90	5,2E-02	0,75	SGK2	1297	suicide
9	0,96	5,2E-02	1,00	ATP8B5P	NA	suicide
3	0,84	5,2E-02	0,88	TNNC1	220	suicide
11	1,00	5,3E-02	1,30	CALCB	1022	suicide
3	0,93	5,3E-02	0,98	RFT1	812	suicide
12	0,80	5,3E-02	0,92	GPR133	464	suicide
9	0,71	5,4E-02	1,19	AKAP2	425	suicide
X	0,89	5,4E-02	0,88	HMGB3	1153	suicide
14	0,25	5,5E-02	1,14	HOMEZ	335	suicide
7	0,95	5,5E-02	0,81	BET1	353	suicide
22	0,97	5,5E-02	1,09	PRAME	149	suicide
6	0,85	5,6E-02	0,97	RIMS1	499	suicide
X	0,92	5,6E-02	1,27	CTPS2	963	suicide
17	0,85	5,6E-02	0,96	PCTP	674	suicide
1	0,87	5,6E-02	0,84	ADORA1	297	suicide

5	0,20	5,7E-02	1,22	AC004507.1	-62	suicide
5	0,20	5,7E-02	0,97	AC004507.1	-71	suicide
7	0,86	5,7E-02	1,00	NPC1L1	58	suicide
15	1,00	5,7E-02	0,97	BMF	145	suicide
X	0,79	5,8E-02	1,38	USP27X	-581	suicide
17	0,62	5,9E-02	0,87	MSL1	-790	suicide
1	0,77	5,9E-02	1,02	TTC4	984	suicide
7	0,74	5,9E-02	1,13	ACCN3	436	suicide
7	0,74	5,9E-02	1,05	ACCN3	414	suicide
17	1,00	5,9E-02	1,12	MIR497	781	suicide
17	0,92	6,0E-02	0,98	NME1-NME2	14	suicide
1	0,64	6,0E-02	1,26	EIF2C1	453	suicide
9	0,95	6,0E-02	1,21	DBH	173	suicide
19	0,73	6,0E-02	1,11	TOMM40	684	suicide
7	0,84	6,1E-02	0,97	ADCY1	419	suicide
9	0,65	6,2E-02	1,50	DOCK8	578	suicide
10	0,97	6,2E-02	1,15	PAPSS2	446	suicide
X	0,92	6,2E-02	0,97	OCRL	99	suicide
20	0,64	6,3E-02	0,92	FAM110A	NA	suicide
X	0,94	6,3E-02	1,09	DDX53	-116	suicide
1	0,90	6,3E-02	1,44	CD58	1213	suicide
19	0,95	6,4E-02	1,04	SHANK1	1097	suicide
9	0,25	6,4E-02	1,32	CENPP	46	suicide
17	0,82	6,4E-02	0,81	WFIKKN2	306	suicide
17	0,84	6,5E-02	1,19	LYZL6	68	suicide
4	0,73	6,5E-02	1,08	CHIC2	925	suicide
8	1,00	6,6E-02	1,39	C8orf71	1208	suicide
8	1,00	6,6E-02	1,22	C8orf71	1223	suicide
2	0,89	6,6E-02	1,11	SH2D6	460	suicide
17	0,62	6,7E-02	0,99	RPL19	996	suicide
11	0,89	6,7E-02	0,83	OMP	NA	suicide
8	0,24	6,7E-02	0,95	ADCY8	618	suicide
8	0,24	6,7E-02	0,88	ADCY8	612	suicide
14	0,88	6,8E-02	0,95	KCNK10	298	suicide
13	0,90	6,8E-02	0,82	STK24	1313	suicide
14	0,41	6,9E-02	1,21	GLRX5	-1049	suicide
2	0,68	7,0E-02	0,82	SCLY	589	suicide
22	1,00	7,1E-02	1,07	TMPRSS6	387	suicide
3	0,36	7,1E-02	0,91	TOPBP1	NA	suicide
19	0,96	7,2E-02	0,95	DAND5	310	suicide
1	0,67	7,2E-02	1,22	OR13G1	39	suicide
1	0,67	7,2E-02	0,90	OR13G1	23	suicide
15	0,77	7,2E-02	1,07	BTBD1	721	suicide
13	0,48	7,3E-02	1,14	RNF6	-147	suicide
22	0,92	7,3E-02	1,23	GSTTP2	539	suicide
16	0,78	7,3E-02	0,93	NTN3	796	suicide
17	0,83	7,4E-02	0,92	NACA2	NA	suicide
X	0,94	7,4E-02	1,01	ZNF185	1070	suicide

9	0,85	7,6E-02	1,09	C9orf91	592	suicide
1	0,41	7,7E-02	1,09	ATP8B2	462	suicide
X	0,11	7,7E-02	1,23	RBMX	-723	suicide
19	0,62	7,7E-02	0,89	PNMAL2	1142	suicide
10	0,56	7,8E-02	0,93	TCF7L2	-75	suicide
12	0,70	7,8E-02	0,84	PHC1B	-694	suicide
12	0,78	7,8E-02	0,84	PHC1B	-845	suicide
5	0,91	7,8E-02	0,76	PCDHGA6	NA	suicide
2	0,17	7,9E-02	1,29	HADHA	-403	suicide
2	0,94	8,0E-02	1,40	UGT1A9	567	suicide
2	1,00	8,0E-02	1,11	UGT1A9	670	suicide
1	0,16	8,0E-02	0,92	JUN	NA	suicide
X	0,69	8,1E-02	1,01	SLC16A2	-404	suicide
3	0,82	8,2E-02	1,20	SST	223	suicide
20	0,92	8,2E-02	1,06	OGFR	261	suicide
19	0,23	8,3E-02	1,12	AKT1S1	-414	suicide
6	0,37	8,3E-02	0,90	ZNF184	-183	suicide
6	0,38	8,3E-02	1,13	ECHDC1	72	suicide
10	0,81	8,4E-02	1,00	DUSP13	415	suicide
22	1,00	8,5E-02	0,83	TMPRSS6	318	suicide
13	0,90	8,7E-02	1,11	GAS6	-179	suicide
16	0,77	8,8E-02	1,11	DPEP2	788	suicide
17	0,81	8,8E-02	1,40	SLC6A4	NA	suicide
9	0,21	8,8E-02	1,25	WDR31	482	suicide
14	0,92	8,9E-02	1,15	C14orf180	1139	suicide
6	1,00	8,9E-02	1,15	DDO	1102	suicide
22	0,98	9,0E-02	1,08	SYNGR1	530	suicide
1	0,22	9,4E-02	0,96	GGPS1	2	suicide
2	0,97	9,4E-02	1,23	ANKMY1	-2108	suicide
3	0,99	9,4E-02	1,11	GP5	-219	suicide
3	1,00	9,4E-02	0,98	GP5	-122	suicide
1	0,45	9,5E-02	1,24	ANKRD34A	-41	suicide
9	0,69	9,5E-02	0,88	CENPP	-927	suicide
22	0,87	9,6E-02	0,96	VPREB3	-7	suicide
5	0,74	9,8E-02	0,69	PCBD2	-271	suicide
Hypomethylated Probes in Suicides						
CHRM	**CH_3 level**	**q-value**	**LFC**	**Gene Name**	**TSS**	**Group**
14	0,62	3,1E-03	-0,89	SNORD114-14	950	control
14	0,58	3,1E-03	-0,86	SNORD114-14	884	control
12	0,08	3,2E-03	-0,97	CLEC12B	708	control
9	0,78	3,2E-03	-1,14	MAPKAP1	-37	control
3	0,63	4,0E-03	-1,21	PLCL2	320	control
Y	0,88	7,1E-03	-1,22	AMELY	211	control
Y	0,58	7,3E-03	-0,93	NLGN4Y	765	control
9	0,64	7,3E-03	-0,95	OR13F1	1177	control
5	0,29	7,6E-03	-1,16	DNAH5	820	control
6	0,63	7,7E-03	-0,98	CLIC5	545	control
10	NA	8,0E-03	-1,47	A1CF	716	control

15	0,84	1,1E-02	-0,82	TGM7	549	control
15	1,00	1,1E-02	-0,96	TGM7	429	control
4	0,62	1,1E-02	-1,29	C4orf21	47	control
18	0,77	1,4E-02	-0,82	MEP1B	214	control
1	0,74	1,6E-02	-1,07	DNAH14	1042	control
13	0,72	1,8E-02	-1,59	POSTN	185	control
5	0,52	1,8E-02	-1,09	PCDHA2	NA	control
1	0,57	2,0E-02	-1,26	NRD1	-8	control
5	0,94	2,2E-02	-0,83	SPEF2	-19	control
14	0,94	2,3E-02	-1,02	CMA1	-94	control
4	0,44	2,3E-02	-1,02	PDE5A	1098	control
11	0,71	2,4E-02	-0,93	OR52M1	607	control
3	0,73	2,6E-02	-1,09	SPINK8	56	control
1	0,16	2,6E-02	-1,06	HNRNPU	1230	control
1	0,90	2,6E-02	-0,93	OR2T1	33	control
1	0,94	2,7E-02	-1,18	VAV3	1210	control
12	0,62	2,8E-02	-0,93	OVOS1	-87	control
17	0,55	2,9E-02	-1,10	ASPA	68	control
10	0,49	3,0E-02	-0,92	MIR107	109	control
2	NA	3,1E-02	-0,97	BX640963	NA	control
10	0,48	3,2E-02	-1,53	MIR1296	402	control
13	0,67	3,2E-02	-1,12	ELF1	1202	control
1	0,72	3,5E-02	-1,04	C8B	-181	control
4	0,72	3,9E-02	-0,94	ADH7	-7	control
1	0,33	4,0E-02	-1,13	PEX19	312	control
X	0,91	4,0E-02	-0,99	AFF2	1082	control
8	0,55	4,0E-02	-1,10	KLHL38	285	control
17	0,94	4,0E-02	-0,86	KRT37	843	control
11	NA	4,1E-02	-1,08	SAA4	452	control
1	0,32	4,2E-02	-1,07	OLFM3	605	control
21	NA	4,2E-02	-0,98	KRTAP20-2	1222	control
13	0,29	4,3E-02	-0,84	FBXL3	752	control
1	0,95	4,5E-02	-0,87	LCE1D	391	control
5	0,56	4,5E-02	-0,91	PCDHA2	NA	control
19	0,94	4,5E-02	-1,04	NLRP8	56	control
X	0,36	4,5E-02	-1,16	GEMIN8	-514	control
20	1,00	4,5E-02	-1,01	LOC284749	NA	control
2	0,58	4,5E-02	-1,18	C2orf82	135	control
2	0,67	4,8E-02	-1,09	LIMS1	680	control
2	0,46	4,9E-02	-0,89	CKAP2L	4515	control
X	0,64	4,9E-02	-1,05	MIR505	-50	control
7	0,85	5,0E-02	-0,88	GRB10	945	control
9	0,15	5,2E-02	-1,45	CDC26	696	control
6	0,68	5,3E-02	-1,14	GJA1	2424	control
18	NA	5,4E-02	-1,41	SLC14A1	-2028	control
10	0,69	5,6E-02	-1,00	LOC728640	NA	control
10	0,75	5,6E-02	-1,04	C10orf11	649	control
14	0,82	5,7E-02	-1,02	JUB	1053	control

14	0,51	6,0E-02	-1,25	MNAT1	1271	control
8	0,85	6,0E-02	-1,18	OC90	1148	control
6	0,00	6,1E-02	-1,08	MAN1A1	772	control
14	0,68	6,2E-02	-0,98	FERMT2	NA	control
14	0,52	6,4E-02	-1,32	ATP5S	943	control
1	0,79	6,5E-02	-0,95	KIAA0467	-1104	control
1	NA	6,5E-02	-1,30	IPP	191	control
6	0,60	6,6E-02	-1,19	VIP	610	control
11	0,35	6,6E-02	-0,90	IMMP1L	-1152	control
5	0,52	6,8E-02	-1,17	PCDHA2	3661	control
12	0,68	6,9E-02	-1,06	PLCZ1	-790	control
8	0,09	7,2E-02	-1,02	CHD7	937	control
19	0,67	7,7E-02	-1,16	ZNF546	141	control
19	0,56	7,7E-02	-0,97	ZNF546	223	control
1	0,62	7,8E-02	-0,85	C1orf120	-199	control
1	0,62	7,8E-02	-0,88	C1orf120	-189	control
8	0,28	7,8E-02	-1,39	FZD6	NA	control
18	0,47	7,9E-02	-1,20	ELAC1	400	control
1	NA	8,1E-02	-1,20	NR1I3	NA	control
7	0,37	8,3E-02	-0,96	HTR5A	693	control
1	0,29	8,3E-02	-0,93	ARID1A	-27	control
X	0,74	8,4E-02	-1,06	PNPLA4	715	control
3	0,81	8,5E-02	-1,28	MECOM	NA	control
22	0,67	8,7E-02	-1,08	MKL1	442	control
1	0,62	8,9E-02	-1,12	SCARNA3	702	control
8	0,59	8,9E-02	-0,96	TPD52	691	control
1	0,68	9,0E-02	-1,15	LASS2	1235	control
1	0,68	9,0E-02	-1,12	LASS2	1220	control
21	0,51	9,0E-02	-1,09	BACE2	1160	control
4	0,41	9,0E-02	-0,85	KLHL5	693	control
17	NA	9,0E-02	-1,34	H3F3B	902	control
2	0,81	9,2E-02	-1,01	COL3A1	936	control
11	0,58	9,7E-02	-0,88	PPP1R14B	1243	control
9	0,43	9,9E-02	-0,96	OR13C3	497	control

Legend: CHRM: chromosome, CH_3 level: methylation level, q-value: corrected p-value, LFC: log fold change, TSS: distance from transcription start site, Groups: group in which hypermethylation was found.

Genes	ABI Cat. Number
CHRNB2	Hs00181267_m1
GRM7	Hs00356067_m1
DBH	Hs01089840_m1
NR2E1	Hs01128417_m1
β-actin	Hs02758991_g1
GAPDH	Hs01060665_g1

FIGURE S1. Methylation levels in CHRNB2 promoter in suicide completers (suicide; black) and controls (CTRL; white) in the neuronal and non-neuronal cell fractions. **A** Individual CpG methylation levels in the promoter of CHRNB2 in the neuronal cell fraction. N: Suicide: 32, CTRL: 11. **B** Total % methylation in CHRNB2 promoter in the neuronal cell fraction. **C** Individual CpG methylation levels in the promoter of CHRNB2 in the non-neuronal cell fraction. N: Suicide: 42, CTRL: 16. **D** Total % methylation in CHRNB2 promoter in the non-neuronal cell fraction. Values are given as mean % of methylation ± SEM. * $p<0.05$. Arrow represents the beginning of TSS.

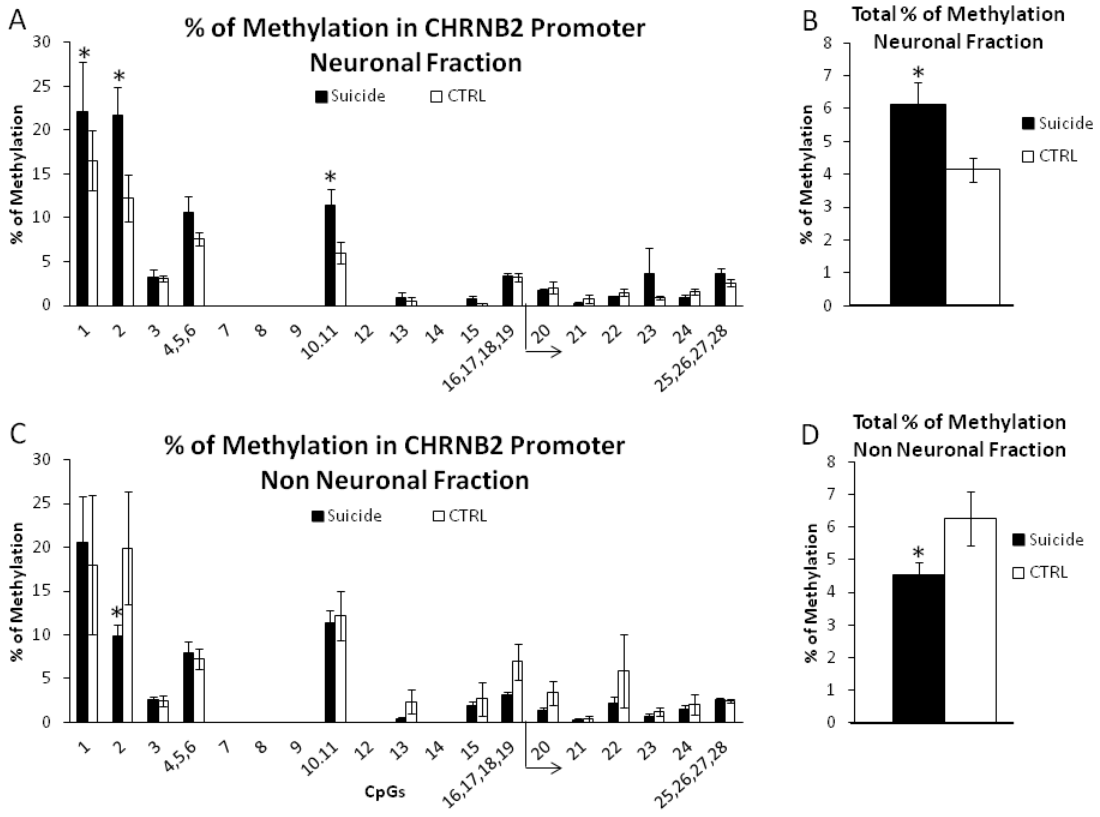


FIGURE S2. Methylation levels in GRM7 promoter in suicide completers (suicide; black) and controls (CTRL; white) in the neuronal and non neuronal cell fractions. **A** Individual CpG methylation levels in the promoter of GRM7 in the neuronal cell fraction. N: Suicide: 39, CTRL: 13. **B** Total % methylation in GRM7 promoter in the neuronal cell fraction. **C** Individual CpG methylation levels in the promoter of GRM7 in the non-neuronal cell fraction. N: Suicide: 46, CTRL: 16. **D** Total % methylation in GRM7 promoter in the non-neuronal cell fraction. Values are given as mean % of methylation ± SEM. * $p<0.05$, † $p<0.1$.

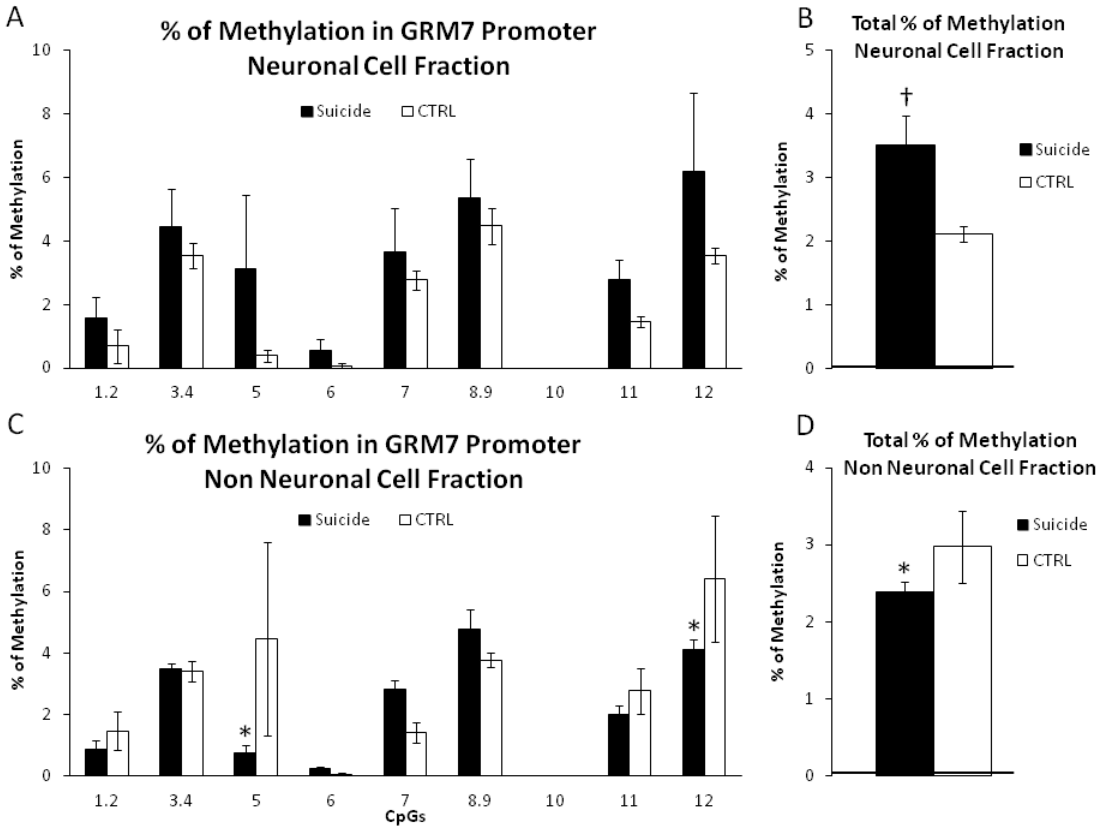


FIGURE S3. Methylation levels in DBH promoter in suicide completers (SA; black) and controls (CTRL; white). **A** Individual CpG methylation levels in the promoter of DBH in the neuronal cell fraction. N: Suicide: 33, CTRL: 13. **B** Total % methylation in DBH promoter in the neuronal cell fraction. **C** Individual CpG methylation levels in the promoter of DBH in the non-neuronal cell fraction. N: Suicide: 46, CTRL: 16. **D** Total % methylation in DBH promoter in the non-neuronal cell fraction. Values are given as mean % of methylation ± SEM. † $p<0.1$. Arrow represents the beginning of TSS.

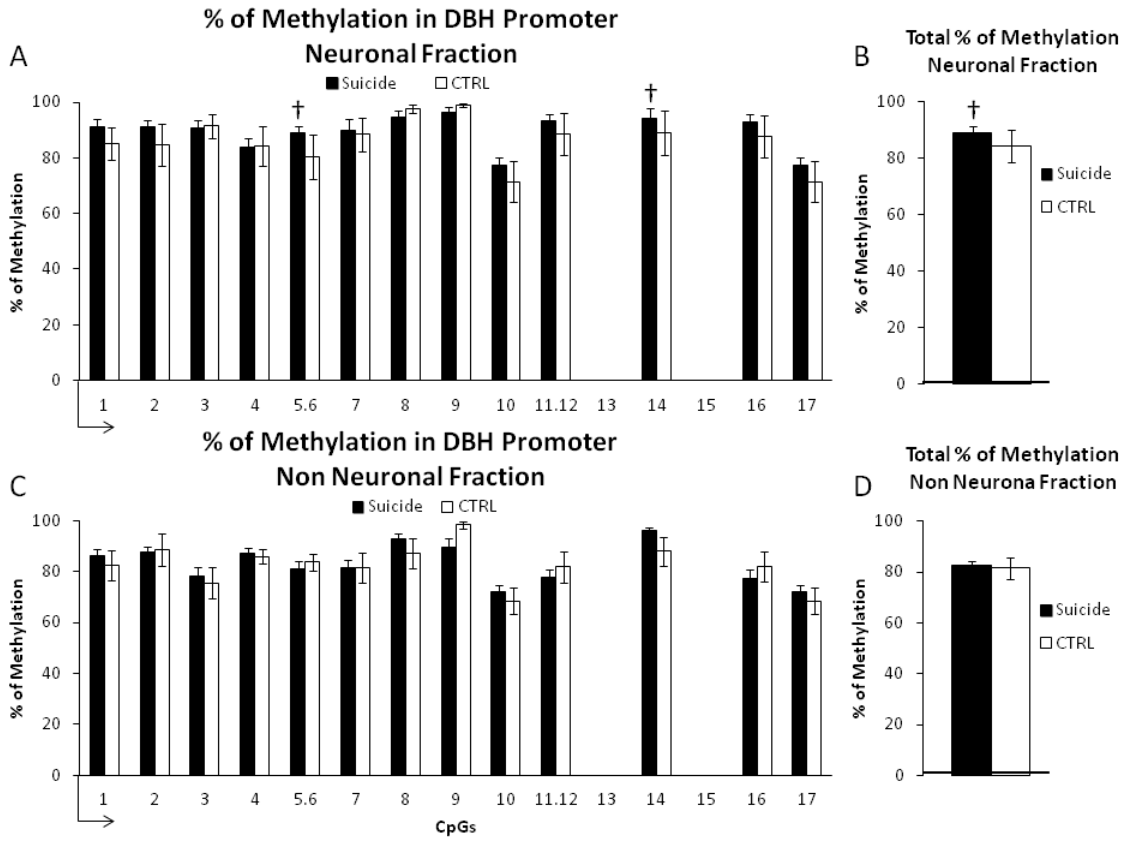
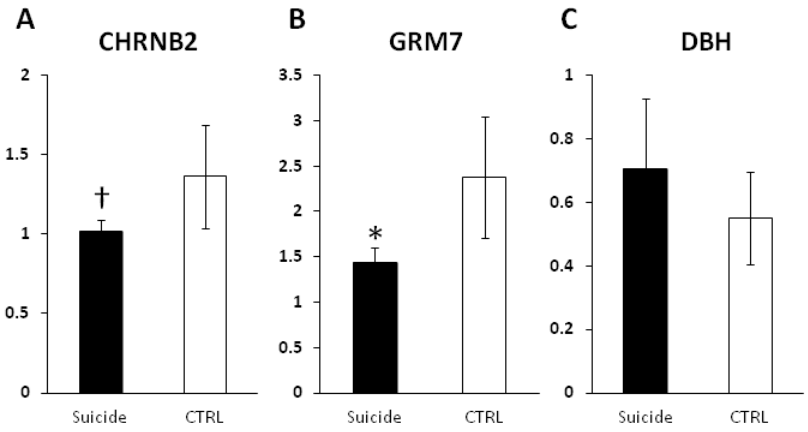


FIGURE S4. Gene expression levels for **A** CHRNB2 (N: Suicide: 41, CTRL: 10), **B** GRM7 (N: Suicide: 42, CTRL: 13) and **C** DBH (N: Suicide: 36, CTRL: 10) genes. Values are given as mean % of methylation ± SEM. * $p<0.05$, † $p<0.1$.



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