Supplemental Methods

Analysis of 5-HT$_{2C}$R Editing

cDNA from each of the 101 subjects was used as a template to PCR-amplify the region that contains all 5 editing sites (region of editing). To minimize the influence of a possibly erroneous amplification in a single reaction, which could alter the proportions of differently edited mRNA variants, three independent PCRs were performed for each subject using forward (F)-GTGATCATGGCAGTAAGCATGGA and reverse (R)-ATCTTCATGATGGCCTTAGTCCG primer-pair and a touch-down cycling program, consisting of 10 min at 95° C; 10 cycles of 15 sec at 95° C, 30 sec at 68-59° C (annealing temperature was decreased 1° C after each cycle), and 30 sec at 72° C, followed by 35 cycles of 15 sec at 95° C, 30 sec at 58° C, and 30 sec at 72° C. The reverse primer was designed within the 95 bp region that contains all five editing sites and is deleted in the truncated mRNA splice variant 5-HT$_{2C}$Rsp1 (see below) (Dracheva et al. 2003; Flomen et al. 2004; Dracheva et al. 2008); therefore, only the full-length 5-HT$_{2C}$R transcript (5-HT$_{2C}$Rsp2) that encodes a full-length receptor was amplified using this primer pair. The PCR products of the three independent reactions generated for each subject were combined and resolved by gel electrophoresis. A single DNA band of the expected size (~305bp) was detected for each subject. The fragment was gel-purified using a MinElute gel extraction kit (Qiagen) and analyzed using Next Generation Sequencing.

Next Generation Sequencing (NGS)

The purified PCR products generated from all 101 individuals were subjected to NGS on the Illumina platform. Next generation multiplex sequencing libraries compatible with the Illumina GAIIx system were prepared from each PCR product with the following modifications from the manufacturer's recommendations: (1) the volume of the end repair step was scaled down from 100 to 25 µl; (2) the volumes of the 3' A-overhang addition and adapter ligation steps were scaled down from 50 to 25 µl; (3) the size selection step was eliminated because each template represented a PCR product and, therefore, had the same size. To reduce the cost, the number of indices was extended from 12-plex to 24-plex, thus allowing a simultaneous run of 24 different samples. This was achieved by synthesizing 12 additional molecular barcode oligonucleotides. To prevent wrong assignments of reads, care was taken to ensure that all 24 barcode sequences were sufficiently different from each other. This was achieved by increasing the length of the molecular barcode from 6 to 8 nucleotides.

The five nucleotides that undergo editing (A, B, E, C and D sites) are closely spaced within 13 base pairs (bp) and are situated in the range of 47 to 59 bp from one of the ends of the PCR product. While these positions are within the reach of a read when the GAIIx system is used, raw error rates are still a concern at base positions over 50 bp from the end of a template. In addition, our method could not rely on alignment to a reference for a consensus error correction. To circumvent this problem, we modified the sequencing protocol. Specifically, custom sequencing primers that anneal within the PCR product were employed instead of a standard Illumina sequencing primer that anneals within the adapter. In addition, because the PCR fragments could be cloned in two different directions relative to the adapter, 2 primers were used to sequence the fragments oriented in the forward and reverse direction, respectively. This approach positioned the variable nucleotides no more than 24 bases away from a sequencing primer, thus minimizing the raw error rates. Cluster generation was performed using the multi-primer-hyb recipe and a pool of the 2 sequencing primers at 100 nM each. Sequencing was performed using a custom single-read-multiplex recipe collecting 27 bases on the primary read and 9 bases on the indexing read.

A PERL script was written to sort each sequence by its barcode, thus assigning it to its corresponding sample. Within each sample, the script counted the number of reads corresponding to each of the 32 expected mRNA variants as well as the percentage of each of the variants relative to the total number of reads obtained for the sample.

Gene Expression Analysis

mRNA expression of 5-HT$_{2C}$R and ADAR1&2, was measured by quantitative real-time PCR (qPCR) using ABI Prism 7900 Sequence Detector (Applied Biosystems) and TaqMan® gene-specific FAM/MGB assays (Applied Biosystems) as described (Dracheva et al. 2009). The reactions were run in triplicates for each sample and for each assay. To control for variation in the amount and quality of mRNA in each sample, expression levels of the target (5-HT$_{2C}$R and ADAR1&2) transcripts were normalized to the
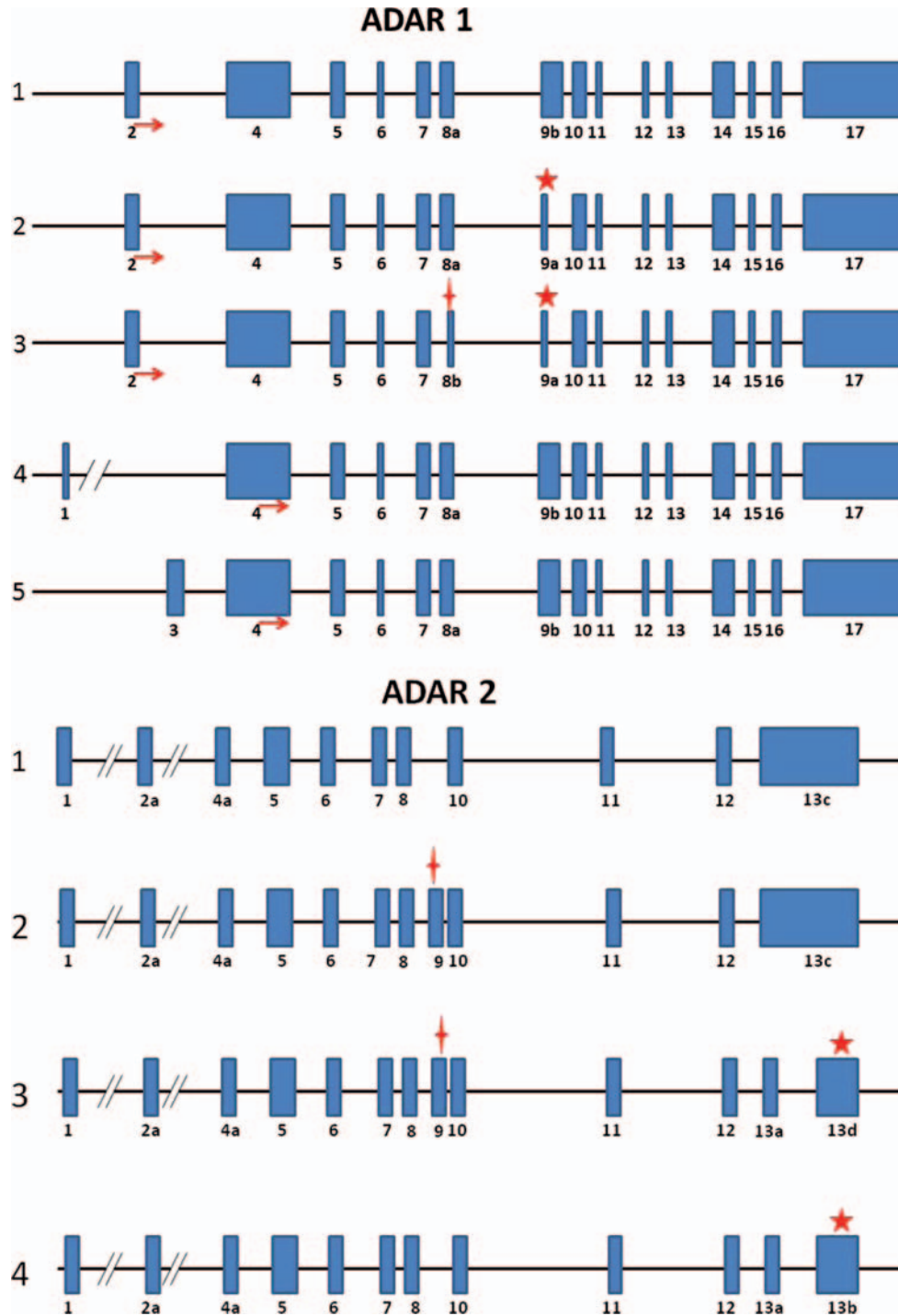
Supplemental Figure 1. Schematic representation of the five ADAR1 and four ADAR2 mRNA splice variants. ADAR1 transcripts vary: *(1)* in their first exon (exon 1, 2, or 3 in variants 4, 1-3, and 5 respectively) and, therefore their translational start codon (translational start and direction is indicated by red arrow) and *(2)* in the length of exon 8 and 9, where exon 8b (red diamond) in variant 3 and exon 9a (red star) in variants 2 & 3 represent shortened versions of those respective exons. ADAR2 transcripts vary: *(1)* in the presence of exon 9 in variants 2 & 3 (red diamonds) and *(2)* the length of exon 13, which is shortened in variants 3 & 4 (red stars). Schematics are not drawn to scale.

expression levels of five endogenous control genes (ECG) [beta-2-microglobulin (*B2M*), beta glucuronidase (*GUSB*), cyclophilin A (*PPIA*), hypoxanthine ribosyltransferase 1 (*HPRT1*),and large ribosomal protein (*RPLPO*)]. A touch-down thermal cycling program was applied to amplify the 5-HT$_{2C}$R transcripts. It consisted of 2 min at 50° C; 10 min at 95° C; 10 cycles of 15 sec at 95° C, 30 sec at 70-61° C (annealing temperature was decreased 1° C after each cycle), and 30 sec at 72° C, followed by

Supplementary Table 1. Demographic Information of the study cohort

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsychotics	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
NORMAL CONTROLS															
1	SMRI: Array	44	F	W	28	6.59	1330	Cardiac	None	None	None	None	Moderate present	Unknown	Not available
2	SMRI: Array	49	M	W	46	6.5	1605	Cardiac	None	None	None	None	Little or none	No	Not available
3	SMRI: Array	53	M	W	9	6.4	1500	Cardiac	None	None	None	None	Little or none	Unknown	Not available
4	SMRI: Array	37	M	W	13	6.5	1600	Cardiac	None	None	None	None	Little or none	Yes	Not available
5	SMRI: Array	51	M	W	31	6.7	1400	Cardiac	None	None	None	None	Little or none	No	Not available
6	SMRI: Array	53	M	W	28	6	1340	Cardiac	None	None	None	None	Little or none	Unknown	Not available
7	SMRI: Array	38	F	W	33	6	1120	Cardiac	None	None	None	None	Moderate present	Unknown	Not available
8	SMRI: Array	38	F	W	28	6.7	1350	Cardiac	None	None	None	None	Little or none	Unknown	Not available
9	SMRI: Array	60	M	W	47	6.8	1460	Cardiac	None	None	None	None	Little or none	Unknown	Not available
10	SMRI: Array	35	M	W	52	6.7	1700	Myocarditis	None	None	None	None	Little or none	Unknown	Not available
11	SMRI: Array	34	M	W	22	6.48	1480	Cardiac	None	None	None	None	Little or none	Unknown	Not available
12	SMRI: Array	47	M	W	21	6.81	1550	Cardiac	None	None	None	None	Little or none	Yes	Not available
13	SMRI: Array	45	M	W	29	6.94	1405	Cardiac	None	None	None	None	Little or none	Yes	Not available
14	SMRI: Array	34	F	W	24	6.87	1255	Cardiac	None	None	None	None	Little or none	Unknown	Not available
15	SMRI: Array	42	M	W	37	6.91	1340	Cardiac	None	None	None	moderate present (cannabis)	Heavy past	Yes	Not available
16	SMRI: Array	44	F	W	10	6.2	1305	Cardiac	None	None	None	None	Little or none	No	Not available
17	SMRI: Array	45	M	W	18	6.81	1585	Cardiac	None	None	None	None	Little or none	No	Not available
18	SMRI: Array	49	M	W	23	6.93	1390	Cardiac	None	None	None	None	Little or none	No	Not available
19	SMRI: Array	35	M	W	24	7.03	1415	Cardiac	None	None	None	None	Moderate past	No	Not available
20	SMRI: Array	55	M	W	31	6.7	1515	Cardiac	None	None	None	None	Little or none	Yes	Not available

(Continued)

Supplementary Table 1. *(continued)*

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsy chotics	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
21	SMRI: Array	49	F	W	45	6.72	1435	Cardiac	None	None	None	None	Little or none	Yes	Not available
22	SMRI: Array	33	F	W	29	6.52	1360	Asthma	None	None	None	social	Little or none	Unknown	Not available
23	SMRI: Array	48	M	W	31	6.86	1580	Cardiac	None	None	None	None	Little or none	Unknown	Not available
24	SMRI: Array	50	M	W	49	6.75	1645	Cardiac	None	None	None	None	Little or none	Yes	Not available
25	SMRI: Array	32	M	W	13	6.57	1410	Cardiac	None	None	None	None	Little or none	Unknown	Not available
26	SMRI: Array	47	M	W	11	6.6	1495	Cardiac	None	None	None	social	Little or none	No	Not available
27	SMRI: Array	46	M	W	31	6.67	1360	Cardiac	None	None	None	None	Little or none	Unknown	Not available
28	SMRI: Array	40	M	W	38	6.67	1498	Cardiac	None	None	None	None	Little or none	Yes	Not available
29	SMRI: Array	51	M	W	22	6.71	1900	Cardiac	None	None	None	None	Little or none	Unknown	Not available
30	SMRI: Array	31	M	W	11	6.13	1335	Pulm Embol	None	None	None	social	Little or none	Unknown	Not available
31	SMRI: Array	48	M	W	24	6.91	1321	Cardiac	None	None	None	social	Little or none	Unknown	Not available
32	SMRI: D/S	39	F	W	58	6.46	1260	Cardiac	None	None	None	None	Heavy past	Yes	Not available
33	SMRI: D/S	47	M	W	36	6.57	1535	Cardiac	None	None	None	None	Little or none	No	Not available
34	SMRI: D/S	41	F	W	50	6.17	1290	Cardiac	None	None	None	None	Little or none	No	Not available
35	SMRI: D/S	34	M	W	9	6.56	1535	MVA	None	None	None	None	Little or none	yes	Not available
36	SMRI: D/S	50	M	W	11	6.5	1530	Cardiac	None	None	None	social	Little or none	Unknown	Not available
37	SMRI: D/S	24	M	W	17	6.6	1595	MVA	None	None	None	heavy past	Heavy past	Unknown	Not available
38	SMRI: D/S	50	F	W	35	6.31	1520	Cardiac	Buspirone	None	None	None	Little or none	Yes	Not available
39	SMRI: D/S	39	F	W	24	6.88	1200	Cardiac	None	None	None	None	Little or none	Unknown	Not available
40	SMRI: D/S	56	F	W	29	6.78	1278	Cardiac	None	None	None	None	Little or none	No	Not available
41	SMRI: D/S	48	M	H	12	6.51	1410	Cardiac	None	None	None	social	Heavy past	No	Not available

(Continued)

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsychotics	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
42	SMRI: D/S	35	M	W	31	6.59	1520	MVA	None	None	None	None	Moderate present	Yes	Not available
43	SMRI: D/S	63	M	W	40	6.91	1410	Cardiac	None	None	None	None	Heavy past	No	Not available
44	SMRI: D/S	56	F	W	31	6.66	1400	Obesity	None	None	None	None	Heavy past	Yes	Not available
45	SMRI: D/S	63	M	W	37	6.5	1530	Cardiac	None	None	None	None	Little or none	Unknown	Not available
46	MBC	72	F	W	17	N/A	1090	MVA	None	None	Unknown	None	Little or none	No	salicylate
47	MBC	16	M	W	20	6.89	1650	MVA	None	None	None	None	Little or none	No	OTC cold meds
48	MBC	35	M	W	16	6.44	1360	Cardiac	None	None	None	None	Little or none	No	None
49	MBC	50	M	W	22	6.38	1450	Cardiac	None	None	None	None	Little or none	No	None
50	MBC	50	F	W	12	6.58	1500	Cardiac	None	None	Unknown	None	Little or none	Yes	codeine, cyclobenzapine, atropine
51	MBC	50	F	B	>24	6.72	1100	Cardiac	None	None	None	None	Dependence	No	None
52	MBC	46	M	W	24	6.64	1850	Cardiac	Unknown	None	None	None	Little or none	No	citalopram
53	MBC	56	M	W	24	6.47	1450	Drown: Accid	None	None	None	None	Little or none	No	None
54	MBC	60	M	W	15	6.98	1480	Drown: Accid	None	None	None	None	Little or none	No	None
55	MBC	45	F	W	16	6.69	1245	Cardiac	None	None	None	None	Abuse	No	None
56	MBC	77	M	W	16	6.80	1700	Cardiac/Drown	None	None	None	None	Little or none	No	None

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsych	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
MDD WITHOUT SUICIDE															
1	SMRI: D/S	53	M	W	21	6.64	1520	Cardiac	None	None	None	moderate past	Little or none	Unknown	Not available
2	SMRI: D/S	36	F	W	32	6.74	1270	Pulm Embol	Trazodone, Mirtazapine	Risperidone	None	None	Little or none	yes	Not available
3	SMRI: D/S	56	F	W	15	6.59	1370	Burns	Antidep. type uncertain	None	None	heavy past	Little or none	No	Not available
4	SMRI: D/S	43	M	W	30	6.65	1500	Pnemonia	Buspirone, Serrtaline	Quetiapine	None	None	Heavy present	Yes	Not available
5	SMRI: D/S	39	M	W	16	6.6	1570	Cardiac	None	None	None	None	Little or none	Yes	Not available
6	SMRI: D/S	55	M	W	43	6.62	1675	Cardiac	Fluoxetine	None	None	None	Heavy present	Unknown	Not available
7	SMRI: D/S	44	M	W	24	6.52	1550	Cardiac	Bupropion, Paroxetine	Chlorpromazine	None	None	Little or none	Unknown	Not available
8	SMRI: D/S	37	F	W	32	6.64	1490	Cardiac	Fluoxetine	None	None	None	Little or none	No	Not available

(Continued)

Supplementary Table 1. (*continued*)

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsychotics	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
9	SMRI: D/S	45	F	W	29	6.9	1350	Cardiac	Sertraline	None	None	None	Little or none	Unknown	Not available
10	SMRI: D/S	49	M	W	86	6.68	1601	Cardiac	Venlafaxine, Amitriptyline	None	None	heavy present	Heavy present	Yes	Not available
11	SMRI: D/S	36	M	W	31	6.6	1540	Cardiac	Sertraline	None	None	social	Little or none	Unknown	Not available
12	MBC	65	M	W	14	N/A	1250	Cardiac	Sertraline	None	None	None	Little or none	No	None
13	MBC	55	F	B	8	N/A	1285	Cardiac	Fluoxetine, Perphenazine	None	None	None	Abuse	No	Acetone, fluoxetine
14	MBC	74	F	B	7	7.01	1150	Cardiac	Paroxetine,	Thioridazine	None	None	Little or none	No	Paroxetine, thioridazine
15	MBC	16	M	W	9	N/A	1600	narcotic intoxication	Paroxetine intoxication	None	None	Opioid dependence	Little or none	No	Morphine, codeine, paroxetine, acetaminophen
16	MBC	14	M	W	11	N/A	1260	MVA	Sertraline	None	None	None	Little or none	No	Sertraline
17	MBC	39	M	W	36	N/A	1635	Fatty Liver	None	Risperidone	None	None	Little or none	No	Thioridazine
18	MBC	46	M	B	20	6.71	N/A	Seizure disorder	Fluoxetine	Risperidone	None	None	Little or none	No	Fluoxetine
19	MBC	59	M	W	20	6.1	1300	Cardiac	Sertraline 1 week	None	None	None	Dependence	Yes	Methadone, sertraline, atropine
20	MBC	46	F	W	23	7.05	1400	Cardiac/mixed drug intoxication	Bupropion	Quetiapine	Gabapentin, Lithium, Lamotrigine, Clonazepam	Cocaine, opioid, hallucinogen abuse (mod)	Abuse	No	Wellbutrin, diphenhydramine, lamictal
21	MBC	29	F	W	22	6.35	1300	Obesity/Cardiac	Unknown	Unknown	None	None	Little or none	No	Fluoxetine, norfluoxetine, propoxyphene, norpropoxyphene

#	Co-hort	Age	Sex	Race	PMI	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsych	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
MDD WITH SUICIDE															
1	SMRI : D/S	45	M	W	29	6.75	1514	Suic: Hung	Trazodone	None	None	None	Moderate past	No	Not available
2	SMRI : D/S	24	M	W	21	6.61	1737	Suic: OD	Venlafaxine	None	None	None	Unknown	Yes	Not available
3	SMRI : D/S	45	F	W	13	6.58	1170	Suic: OD	Bupropion	Quetiapine	None	moderate present	Heavy past	Unknown	Not available
4	SMRI : D/S	48	F	W	24	6.36	1330	Suic: OD	Desipramine	Thiothixene	None	None	Little or none	Yes	Not available

(*Continued*)

Supplemental Table 1. (continued)

#	Co-hort	Age	Sex	Race	PMI (hr)	pH	Brain Weight (g)	COD	Presc. Antidep.	Prescr. Antipsychotics	Other Prescr. Drugs	Drug abuse	Alcohol use	Smoking	Toxicology
5	SMRI: D/S	33	M	W	25	6.86	1640	Suic: Hung	None	None	None	moderate past	Little or none	Unknown	Not available
6	SMRI: D/S	56	M	W	38	6.59	1365	Suic: OD	Venlafaxine, Bupropion	Risperidone	None	None	Moderate present	No	Not available
7	SMRI: D/S	32	F	W	19	6.8	1470	Suic: Hung	Trazodone, Paroxetine	None	None	None	Little or none	Unknown	Not available
8	SMRI: D/S	34	M	W	24	6.79	1425	Suic: Jump	Fluoxetine	None	None	None	Heavy present	Unknown	Not available
9	SMRI: D/S	47	F	W	25	6.88	1498	Suic: GSW	Bupropion	None	None	None	Little or none	No	Not available
10	SMRI: D/S	35	M	H	19	6.6	1335	Suic: Hung	None	None	None	None	Little or none	Unknown	Not available
11	SMRI: D/S	62	M	W	65	6.57	1490	Suic: Stab	Nefazodone	None	None	None	Heavy present	Unknown	Not available
12	MBC	43	M	W	20	6.31	N/A	Suic: Hung	Unknown	Unknown	None	None	Little or none	No	None
13	MBC	22	F	W	20	6.66	1530	Suic: drug & ETOH intoxication	Unknown	Unknown	None	None	Little or none	No	Diphenhydramine, codeine
14	MBC	49	M	W	17	N/A	N/A	Suic: Stab	Norrtriptyline	None	None	None	Little or none	No	Tramadol, nortriptyline
15	MBC	18	M	W	19	N/A	1485	Suic: Hung	Unknown	Unknown	None	None	Little or none	No	None
16	MBC	44	F	W	30	N/A	1450	Suic: drug & ETOH intoxication	Fluoxetine	None	None	opioid abuse	Abuse	Yes	Fluoxetine, morphine,
17	MBC	17	M	W	23	6.66	1565	Suic: Hung	Unknown	Unknown	None	None	Abuse	Yes	None
18	MBC	63	M	W	19	6.84	1400	Suic: ETOH & meperidine intoxication	Fluoxetine	None	None	cannabis use	Little or none	No	Meperidine, prozac, diazepam
19	MBC	50	F	W	24	6.44	1430	Suic: Hung	Excitalopram	Olanzapine	None	None	Abuse	No	None
20	MBC	67	M	W	22	6.46	1450	Suic: GSW	Unknown	None	None	None	Little or none	Yes	Prozac, effexor
21	MBC	79	M	W	23	6.98	1340	Suic: Stab	Unknown	Unknown	None	None	Dependence	No	Citalopram, diphenhydramine, doxylamine, aceta-minophen, pseudophed-rine, phenylpropanolamine
22	MBC	30	M	W	24	6.53	1500	Suic: Hung	Unknown	Unknown	None	None	Little or none	No	None
23	MBC	40	F	W	20	6.51	1390	Suic: OD (medication overdose)	Bupropion, Venlafaxine	None	alprazolam, clonazepam	None	Little or none	No	Acetaminophen, hydrocodone, diphenhydramine, xanax
24	MBC	53	M	W	>24	6.6	1500	Suic: Stab	Sertraline	None	Lisinopril	None	Little or none	No	Desmethysertraline
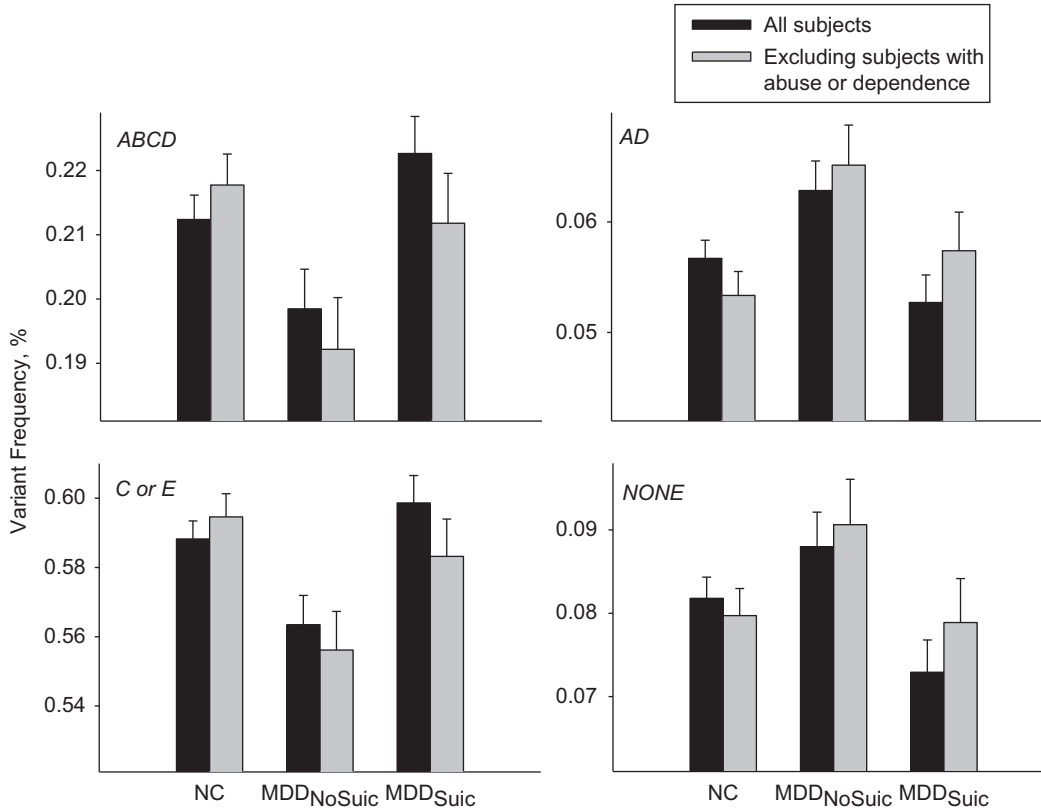
Supplemental Figure 2. Frequencies of the 5-HT$_{2C}$R editing transcripts in all subjects and excluding subjects with evidence of substance abuse or dependence. All subjects: NC, N = 56; MDD$_{NoSuic}$, N = 21; MDD$_{Suic}$, N = 24. Excluding subjects with abuse or dependence: NC, N = 48; MDD$_{NoSuic}$, N = 12; MDD$_{Suic}$, N = 16. Shown are Means ± SEM. Although the smaller sample size reduced statistical significance, the pattern and magnitude of the differences among groups after excluding subjects with abuse and dependence were similar the those in all subjects.

35 cycles of 15 sec at 95° C, 30 sec at 60° C, and 30 sec at 72° C. A standard cycle was applied for amplification of the ADAR and ECG transcripts.

The relative expression levels of the target transcripts and the ECGs were determined using the Relative Standard Curve Method (see Guide to Performing Relative Quantitation of Gene Expression Using Real-Time Quantitative PCR, Applied Biosystems). This method provides accurate quantitative results by accounting for differences in the efficiencies between target and ECG amplifications. Standard curves were generated by the association between threshold cycle (Ct) values and different quantities of a "calibrator" cDNA, which was prepared by mixing small quantities of all experimental samples. The relative amounts of the target and the ECG transcripts were calculated in each sample using the linear equations of the standard curves. Normalization procedure was determined using geNorm software (Vandesompele et al. 2002). The analysis revealed comparable gene stability measures (M) for all five ECG in the entire cohort and the pairwise variation comparison determined that including all five control genes was advantageous for optimal normalization (Vandesompele et al. 2002).

Therefore, the relative mRNA expression of the target transcripts was computed as the ratio between the amount of the target transcripts and the geometric mean of the amounts of all five ECGs.

5-HT$_{2C}$R expression: In addition to a regular 5' splice site (sp2), 5-HT$_{2C}$R pre-mRNA undergoes alternative splicing between exons 5 and 6 with two alternative splice sites described—sp1 and sp3 (Canton et al. 1996; Flomen et al. 2004). While the mRNA variant generated from splicing at sp2 is translated into a functional receptor, both of the resulting alternative splice variants are translated into truncated proteins that are unlikely to retain adequate receptor function. The splicing at the sp3 site was found to be extremely rare in the DLPFC (Dracheva et al. 2003). Therefore, two different custom-designed TaqMan assays were employed to distinguish between 5-HT$_{2C}$Rsp1 and 5-HT$_{2C}$Rsp2 variants (see Supplemental Table 3). In the 5-HT$_{2C}$Rsp2 assay, the forward primer and the TaqMan probe were situated inside the 95-bp region that contains all five editing sites and is present in 5-HT$_{2C}$Rsp2, but is deleted in 5-HT$_{2C}$Rsp1; therefore, only 5-HT$_{2C}$R-sp2 was amplified.

Supplemental Table 2. Efficiency of editing at the five editing sites of the 5-HT$_{2C}$R mRNA. Shown are Means±SEM.

Editing Site	NC (N = 56)	MDD$_{NoSuic}$ (N = 21)	MDD$_{Suic}$ (N = 24)
A	78.26 ± 0.44	77.09 ± 1.15	79.06 ± 0.68
B	52.02 ± 0.66	50.11 ± 1.58	52.51 ± 0.98
E	18.81 ± 0.27	17.66 ± 0.55	18.89 ± 0.34
C	53.64 ± 0.54	51.55 ± 1.09	54.83 ± 0.57
D	62.98 ± 0.44	61.83 ± 0.96	62.62 ± 1.09

Analysis of ADARs' mRNA expression:

ADAR1: Five different splice variants of ADAR1 gene (*ADAR*), which originate from 3 transcription initiation sites and several alternative splicing events, are reported by the NCBI (accession #s: NM_001111.4, NM_015840.3, NM_015841.3, NM_001025107.2, and NM_00193495.1; Supplemental Figure 1). Each of these transcripts encodes a protein isoform that possesses three double-stranded RNA binding domains (RBDI, RBDII, and RBDIII), a catalytic domain, and one or two Z-DNA-binding domains. The RNA transcripts differ in three regions: alternative exons 1-3 in 5' region, exon 8, and exon 9 (see Supplemental Figure 1). The longest transcript (variant 1) encodes the longest protein isoform and is recognized as the canonical sequence. Variants 2 and 3 use a different in-frame splice site in exon 9, and their respective proteins have a 26 amino acid (AA) deletion between the third RBD and the catalytic domain. Compared to variant 2, variant 3 uses an alternative in-frame splice site at exon 8, thus resulting in a protein isoform with a 19 AA deletion between RBDII and RBDIII. Variants 4 and 5 have different 5' UTRs (compared to 1-3 and to each other), but encode identical proteins. Compared to protein isoforms 1-3, this protein is translated from a downstream start codon and has a significantly shorter N-terminus, which lacks the nuclear export signal and therefore only found in the nucleus. In addition, it has been demonstrated that transcripts 1-3 (and their corresponding proteins) are interferon inducible, while transcripts 4 & 5 are constitutively expressed (Strehblow et al. 2002).

Supplementary Table 3. Description of the TaqMan assays used in the study. Both pre-designed assays (Applied Biosystems) and custom assays, designed using Primer Express (Invitrogen) were employed.

Gene	Variants measured	RefSeq	Assay Position	Assay Design: Forward (F) and Reverse (R) Primer and Probe$	Included in study*
5-HT$_{2C}$R	sp2	NM_000868.2	Exon 5, 6	F- CGTTTCAATTCGCGGACTAAG R-CACCTATAGAAATTGCCCAAACAA Probe: CCATCATGAAGATTGC	Yes
5-HT$_{2C}$R	sp1	AK295753	Exon 5#, 6	F- CGCTGGATCGGTGTATCAGTT R- CGCACGTCGTGTTGTTCAC Probe: CTATCCCTGTGATTGGAC	Yes
ADAR1	V1, 2, 4, 5	NM_001111.4, NM_015840.3, NM_001025107.2, NM_001193495.1	Exon 7, 8a	F-GGCTTCTGATAACCAGCCTGAA R-GGGCATCATGGATTCCAAGT Probe: TATGATCTCAGAGTCACTTGA	Yes
ADAR1	V3	NM_015841.3	Exon7, 8b	Pre-designed Applied Biosystems Hs01017600	No
ADAR1	V4	NM_001025107.2	Exon 1, 4	Pre-designed Applied Biosystems Hs01017596	Yes
ADAR1	V1, 4, 5	NM_001111.4, NM_001025107.2, NM_001193495.1	Exon 9b, 10	Pre-designed Applied Biosystems Hs01020779	Yes
ADAR1	V2, 3	NM_015840.3, NM_015841.3	Exon 9a, 10	Pre-designed Applied Biosystems Hs01017602	Yes
ADAR1	V1, 2, 3, 4, 5	NM_001111.4, NM_015840.3, NM_015841.3, NM_001025107.2, NM_001193495.1	Exon 4, 5	Pre-designed Applied Biosystems Hs00241666	Yes
ADAR2	V1, 4	NM_001112.3, NM_001160230.1	Exon 8, 10	Pre-designed Applied Biosystems Hs00955199	Yes
ADAR2	V2, 3	NM_015833.3, NM_015834.3	Exon 9, 10	F- CGATCCTTCCACCTCAACCTT R- ATTTGGGTGTCTATCTGCTGGTT Probe: CAAGGAGCTGGGACTACA	Yes

*Assays that yielded Ct > 30 in the generic specimen were not analyzed (see Supplementary methods). $All TaqMan probes contained FAM and MGB. #Alternative splice site.

Supplementary Table 4. Interdependence of editing among different editing sites. (+) denotes an editing event (from A to I residue) and (−) denotes an absence of an editing event (a genomic A residue). Subscripts refer to the editing status of the context site, i.e. $A+_{B+}$ is the ratio of $A+_{B+}$ to $(A+_{B+} + A-_{B+})$, where edited B site is the context site. Shown is an analysis for the entire cohort (N = 101). The results demonstrate that editing at any of the five sites is dependent on editing at any other site (all t-values ≥ 10.76, all p values < 0.000001, by paired Student t-test). *Difference between editing frequencies at a site when the status of editing at another site is (+) or (−) (i.e., $X^+_{Y+} - X^+_{Y-}$, where X and Y are any editing site).

		Frequency of Editing at a Site in the Context of Editing at Another Site, Mean ± SEM, %	*Δ, %
Pair 1	$A+_{B+}$	93.63 ± 0.19	31.77
	$A+_{B-}$	61.86 ± 0.41	
Pair 2	$B+_{A+}$	61.82 ± 0.47	46.55
	$B+_{A-}$	15.27 ± 0.38	
Pair 3	$A+_{E+}$	88.35 ± 0.72	12.48
	$A+_{E-}$	75.87 ± 0.39	
Pair 4	$E+_{A+}$	21.01 ± 0.27	11.39
	$E+_{A-}$	9.63 ± 0.33	
Pair 5	$A+_{C+}$	87.43 ± 0.37	19.68
	$A+_{C-}$	67.74 ± 0.42	
Pair 6	$C+_{A+}$	59.73 ± 0.37	29.08
	$C+_{A-}$	30.66 ± 0.60	
Pair 7	$A+_{D+}$	87.90 ± 0.28	25.81
	$A+_{D-}$	62.09 ± 0.47	
Pair 8	$D+_{A+}$	70.39 ± 0.32	35.56
	$D+_{A-}$	34.83 ± 0.46	
Pair 9	$B+_{E+}$	38.30 ± 0.76	−16.49
	$B+_{E-}$	54.79 ± 0.57	
Pair 10	$E+_{B+}$	13.78 ± 0.29	−10.02
	$E+_{B-}$	23.79 ± 0.30	
Pair 11	$B+_{C+}$	57.66 ± 0.50	12.64
	$B+_{C-}$	45.02 ± 0.63	
Pair 12	$C+_{B+}$	59.68 ± 0.42	12.66
	$C+_{B-}$	47.02 ± 0.46	
Pair 13	$B+_{D+}$	65.73 ± 0.56	37.37
	$B+_{D-}$	28.36 ± 0.47	
Pair 14	$D+_{B+}$	79.66 ± 0.31	35.18
	$D+_{B-}$	44.49 ± 0.46	
Pair 15	$C+_{E+}$	72.55 ± 0.57	23.4
	$C+_{E-}$	49.15 ± 0.40	
Pair 16	$E+_{C+}$	25.20 ± 0.28	14.26
	$E+_{C-}$	10.94 ± 0.22	
Pair 17	$C+_{D+}$	58.25 ± 0.48	12.58
	$C+_{D-}$	45.67 ± 0.41	
Pair 18	$D+_{C+}$	68.16 ± 0.34	11.86
	$D+_{C-}$	56.29 ± 0.55	
Pair 19	$D+_{E+}$	57.27 ± 0.74	−6.59
	$D+_{E-}$	63.86 ± 0.39	
Pair 20	$E+_{D+}$	16.99 ± 0.27	−4.2
	$E+_{D} -$	21.19 ± 0.30	

ADAR2: Seven different transcript variants of ADAR2 (*ADARB1*) are reported by NCBI, but only five of them are linked to corresponding proteins (accession #s: NM_001112.3, NM_015833.3, NM_015834.3, NM_001160230.1; Supplementary Fig. 1). Each of the protein isoforms contains two dRBDs and a C-terminal catalytic domain. The transcripts originate from alternative splicing of exon 9, which represents an Alu cassette, and exon 13, which encodes the catalytic domain. Compared to variants 3&4, variants 1&2 possess a longer 3' exon, and, therefore, encode proteins with a longer C-terminus. Variants 1&2 differ from each other by inclusion of exon 9 in variant 2, while variants 3&4 differ from each other by inclusion of exon 9 in variant 3. ADAR2 lacks the homologous N-terminal nuclear export signal found in ADAR1 and, therefore, is confined to the nucleus (Desterro et al. 2003).

Because, of the large distances between different ADARs' transcription initiation and splicing sites, it is unachievable to generate qPCR assays for each individual transcript. Thus, we attempted to achieve a complete analysis of the ADARs transcription, by using a number of pre-designed (Applied Biosystems) and custom TaqMan assays (Supplemental Table 3). The custom assays were designed using Primer Express software (Invitrogen). Each assay was tested using generic cDNA. Those with late appearances [threshold cycle (Ct) > 30 at threshold of 0.2], which is indicative of low expression, were excluded from analysis (Supplemental Table 3).

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Supplementary Table 5. Analysis of ADARs mRNA expression by ANCOVA. Comparison among three study groups (MDD$_{NoSuic}$, MDD$_{Suic}$, and NC) is presented; PMI and age were used as covariates. The expression was assessed using several TaqMan assays (see Supplemental Methods). The expression of target transcripts was normalized to geometric mean of five endogenous controls *(B2M, GUSB, PPIA, RPLPO, HPRT1)*. Shown are Mean ± SEM of relative expression values. Significant differences ($p < 0.05$) are **bolded**.

Assay	Relative mRNA Expression NC (N = 55)	Relative mRNA Expression MDD$_{NoSuic}$ (N = 24)	Relative mRNA Expression MDD$_{Suic}$ (N = 21)	Groups	p (Tukey-Kramer Adjusted)
ADAR1 V1, 2, 4, 5	**1.0139 ± 0.01**	**0.9566 ± 0.02**	**0.9718 ± 0.02**	**MDD$_{NoSuic}$ vs. NC**	**0.0355**
				MDD$_{Suic}$ vs. NC	0.1350
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	0.8343
ADAR1 V1, 4, 5	0.94 ± 0.02	0.93 ± 0.02	0.91 ± 0.02	MDD$_{NoSuic}$ vs. NC	0.9998
				MDD$_{Suic}$ vs. NC	0.6113
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	0.7273
ADAR1 V2, 3	1.03 ± 0.03	0.98 ± 0.05	0.96 ± 0.05	MDD$_{NoSuic}$ vs. NC	0.7084
				MDD$_{Suic}$ vs. NC	0.5208
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	0.9742
ADAR1 V4, 5	1.05 ± 0.02	1.09 ± 0.03	1.05 ± 0.03	MDD$_{NoSuic}$ vs. NC	0.6131
				MDD$_{Suic}$ vs. NC	0.9997
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	0.6840
ADAR2 V1, 4	**1.20 ± 0.03**	**0.97 ± 0.05**	**1.02 ± 0.05**	**MDD$_{NoSuic}$ vs. NC**	**0.0002**
				MDD$_{Suic}$ vs. NC	**0.0029**
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	0.7288
ADAR2 V2, 3	**1.17 ± 0.03**	**1.03 ± 0.04**	**1.03 ± 0.04**	**MDD$_{NoSuic}$ vs. NC**	**0.0086**
				MDD$_{Suic}$ vs. NC	**0.0057**
				MDD$_{Suic}$ vs. MDD$_{NoSuic}$	1.0000