Supplementary Methods

Samples

NICHD cohort: A cohort of *post mortem* frontal cortical samples with major depression and matched controls was obtained from the NICHD University of Maryland Brain Bank of Developmental Disorders. Approximately 21% of the sample was African American, 78% was Caucasian, and 1% was Asian.

SMRI cohort: A cohort of *post mortem* prefrontal cortical samples with bipolar disorder, schizophrenia, and matched controls was obtained from the Stanley Medical Research Institute. Approximately 1% of the sample was African American, 1% was Hispanic, 1% was Native American, and 97% was Caucasian.

McL cohort: A cohort of *post mortem* prefrontal cortical samples with bipolar disorder and matched controls was obtained from the Harvard Brain Bank at McLean Hospital. 100% of the sample was Caucasian.

GenRED Offspring Study: Adolescent and young adult offspring were ascertained through probands available from the Johns Hopkins and University of Iowa sites of the Genetics of Recurrent Early Onset Depression Study (1, 2). Probands were characterized using the Diagnostic Interview for Genetic Studies (DIGS) (3) and the FIGS (Family Instrument for Genetic Studies) (4) and received a best-estimate diagnosis of recurring major depression with at least two lifetime major depressive episodes, onset before age 31 (or a single episode of major depression that lasted three years and began before age 31), at least one sibling or parent with recurrent major depression with onset before age 41, major depression independent of substance dependence (that is, no lifetime dependence, major depression before dependence, or major depression after at least two years of remission from dependence), no diagnosis of bipolar or schizoaffective disorder or schizophrenia, and no suspected bipolar-I disorder in a parent or sibling. GenRED I and II participants were approached for the offspring study between October 2009 and August 2013. All offspring in the 12-21 age range were invited to participate by being interviewed (with the K-SADS) and providing serial cortisol samples at waking, 30 minutes after waking and 60 minutes after waking on a weekday and a weekend day as well as a blood specimen for DNA methylation studies. Only those offspring who provided blood samples were included in this study. At least one parent had to be available for an interview about all of their participating offspring (with the Kiddie Schedule for Affective Disorders (K-SADS) (5). IQ in offspring was not formally tested, but each subject was required to be able to complete the interview and the individual questionnaires as part of the study protocol. Offspring with brain disease, schizophrenia, mental retardation and those taking glucocorticoids (e.g., prednisone for asthma) were not included. Informed consent (or assent with parental consent, for subjects < 18) was obtained after a thorough explanation of the study. All clinical procedures were approved by institutional review boards at the Johns Hopkins School of Medicine and the University of Iowa School of Medicine.

Johns Hopkins Center for Prevention Research Study (PRC) : Data are from a prospective study conducted in the context of an epidemiologically-based group-randomized prevention trial (6, 7). Details of the trial are available elsewhere (6, 7). In brief, the trial recruited two successive cohorts of students [1,196 from Cohort 1 in 1985 and 1,115 from Cohort 2 in 1986] as they entered first grade in 19 elementary schools in Baltimore, MD (49.8% male and 67.1% ethnic minority consistent with the population in Baltimore City schools). Since 1985, participants have been assessed through middle school, twice in young adulthood, and most recently when participants were 30-32 years old. Data for this study were derived from blood collected at the age 30-32 year follow-up wave. DNA methylation analyses were restricted to the 328 individuals participating in the age 30-32 wave who at the time of this analysis provided a blood sample (60% female and 76% African American, lacking another 12 who provided blood later). Attrition in the cohort was slightly greater among males and whites ($p<.01$). Standardized assessments were conducted by trained non-clinical interviewers with the most recent wave collected via a computerized interview that was conducted by the interviewer, and when assessing potentially sensitive topics such as drug involvement, conducted by the respondent using the computer). This study was approved by the Institutional Review Board at Johns Hopkins University. All participants provided informed consent to participate.

Prospective sample: We assayed 51 women who contributed blood from a larger collection of 93 pregnant women with a history of either Major Depression or Bipolar Disorder (I, II or NOS) who were recruited and prospectively followed during pregnancy and after delivery in order to identify genetic and clinical characteristics that precede the development

of a postpartum depressive episode. The average age of the participants was 30.6 and 70% of the sample was Caucasian. Participants were managed by their treating psychiatrist as clinically indicated and were evaluated during each trimester of pregnancy and then 1 week, 1 month and 3 months postpartum. Women were classified as being depressed if they met DSM-IV criteria for a Major Depressive Episode (MDE) based on a psychiatric interview at each time point (first, second, and third trimester and 1 week and 1 month postpartum). All participants provided informed consent to participate.

Study metrics

Suicidal ideation, anxiety, and stress metrics were obtained through different scales per cohort. For the GenRED offspring cohort, suicidal ideation and suicide attempt were derived from the Composite International Diagnostic Interview (CIDI) Suicidality Questionnaire. A positive anxiety metric was determined by a score of $\geq$ 25 on the Self-Report for Childhood Anxiety Related Disorders (SCARED) (8). For the prospective cohort, suicidal ideation was measured by numeric responses to question 10 of the Montgomery Asberg Depression Rating Scale (MADRS), anxiety was measured by numeric responses to question 4 of the Edinburgh Postnatal Depression Scale (EPDS) (9), and perceived stress was measured by the total of the Perceived Stress Scale (PSS) (10). For prospective sample receiver operator characteristic curve predictions, suicidal ideation metrics were converted to a binary format by reducing quantitative scores of greater than zero to one. A more stringent suicidal ideation classification was also tested by classifying only those suicidal ideation scores greater than or equal to two as a positive suicidal ideation status for evaluation of predictive accuracy. For the PRC cohort, all metrics were derived as responses to a standardized interview (6, 7). Suicidal ideation was measured as a binary response to the question: Have you ever felt so low you thought of committing suicide?; suicide attempt was measured as a binary response to the question: Have you ever attempted suicide?; anxiety was measured as a binary response to the question: Do you consider yourself a nervous person? Following an affirmative response to the suicide attempt question, intent to die was measured as a binary response to the question: Did you intend to die?

Isolation of Neuronal and Non-neuronal Nuclei by Fluorescence Activated Cell Sorting (FACS)

Neuronal nuclei were isolated from prefrontal cortical tissue as described previously (11). Briefly, 250 – 750 mg of frozen tissue was homogenized in lysis buffer (0.32 M sucrose, 5 mM calcium chloride, 3 mM magnesium acetate, 0.1mM EDTA, 10mM dithiothreitol, 0.1% Triton X-100) and nuclei were isolated via sucrose cushion ultracentrifugation (1.8 M sucrose, 3 mM magnesium acetate, 1 mM dithiothreitol, 10 mM Tris-HCl, pH 8). Ultracentrifugation was performed at 25,000 rpm for 2.5 hours at 4°C (Beckman, L-90K ultracentrifuge, SW32 rotor). For nuclei immunofluorescence staining, anti-NeuN (Ms) and anti-Ms IgG antibodies were incubated together at room temperature before nuclei were added and incubated further in the dark at 4°C for 45-60 minutes before Fluorescence Activated Cell Sorting (FACS). FACS was performed at the Johns Hopkins Flow Cytometry Core Facility (FACSAria II, BD Biosciences). The sorting primary gate was set to properly capture nuclei based on size and density, while secondary gates were set based on fluorescence signals. Immunonegative (NeuN-) nuclei were counted, collected, and processed in parallel with the fraction of neuronal (NeuN+) nuclei. All nuclei were sorted with an efficiency of greater than 90%. After FACS, nuclei were pelleted and frozen at -80°C in Tissue and Cell Lysis Buffer (MasterPure DNA Purification Kit, Epicentre Biotechnologies) until DNA extraction. All genomic DNA from nuclei was isolated with the MasterPure DNA Purification Kit (Epicentre Biotechnologies) according to the manufacturer's instructions.

Illumina DNA methylation profiling

Samples quality assessment and microarray analysis were conducted at The Sidney Kimmel Cancer Center Microarray Core Facility at Johns Hopkins University. Genomic DNA quality was assessed by low concentration agarose gel (0.6%) electrophoresis and spectrometry of OD260/280 and OD 260/230 ratio. DNA bisulfite conversion was carried out using EZ DNA Methylation Kit (Zymo Research) by following manufacturer's manual with modifications for Illumina Infinium Methylation Assay. Briefly, 0.5 – 1.0 ug of genomic DNA was first mixed with 5 ul of M-Dilution Buffer and incubate at 37C for 15 minutes and then mixed with 100 ul of CT Conversion Reagent prepared as instructed in the kit's manual. Mixtures were incubated in a thermocycler with 16 thermal cycles at 95C for 30 seconds and 50C for one hour. Bisulfite-converted DNA samples were loaded onto 96-column plates provided in the kit for desulphonation and purification. Concentration of eluted DNA was measured using Nanodrop-1000 spectrometer.

Infinium Chip Assay. Bisulfite-converted DNA was analyzed using Illumina's Infinium Human Methylation450 Beadchip Kit (WG-314-1001) by following manufacturer's manual. Beadchip contains 485,577 CpG loci in human genome. Briefly, 4 ul of bisulfite-converted DNA was added to a 0.8 ml 96-well storage plate (Thermo Scientific), denatured in 0.014N sodium hydroxide, neutralized and amplified with kit-provided reagents and buffer at 37C for 20-24 hours. Samples were fragmented using kit-provided reagents and buffer at 37C for one hour and precipitated by adding 2-propanol. Re-suspended samples were denatured in a 96-well plate heat block at 95C for 20 minutes. 12 ul of each sample was loaded onto a 12-sample chip and the chips were assembled into hybridization chamber as instructed in the manual. After incubation at 48C for 16-20 hours, chips were briefly washed and then assembled and placed in a fluid flow-through station for primer-extension and staining procedures. Polymer-coated chips were image-processed in Illumina's iScan scanner.

Data Acquisition. Data were extracted using Methylation Module of GenomeStudio v1.0 Software and processed using the wateRmelon package in R (12). Raw data was trimmed of probes failing quality assessment, followed by scale based data correction for Illumina type I relative to type II probes. Methylated and un-methylated intensity values were then quantile normalized separately prior to the calculation of the β (beta) value based on following definition:

β *value = (signal intensity of methylation-detection probe)/(signal intensity of methylation- detection probe + signal intensity of non-methylation-detection probe + 100).*

Sodium bisulfite pyrosequencing

Bisulfite conversion was carried out using EZ DNA Methylation Gold Kit (Zymo Research, Irvine, California, USA) according to the manufacturer's instructions. Nested PCR amplifications were performed with a standard PCR protocol in 25 ml volume reactions containing 3-4 μl of sodium-bisulfite-treated DNA, 0.2 uM primers, and master mix containing Taq DNA polymerase (Sigma-Aldrich, St. Louis, Missouri, USA). Primer sequences for the *SKA2* 3'UTR CpG and those two CpGs analyzed upstream can be found included:

SKA2 3'UTR:

*SKA2*_Forward Outside: 5'- GAGAAATAAGTTATATTTTAGTATTAGATA-3';

*SKA2*_Reverse Outside: 5'- AAAATAATACAATCTAATTTTTCTCCCT-3';

*SKA2*_Forward Inside: 5'- biotin-GAGATGGTTTTGGGATGTGATG-3';

*SKA2*_Reverse Inside: 5'- TAACTAAAAACAAAACCACTTTTAATACTA-3';

*SKA2*_Pyrosequencing Primer: 5'- ATTATAATCTCTCCATAATACTACC-3';

*SKA2*_upstream:

*SKA2*_upstream_Forward Outside: 5'-AATTGTTTTGTTTAGTTTGAATATTTTAAG-3';

*SKA2*_upstream_Reverse Outside: 5'-TATCTAATACTAAAATATAACTTATTTCTC-3';

*SKA2*_upstream_ Forward Inside: 5'- biotin-TGTTTAGGTTGGAATGTAGTGGTA-3';

*SKA2*_upstream_ Reverse Inside: 5'- CCTAATCAAAATAATAAAACCCCATC-3';

*SKA2*_upstream_ Pyrosequencing Primer: 5'- CTCTACTAAAAATACAAAAAAATAACC-3';

PCR amplicons were processed for pyrosequencing analysis according to the manufacturer's standard protocol (Qiagen, Gaithersburg, MD, USA) using a PyroMark MD system (Qiagen) with Pyro Q-CpG 1.0.9 software (Qiagen) for CpG methylation quantification. Only those data values receiving a "Pass" value or "Check" were considered for downstream analysis. "Check" signals were accepted only in the case of failed reference sequence patterns upstream of the CpG of interest involving failure of the pyrosequencing chemistry to properly account for long runs of thymines. All data incorporated into analyses demonstrated proper bisulfite conversion based on internal pyrosequencing assay checks of cytosines not located within CpG dinucleotides.

Quantitative Real Time PCR

All *SKA2* gene expression data and rs7208505 genotyping was performed using quantitative real time PCR (RT-qPCR). The exception was for the SMRI cohort, which was downloaded from the Stanley Genomics Database at www.stanleygenomics.org. Genotype calls for rs7208505 were obtained from Study 20. Genotyping of rs7208505 was performed on genomic DNA using an Life Technologies Taqman assay for rs7208505 (C_23546_20). For gene expression, mRNA was extracted from brain tissue using the RNeasy Lipid and Tissue kit (Qiagen) and from tissue culture using the RNeasy Mini kit (Qiagen) according to the manufacturer's protocols. RNA integrity numbers (RIN) were generated using a Bioanalyzer (Agilent). Samples with RIN values <6.7 were removed from subsequent analysis

while samples with RIN < 7 had acceptable quality visually confirmed by Bioanalyzer technician at the JHMI Deep Sequencing and Microarray Core. Reverse transcription was carried out using a combination of oligo DT and random primers using the Quantitect Reverse Transcription kit (Qiagen), according to the manufacturer's protocol. Quantitative real-time PCR was performed on an ABI 7900HT Fast Real-Time PCR system to assess steady state mRNA levels. ABI Taqman probes (Life Technologies, Carlsbad, CA) were obtained from the manufacturer's website (https://www.lifetechnologies.com/us/en/home/brands/applied-biosystems.html). Assays for *SKA2* (hs00735057_m1) were run in triplicate alongside three reference genes, β-actin (Hs03023943_g1), GAPDH (Hs99999905_m1), and RPLP0 (HS99999902_m1), selected based on studies identifying their appropriateness for gene expression analyses in *post mortem* brain studies in psychiatric phenotypes (13). To determine relative expression values, the −ΔΔCt method (Applied Biosystems) was used, where triplicate Ct values for each sample were averaged and subtracted from the geometric mean of reference gene Ct values according to previously published methods (14). The Ct difference for a calibrator sample consisting of the average Ct value for non-suicide control samples, was subtracted from those of the test samples, and the resulting −ΔΔCt values were raised to a power of 2 to determine normalized relative expression. Adjustment for neuronal proportion was performed by taking the residuals from a linear model of neuronal proportions as determined by FACS gates as a function of *SKA2* gene expression.

Salivary cortisol

The GenRED offspring sample provided salivary cortisol samples were taken at 0, 30, and 60 minutes after waking during a weekday. Saliva was separated from Salimetrics (State College, PA) oral swabs by centrifugation and submitted to the Center for Interdisciplinary Salivary Bioscience Research at Johns Hopkins (Baltimore, MD) for salivary cortisol measurement. Cortisol measurements were determined by sandwich ELISA assay using the Salivary Cortisol Enzyme ImmunoAssay Kit (Salimetrics) according to the manufacturer's instructions.

Weighted Genome Co-expression Network Analysis

Weighted Genome Co-expression Network Analysis (WGCNA) (15) was performed using the WGCNA package in R. For neuronal and glial analyses, respectively, 9,784 and 16,644 nominally significant loci from the NICHD neuronal and glial DNA specific HM450 microarray datasets were used for correlation with a power of 6 and minimum module size of 5.

Analysis of ENCODE data for transcription factor binding regions

ENCODE data from A549 cells and ECC1 cells stimulated with 0.5nM, 5nM, 50nM, and 100nM of dexamethasone were downloaded from Gene Expression Omnibus accession GSE32465. After defining overlapping regions, linear models determined those locations with significant dose responsive increases in GR binding in response to dexamethasone. Significant peaks are depicted in Figure 1D and Figure S2 for the *SKA2* and *SAT1* genes, respectively. In a similar manner, data was downloaded for FOXA1binding from T-47D and HEPG-2 cells and ERα binding in from ECC1 and T-47D cells; however, varying dosages enabling linear model based determination of significance were not available. As such, only the frequency of sequences aligning to a genomic coordinates following chromatin immunoprecipitation with antibodies for FOXA1 and ERα are depicted in Figure S1.

Identification of confounding factors

We assessed the effect that psychiatric medications, substance use, or early life trauma had on DNA methylation at rs7208505 using available information across the cohorts investigated. After controlling for rs7208505 genotype, age, sex, and race, potential covariate measures were binarily coded and assessed for both association to DNA methylation as well as added into the previously identified linear models of suicidal behavior as an additive covariate to assess any potential confounding effect on the analyses presented in Table 2. The results are depicted in Table S2. We adopted the strategy put forth by Bursac et al., (16) regarding the selection of model covariates with potential confounding effects. Those covariates that change the beta value of the methylation metric by greater than 15% were taken as potentially confounding and were included in the linear models as additive covariates. In the SMRI sample, Mood Stabilizer status exhibited a

confounding effect and was controlled for in all subsequent analysis for this cohort (Table S2). In the PRC sample, dependence on hallucinogens and marijuana met covariate inclusion criteria and were subsequently controlled for in this cohort.

Supplementary Results

Result S1

We investigated the association of rs7208505 corrected DNA methylation with the method of death in suicide decedents in all *post mortem* brain cohorts in efforts to assess if suicide associated DNA methylation increases at SKA2 are the result of the process of dying. Methods of death were classified into those involving asphyxiation, including hanging and drowning, overdose, violent means, and unknown method. No significant differences were observed across groups in a combined analysis of all three brain cohorts (ANOVA, F= 0.53, df= 3, p= 0.66). Results were similar when performed for each cohort separately (ANOVA, NICHD, F= 0.59, df= 3, p= 0.63 ; SMRI, F= 0.26, df= 2, p= 0.77; McL F=1.25, df=2, p=0.53).

Result S2

We investigated relationships within the other CpGs located within *SKA2* that were present on the microarray in order to understand the potential mechanisms by which 3'UTR epigenetic variation may influence gene expression.

One CpG (Illumina Probe: cg10822495) located within miR-301a within intron 1 of *SKA2* was significantly associated with neuronal but not glial genotype corrected 3'UTR DNA methylation; however this CpG was not associated with *SKA2* gene expression. Average levels of DNA methylation of CpGs in the region upstream of the miR-301a were lower in glial relative to neuronal DNA (Fig. S2E), possibly accounting for the observed neuron specific correlations of DNA methylation with gene expression.

We reasoned that rs7208505 T/T homozygotes that cannot be methylated may be reducing the sensitivity of the correlation across other *SKA2* CpGs. Removal of these individuals resulted in numerous significant correlations of *SKA2* 3'UTR DNA methylation at rs7208505 with other CpGs. Using publically available ENCODE data, we determined the regions of dose responsive GR binding in response to dexamethasone and determined that many of the observed correlations are localized in GR binding regions across *SKA2* (Fig S2D). Two of these CpGs, cg17989037 and cg27512082, immediately flank the CREB binding site shown to be important for *SKA2* gene expression (17). Out of the above implicated CpGs correlating with rs7208505 epigenetic variation, only the miR proximal CpG, cg19273756, demonstrated evidence for moderate association to SKA2 gene expression levels after correcting for neuronal proportion as quantified by fluorescence activated cell sorting (F= 4.13, df=2/51, p=0.022) (Fig S2B). We averaged all CpG methylation inclusive and upstream of the first exon of SKA2 to obtain an average promoter region methylation signature, which exhibited a trend towards decreasing *SKA2* gene expression (F= 2.88, df= 2/51, p= 0.065)(Fig S2C). We modeled epigenetic variation in the promoter, miR proximal region, and 3'UTR and identified a significant three way interaction that accounted for 39.52% of the variance in *SKA2* gene expression (Table S3). Cumulatively, the data suggest that epigenetic variation in the *SKA2* 3'UTR may be a reflection of GR dependent epigenetic reprogramming. However, variation in gene expression was not accounted for by variation in any one region implicated in GR binding, suggesting other factors beyond GR mediated epigenetic change may be important for altering expression. As noted in previous analyses, rs7208505 genetic variation was not independently associated with *SKA2* gene expression measures, while DNA methylation variation at rs7208505 was (Table S3). As the genetic and epigenetic variation at rs7208505 are highly correlated, it is difficult to ascertain the effects of genotype statistically independently from DNA methylation at rs7208505. In the case of DNA methylation, there is an additional level of variation beyond the genotype alone that allows it to be more informative after correction for genotype. Despite this, there remains the possibility that rs7208505 may exert effects on gene expression through alternative mechanisms. As an exploratory analysis, we investigated for the presence of long range genetic variation occurring in linkage disequilibrium (LD) with rs7208505. First, we tested each CpG on the microarray for association to rs7208505 genetic variation alone. DNA methylation at the miR-301a proximal CpG, cg19273756, exhibited a trend towards association with rs7208505 (F= 1.8, df= 2/55, p= 0.063), we investigated genetic variants within 2 kb of the miR-301a. Two genetic variants were located in this region, including rs7502947 and rs58604484. These variants encode a C/T transition and an insertion of the sequence : AACTAGCATTGACTATT on the antisense strand, both of which exhibit similar minor allele frequencies around 50% as the alternative C allele of rs7208505 according to the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP). Genomic sequences containing

alternate alleles of these variants were input into the MATCH algorithm (http://www.gene-regulation.com/cgi-bin/pub/programs/match/bin/match.cgi) to search the TRANSFAC database for differential transcription factor binding motifs created by these sequence variants. Using a stringent matrix similarity cut off of 0.9 and core similarity cut off of 0.75, the insertion at rs58604484 generated a binding site for a single transcription factor, AP-1.

Interestingly, recent research has demonstrated that GR binding may occur at estrogen receptor alpha (ERα) binding elements (EREs) after stimulation with dexamethasone, but that this binding requires the facilitation of both FOXA1 and AP-1 (18). ENCODE annotation tracks implicate a FOXA1 binding site is located approximately 200 bp downstream of rs58604484, while MATCH identifies an ERE approximately 30 bp downstream of rs58604484. Investigation of FOXA1 and ERα immunoprecipitation peaks from ENCODE data confirm the presence of these transcription factors at the predicted locations upstream of the miR-301a (Fig S3). Taken together, the results suggest that creation of an AP-1 binding site through an insertion mutation at rs58604484 in linkage disequilibrium with rs7208505 may facilitate the occupation of an ERE by GR and lead to alteration of miR-301a proximal DNA methylation at cg19273756. This potential mechanism by which rs7208505 genetic variation may influence expression should be validated with future experimental studies.

Result S3

A random effects meta-analysis employed to combine data across the three blood cohorts demonstrated significant increases in DNA methylation (Summary effect = 0.055, heterogeneity variance = 0.0029, 95% CI= -0.0149: 0.126, p= $1.2x10^{-4}$) and decreases in rs7208505 C/T heterozygotes (Summary effect = -2.29, heterogeneity variance = 5.4, 95% CI= -5.37: 0.80, p= 0.0011) and C/C homozygotes (Summary effect = -4.75, heterogeneity variance = 22, 95% CI= -10.9:1.45, p= $3.1x10^{-4}$) across the three cohorts.

Result S4

In the prospective cohort, most women gave blood samples at a single time point, so a complete longitudinal analysis of DNA methylation change with time was not possible; however, all women were measured by the Edinburg Postnatal Depression Scale and the Montgomery Asberg Depression Rating Scale at each trimester, enabling analysis of earlier blood samples relative to later outcomes. We attempted to look for associations with rs7208505 epigenetic and genetic variation in our model at the third trimester, but using DNA methylation deriving only from blood samples taken during either the first or second trimester. The model terms remained significant when the analysis was confined to either the third trimester suicidal ideation scores in only those N=30 women who provided blood at earlier time points during the first or second trimester. The consistent associations of the model from these earlier time points suggested that DNA methylation variation at SKA2 preceded the transition to forming suicidal thoughts; however, this interpretation would not be correct if the levels of suicidal ideation were comparable between the earlier time points and the third trimester period at which suicidal ideation was measured. To evaluate this possibility, the change in suicidal ideation was investigated from third trimester relative to the earlier time points. Both increases and decreases in suicidal ideation were observed from the earlier trimesters to the third trimester. Importantly, the change in suicidal ideation from first and second trimester to third trimester was also associated (Table S5), suggesting that *SKA2* 3'UTR DNA methylation variation associated with suicidal ideation precedes the transition to the ideating state.

Result S5

We performed weighted gene co-expression network analysis (WGCNA), followed by gene ontology analysis of significant co-regulated networks for the neuronal and glial cortical samples to assess the cell type specific function of genotype corrected *SKA2* DNA methylation. WGCNA in blood derived data from the prospective cohort generated previously (19) (Gene Expression Omnibus accession: GSE44132) was assessed to generate an indication of whether peripheral epigenetic variation is a marker of neuronal or glial processes. We limited networks to those demonstrating significant non-parametric correlation between module membership and correlation significance per group. Genes within identified *SKA2* co-regulated modules were assessed for over-represented gene pathways using the g.Profiler analysis

suite (20). Significant modules were detected in neurons (Rho= 0.41, p=0.026) and blood (Rho= 0.4, p=0.003), where an enrichment for genes within the category 'Axon Guidance' was observed in both neurons (KEGG04360: Observed=0.075, Expected= 0.023, p=0.04) and blood (KEGG04360: Observed=0.12, Expected= 0.016, p=0.019). Other neuron specific processes were enriched in the blood derived co-regulated module including 'Transmission of Nerve Impulse'(GO:0035637: Observed=0.087, Expected= 0.064, p=0.023) and 'Synaptic Transmission' (GO:0035637: Observed=0.088, Expected= 0.056, p=0.03), suggesting that epigenetic variation in brain relevant processes are being detected in peripheral blood.

In glia, a single module of *SKA2* 3'UTR co-regulated genes was identified that demonstrated significant over representation of a Biogrid interaction pathway containing the *PARP1*, *MAD1L1*, and *SYN2* genes (Frequency observed = 0.33, Frequency expected= 0.023, p= 0.022).

Our data is consistent with reports demonstrating that early life trauma and associated elevated cortisol may inhibit prefrontal cortical synapse formation and attenuate regulation of the HPA axis (21) possibly through reduced inhibition of amygdala driven stress response (22). In glia, enriched gene interactions identified numerous genes with potential functional relevance to psychiatric phenotypes. PARP1 has been directly associated with modulating astrocyte specific uptake of glutamate (23), while epigenetic variation at SYN2 has been implicated in expression differences in bipolar disorder, major depression, and lithium treatment (24, 25). SYN2 functions at the tripartite synapse in astrocytes and plays a key role in modulating cross talk with neurons to promote neuronal synapse stabilization (26, 27). Together, the data suggest that factors involved in epigenetic reprogramming of the *SKA2* 3'UTR region may affect glial specific processes with relevance to neuronal synapse formation. One possibility is that exposure to stress may be causing epigenetic variation at both *SKA2* and these co-regulated genes, a hypothesis which is consistent with the reports of glucocorticoid induced disruption of neuronal synapse stability (28). Similar to previous studies identifying epigenetic biomarkers in a disease with a hormonal etiology (19), the pathway analyses performed suggest that while not every gene may show evidence of cross tissue relevance to the brain, numerous genes in relevant pathways may record more of the etiologically relevant systemic epigenetic reprogramming events and thus be detectable in blood. The function of pathways specific genes appeared to be relevant to the known molecular processes of either neurons or glia in the analyses performed for each respective cell type. Importantly, our analyses demonstrate that epigenetic variation in blood co-regulated with brain specific epigenetic associations in suicide appear to mark brain specific biological processes.

Result S6

We investigated if CpGs proximal to rs7208505 exhibited evidence for association to suicidal ideation, suicide attempt, or salivary cortisol measurements. Pyrosequencing was performed on 4 CpGs located between 280-296 bp upstream of rs7208505 in the GenRED offspring cohort at chr17: 57188008-57188020. The mean DNA methylation in the region was not associated with suicidal ideation (F= 0.26, df=1/15, p= 0.62) or suicide attempt (F= 0.2, df=1/18, p= 0.66). Mean DNA methylation exhibited a trend for association with waking cortisol (F= 3.81, df=1/15, p=0.07). This correlation was significantly weaker than that observed for genotype corrected DNA methylation at rs7208505 (F= 14.69, df= 1/17, p= 0.0013), suggesting any cortisol induced variation on suicidal behavior measurable in DNA methylation is more prominently detected at rs7208505.

Result S7

As an exploratory analysis, we assessed CpGs located within suicidal ideation and suicide attempt associated *SAT1*(29) and identified a trend for an interaction with *SKA2* 3'UTR epigenetic and genetic variation with a promoter CpG located within an ENCODE implicated GR binding region (Fig S4 C,D), suggesting that *SKA2* mediated changes in glucocorticoid signaling may influence and interact with other suicidal ideation related biological variation.

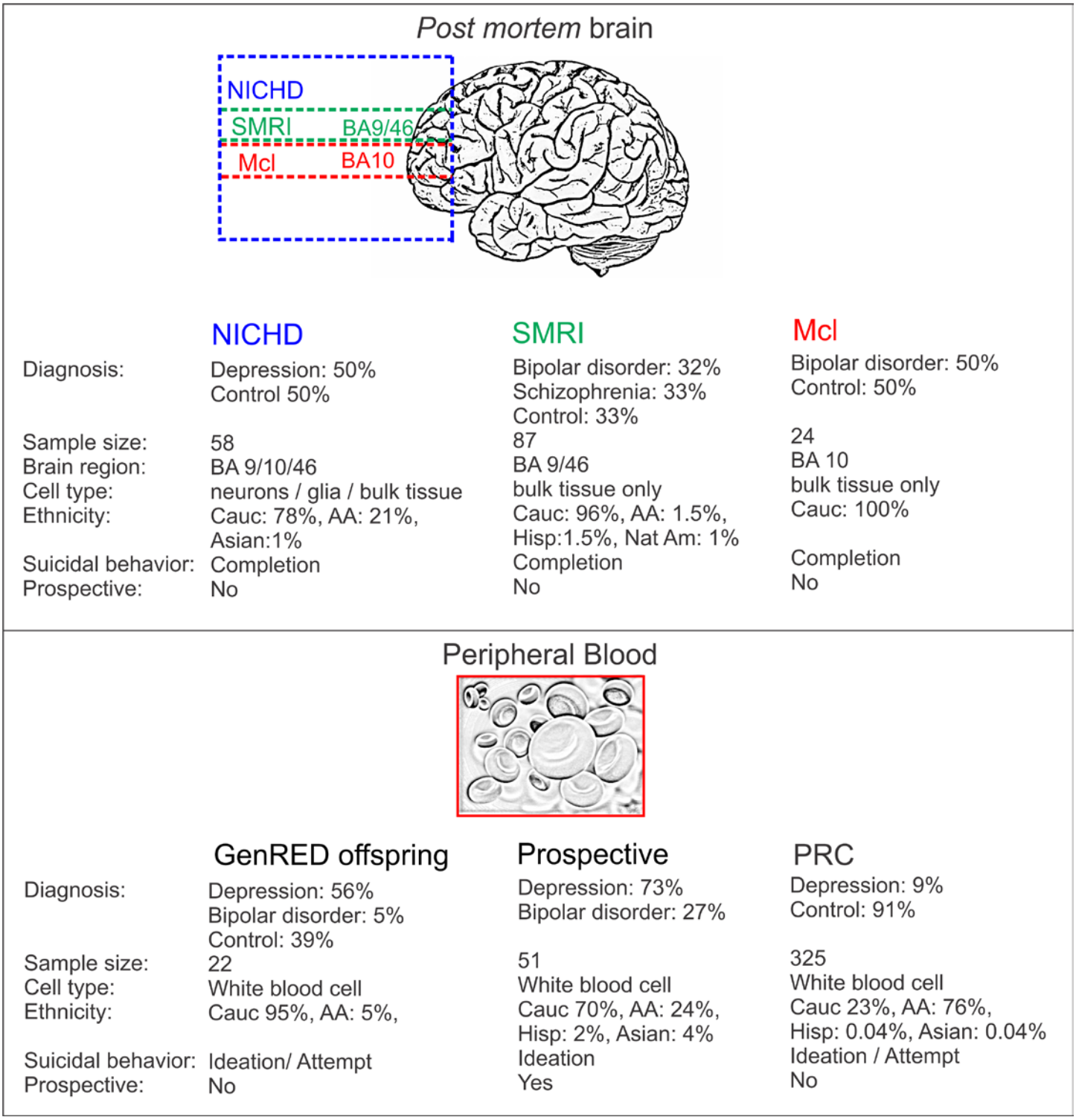

Figure S1. Sample Overview

A schematic representation of relevant variables differing across cohorts. The section of brain assessed is denoted by a dashed color box for the NICHD (blue), SMRI (green), and McL (red) *post mortem* brain bank samples. Dashed lines represent estimations of sample origins corresponding to the Brodmann Areas (BA) depicted. Psychiatric diagnosis and ethnicity proportions are also depicted. Ethnicity categories include Caucasian (Cauc), African American (AA), Hispanic (Hisp), and Asian.

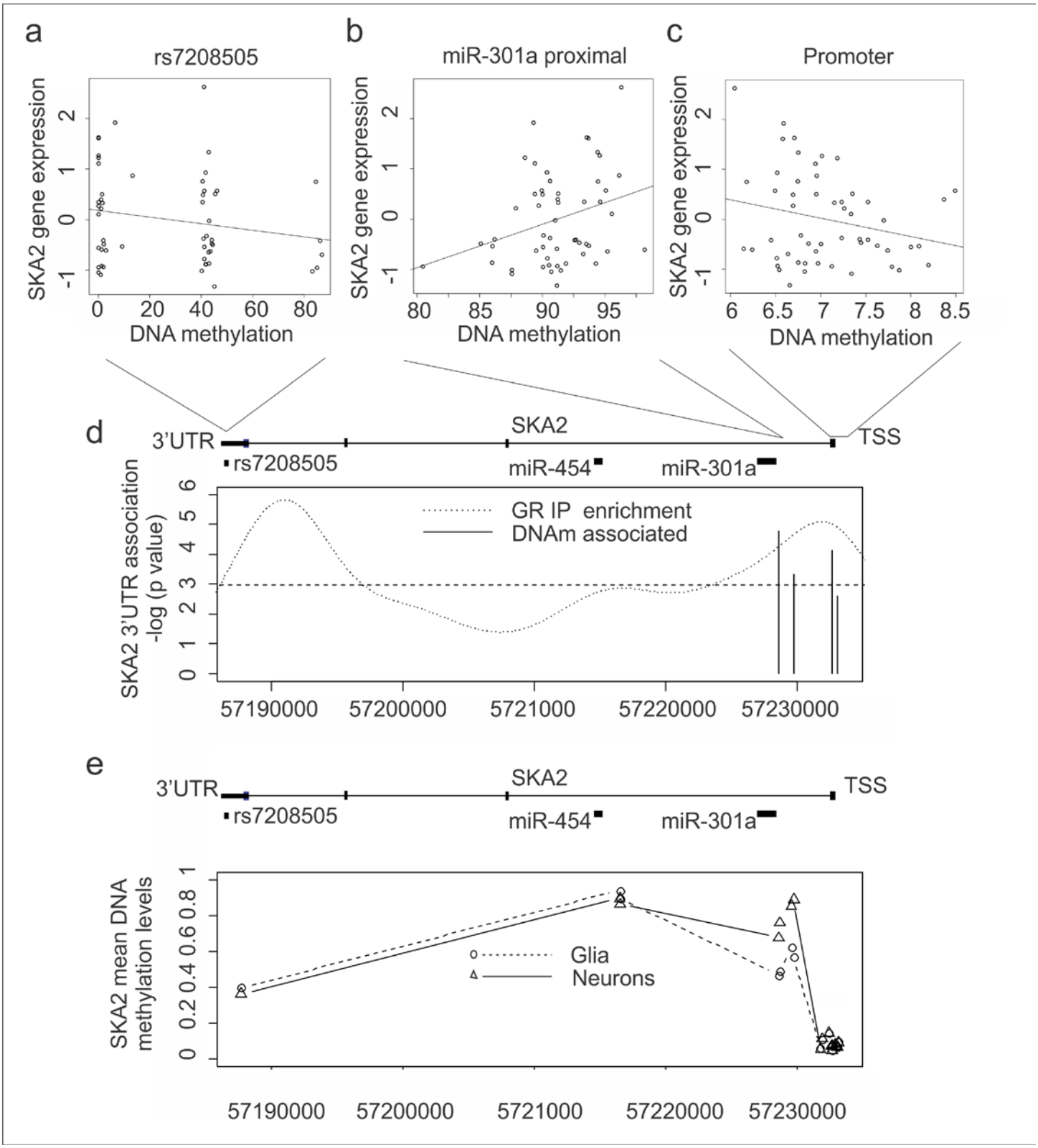

Figure S2. Genomic regions regulating *SKA2* gene expression

a.) Scatterplot of the neuronal proportion adjusted *SKA2* gene expression levels (y axis) as a function of DNA methylation at rs7208505 (x axis).b.) Scatterplot of the neuronal proportion adjusted *SKA2* gene expression levels (y axis) as a function of DNA methylation at miR-301a proximal CpG, cg19273756 (x axis).c.) Scatterplot of the neuronal proportion adjusted *SKA2* gene expression levels (y axis) as a function of DNA methylation at the SKA2 promoter, comprised of the

mean methylation level of all exon1 and 5'UTR CpGs (x axis). d.) Plot of the negative natural log of the significance of the association of rs7208505 genotype corrected *SKA2* 3'UTR DNA methylation vs. HM450 microarray CpGs located in the *SKA2* gene (y axis) plotted as a function of genomic coordinate (x axis). For methylation correlations, only N= 32 C/T and C/C genotype individuals capable of DNA methylation modification were assessed in the correlation. *SKA2* 3'UTR DNA methylation associated CpGs were located primarily in two regions including proximal to miR-301a and within the gene promoter. CpGs included cg10822495 (rho= 0.46, p= 0.0083) and cg19273756 (rho= -0.38, p=0.035) proximal to miR-301a, and cg17663700 (rho=0.32, p=0.077), cg17989037 (rho=0.36, p=0.043), cg27512082 (rho= 0.42, p=0.016), and cg24616461 (rho= 0.32, p= 0.074) located within the promoter region. Only those CpGs with associations below a trend level of $p \leq 0.1$ are depicted. Also depicted are regions of dose dependent GR immunoprecipitation (IP) based binding in response to dexamethasone derived using ENCODE data. e.) Plot of mean DNA methylation level at those HM450 microarray CpGs located across *SKA2* for N=58 NICHD samples. A schematic representation of the *SKA2* gene is depicted at the top of panels d and e to scale relative to the plotted data points complete with the location of intronic microRNAs and rs7208505.

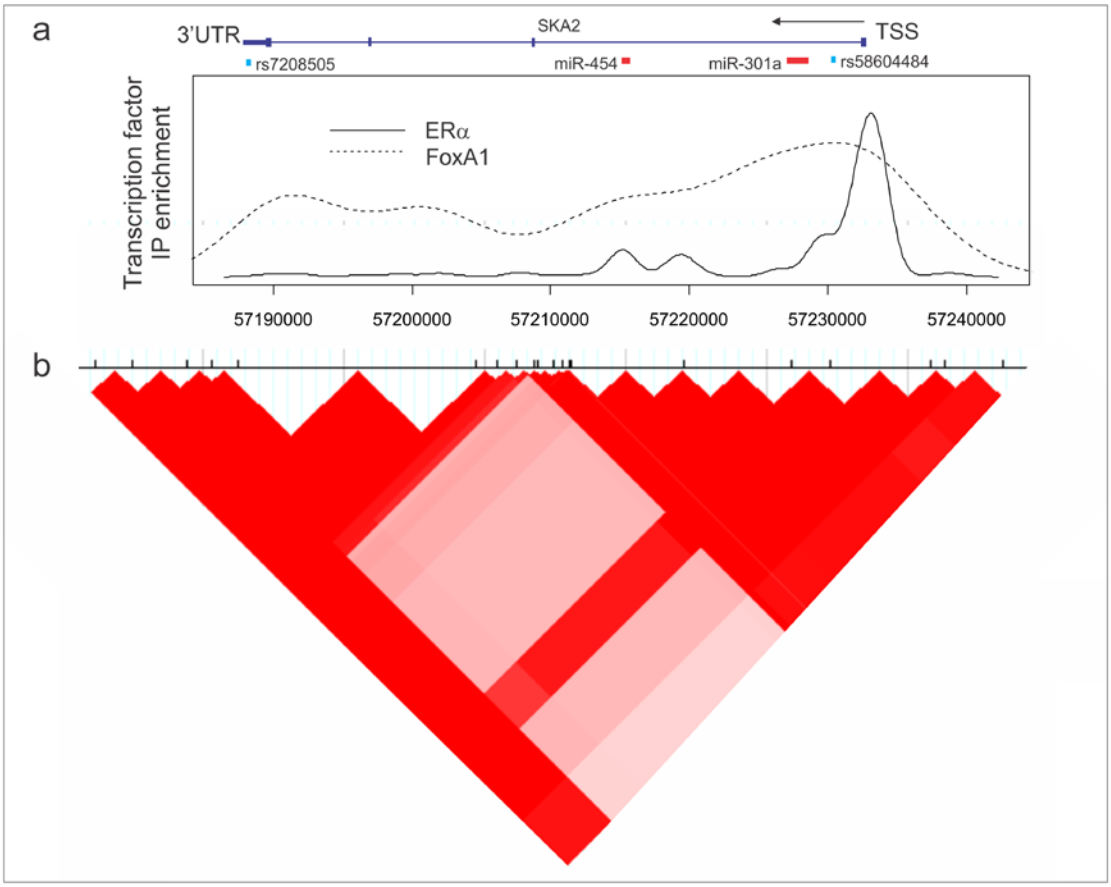

Figure S3. Transcription factor binding and linkage disequilibrium across *SKA2*

a.) Density plots of regions binding ERα and FOXA1 transcription factors from ENCODE data in the region of *SKA2*. b.) An LD plot generated using HapMap (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap27_B36) demonstrating the strength of LD with stronger dprime values depicted in increasing shades of red. A schematic of *SKA2* is depicted to scale to denote the positions of rs7208505 and rs58604484 as a function of both LD and transcription factor binding.

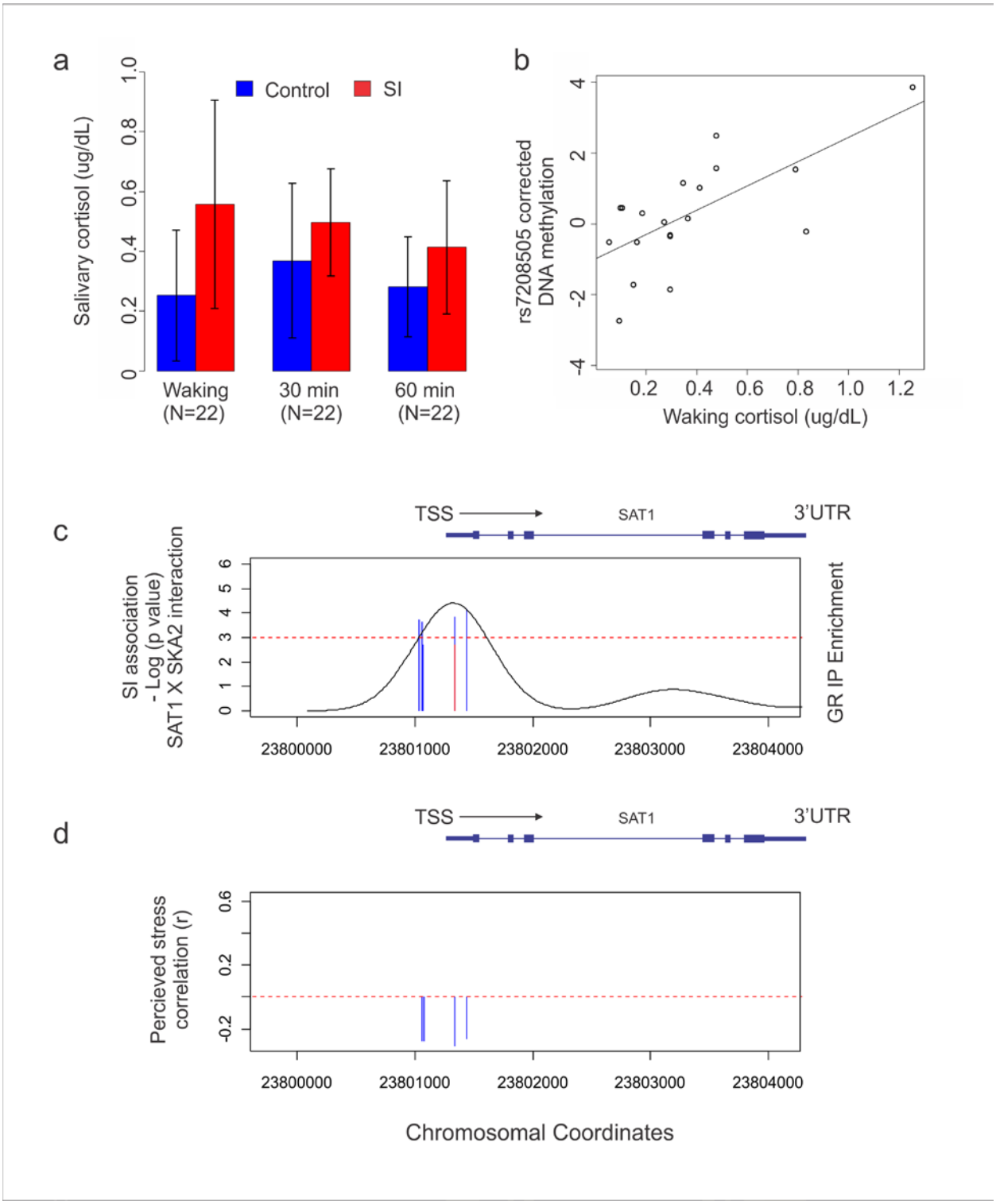

Figure S4. Glucocorticoid relationships to suicidal ideation and suicidal ideation related genes

a.)Barplot of salivary cortisol levels between suicidal ideation and controls in the GenRED cohort at waking (Wilcoxon Rank Sum, W= 13.5, df= 8.8, p= 0.018) , 30 min (Wilcoxon Rank Sum, W= 23, df= 16.09, p= 0.12), and 60 min (Wilcoxon Rank Sum, W= 27, df= 10, p= 0.22) after waking. Error bars represent standard deviations. b.) Scatterplot of rs7208505 corrected DNA methylation (y axis) as a function of waking cortisol levels (x axis) in the GenRED offspring

cohort (F= 14.69, df= 1/17, p= 0.0013). c.) A plot of the – natural log of the significance of CpGs within the *SAT1* gene with suicidal ideation as measured by MADRS in the prospective cohort (y axis) as a function of genomic coordinate (x axis). Associations of *SAT1* appear in blue and associations of interaction with *SKA2* 3'UTR DNA methylation appear in red. Only CpGs reaching statistical significance or trend level are depicted. A CpG at Illumina probe cg18154784 interacted with rs7208505 genetic and epigenetic variation to significantly associate with suicidal ideation (F= 4.47, df= 7/43, p= $8.2x10^{-4}$). The frequency of ENCODE GR immunoprecipitation peaks are depicted in black. A scale representation of the *SAT1* gene is depicted above the graph. d.) A plot of the correlation coefficient with perceived stress in the prospective cohort (y axis) as a function of genomic coordinate for significantly associated CpGs. CpGs significantly associated with perceived stress are localized under an ENCODE GR binding peak, suggesting that stress, possibly influenced by *SKA2* variation, may be an important modulator of *SAT1* epigenetic variation in the region.

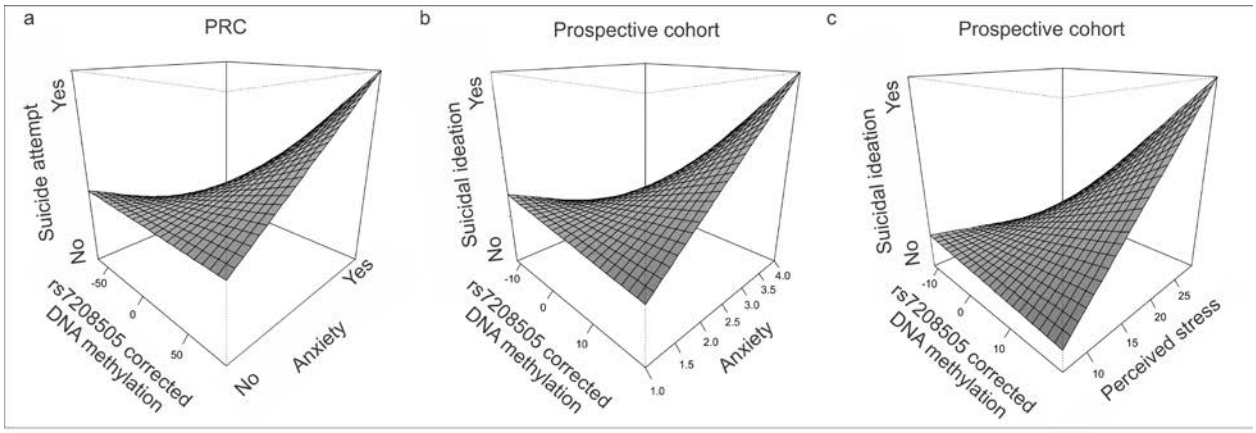

Figure S5. Suicidal behavior prediction models

a.) A three dimensional depiction of the effect of the rs7208505 genotype corrected *SKA2* 3'UTR DNA methylation (z axis) interaction with anxiety status (x axis) on suicide attempt in the PRC cohort (y axis) ($F= 3.2$, $df= 3/321$, $p= 0.024$). b.) A three dimensional depiction of the effect of the rs7208505 genotype corrected *SKA2* 3'UTR DNA methylation from first or second trimester blood (z axis) interaction with third trimester anxiety (x axis) on third trimester suicidal ideation in the prospective cohort (y axis) ($F= 8.1$, $df= 18$, $p= 1.2x10^{-4}$). c.) A three dimensional depiction of the effect of the rs7208505 genotype corrected *SKA2* 3'UTR DNA methylation from first or second trimester blood (z axis) interaction with third trimester perceived stress (x axis) on third trimester suicidal ideation in the prospective cohort (y axis) ($F= 0.33$, $df= 19$, $p= 5.6x10^{-6}$).

Table S1: *Sample Quality*

DNA	**Mean DNA 260/280**	**Error (SD)**
NICHD	1.84	0.05
SMRI*	na	na
McL	1.93	0.09
GenRED Offspring	1.80	0.07
Prospective	1.76	0.05
PRC	1.70	0.07
RNA	**Mean RIN**	**Error (SD)**
NICHD	8.20	0.77

*Amounts of DNA obtained from the SMRI were only enough to enable experimental procedures and not quality assessment

Table S2: *Effects of Substance and Medication on DNA methylation*

Test 1						Test 2					
NICHD Neurons Suicide (N=58)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Alcohol	-2.2	4	0.29	1/56	0.59	0.015	0.0068	0.028	1.9	9/47	0.069
Opiates	5.6	3.7	2.3	1/56	0.14	0.015	0.0069	0.039	2	9/47	0.063
Antipsychotics	3.1	9.4	0.11	1/56	0.75	0.015	0.0066	0.03	2.3	9/47	0.034
Mood Stabilizers	-4	9.4	0.18	1/56	0.67	0.015	0.0068	0.029	1.9	9/47	0.068
Antidepressants	-0.98	3.1	0.1	1/56	0.75	0.016	0.0066	0.019	2.4	9/47	0.025
SMRI Brain Suicide (N= 87)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Alcohol	1.2	4	0.086	1/83	0.77	0.0054	0.0027	0.048	1.8	10/74	0.083
Opiates	-1.3	3.8	0.12	1/82	0.73	0.0059	0.0026	0.026	2.4	10/73	0.017
Antipsychotics	-2.6	3.7	0.49	1/84	0.48	0.0056	0.0027	0.038	1.7	10/75	0.094
Mood Stabilizers	-2.2	4.1	0.29	1/84	0.59	0.0063	0.0026	0.018	2.4	10/75	0.017
Antidepressants	0.47	4.1	0.013	1/84	0.9	0.0052	0.0026	0.051	2	10/75	0.041
McL Brain Suicide (N= 24)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Opiates	-1.3	1.2	1.3	1/22	0.27	0.076	0.023	0.005	7.7	7/16	0.0004
Antipsychotics	1.5	1.1	2	1/22	0.17	0.058	0.023	0.021	10	7/16	$7x10^{-5}$
Mood Stabilizers	1.5	0.98	2.3	1/22	0.14	0.07	0.024	0.01	7.9	7/16	0.0003
Antidepressants	1.7	1.2	1.9	1/22	0.18	0.06	0.024	0.021	9.3	7/16	0.0001
GenRED offspring (N= 22)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Alcohol Dependence	-0.56	1.2	0.24	1/16	0.63	0.18	0.067	0.025	2.3	7/10	0.11
Substance Dependence	0.011	1.6	$4x10^{-7}$	1/16	1	0.17	0.076	0.048	1.6	7/10	0.25
Antipsychotics	-0.7	0.77	0.83	1/18	0.37	0.16	0.11	0.2	0.89	7/9	0.55
Mood Stabilizers	-0.21	0.7	0.088	1/18	0.77	0.16	0.11	0.2	0.89	7/9	0.55
Antidepressants	-0.67	0.63	1.1	1/18	0.31	0.15	0.12	0.24	0.85	7/9	0.58
Any Medication	-0.093	0.58	0.026	1/18	0.87	0.15	0.11	0.22	0.85	7/9	0.57
Childhood Trauma	1.5	0.77	3.9	1/20	0.063	0.11	0.076	0.2	2.5	7/11	0.084
Prospective cohort (N= 51)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Alcohol	-1	5.2	0.04	1/50	0.84	0.068	0.018	0.0003	3.8	5/45	0.0056
SSRI	-1.1	2	0.31	1/49	0.58	0.065	0.017	0.0004	5	5/44	0.001
Mood Stabilizer /Antipsychotic	0.0021	2.9	$5x10^{-7}$	1/49	1	0.068	0.018	0.0004	3.8	5/44	0.0063
Antidepressants	-1.6	2	0.64	1/49	0.43	0.064	0.017	0.0006	4.8	5/44	0.0013
Any Medication	-1.2	2.1	0.34	1/49	0.56	0.065	0.017	0.0005	4.5	5/44	0.0022

Childhood Sexual Trauma	2.5	2.1	1.4	1/47	0.24	0.072	0.018	0.0002	4.3	5/42	0.003
PRC (N= 325)											
Covariate	**β value**	**Error**	**F**	**DF**	**Model P**	**β value**	**Error**	**DNAm P**	**F**	**DF**	**Model P**
Alcohol Dependence	0.11	2.7	0.0017	1/323	0.97	0.0017	0.0011	0.13	4.2	9/315	$4.4x10^{-5}$
Opiate Dependence	-4.4	9.4	0.21	1/323	0.64	0.0018	0.0011	0.1	4.2	9/315	$4.1x10^{-5}$
Tranquilizer Dependence	21	15	2	1/323	0.16	0.0016	0.0011	0.15	2.5	9/315	0.0095
Pain Medication Dependence	9	7.5	1.4	1/323	0.23	0.0016	0.0011	0.16	2.6	9/315	0.0065
Stimulant Dependence	21	15	2	1/323	0.16	0.0016	0.0011	0.15	2.5	9/315	0.0095
Marijuana Dependence	-7.8	5.5	2	1/323	0.16	0.002	0.0011	0.073	3.9	9/315	0.0001
Hallucinogen Dependence	-38	15	6.8	1/323	0.0097	0.0021	0.0011	0.067	3.1	9/315	0.0014
Crack Dependence	-6.5	11	0.38	1/323	0.54	0.0018	0.0011	0.1	3.9	9/315	$9.8x10^{-5}$
Cocaine Dependence	-1.1	15	0.0051	1/323	0.94	0.0017	0.0011	0.13	2.9	9/315	0.0025
Heroin Dependence	11	8.6	1.5	1/323	0.22	0.0015	0.0011	0.19	3.3	9/315	0.0007
Childhood Sexual Trauma	3.4	5	0.48	1/269	0.49	0.001	0.0012	0.4	4.2	8/262	$8.5x10^{-5}$
Assaultive Trauma	2	3.1	0.43	1/247	0.51	0.0017	0.0013	0.18	3	9/240	0.003

Test 1: DNA methylation association with substance
Test 2: Suicide association with methylation controlling for substance

Table S3: *Gene expression associations*

Uncorrected 3'UTR DNAm			
Model Term	**Spearman's ρ**	**DF**	**P value**
3'UTR DNAm	-0.31	52	0.022
Uncorrected rs7208505			
Model Term	**Kruskal-Wallis χ2**	**DF**	**P value**
rs7208505	1.55	2	0.46
rs7208505 Genetic and Epigenetic Model			
Model Term	**β value**	**Error**	**P value**
3'UTR DNAm	-0.032	0.014	0.024
rs7208505 C/T	1.1	0.56	0.054
rs7208505 C/C	2.1	1.2	0.085
F	1		
DF	8/44		
Model R^2	0.16		0.43
Interactive Model			
Model Term	**β value**	**Error**	**P value**
3'UTR DNAm	-8.5	2.9	0.0054
Promoter	-2266	1470	0.13
miR-301a	-168	115	0.15
rs7208505 C/T	1	0.52	0.063
rs7208505 C/C	1.2	1.1	0.29
Neuronal Proportion	0.015	0.012	0.19
3'UTR DNAm X Promoter	119	41	0.0062
3'UTR DNAm X miR-301a	9.5	3.2	0.0054
Promoter X miR-301a	2508	1645	0.13
3'UTR DNAm X Promoter X miR-301a	-1.34	4.63	0.0061
F	2.8		
DF	10/43		
Model R^2	0.4		0.009

DNAm= DNA methylation

Table S4: *Independent genetic and epigenetic effects on suicidal behavior*

rs7208505 Effects	**Kruskal Wallace χ2**	**DF**	**P value**
NICHD	0.19	2.00	0.91
SMRI	0.21	2.00	0.90
McL	5.44	2.00	0.066
GenRED Offspring	1.97	2.00	0.37
Prospective	5.12	2.00	0.077
PRC	1.22	2.00	0.54
DNA methylation Effects	**Wilcoxon W**	**DF**	**P value**
NICHD	317	50.61	0.18
SMRI	566.5	26.18	0.47
McL	18	20.87	0.087
GenRED Offspring	22	16.14	0.099
Prospective	112	20.39	0.0036
PRC	8660.5	134.85	0.15

Table S5: *Prospective Suicidal Ideation Associations*

	3rd Trimester Suicidal Ideation from 1st and 2nd Trimester Blood (N=30)			2nd - 3rd Trimester Suicidal Ideation (N=30)		
Model Terms	**β value**	**Error**	**P value**	**β value**	**Error**	**P value**
DNAm	0.056	0.013	$3x10^{-4}$	0.069	0.024	0.0084
C/T	-2.5	0.69	$1.4x10^{-3}$	-3.1	1.3	0.021
C/C	-5	1.2	$3.7x10^{-4}$	-5.7	2.2	0.018
Age	0.035	0.016	0.035	0.023	0.029	0.42
F	4.09			2.2		
DF	6/24			6/24		
Model R^2	0.5		0.0058	0.2		0.078

DNAm= DNA methylation
C/T= rs7208505 heterozygotes
C/C= rs7208505 alternative homozygotes
* While psychiatric medication changes may have occurred over this period in women becoming depressed during the third trimester, controlling for third trimester antenatal depression status as an additive covariate did not alter the significance of any model factors reported above. Similarly, controlling for blood cellular heterogeneity using cell subtype proportions reported previously (19) did not affect the significance of the model. Race is included in the above regression analysis but not shown.
DNAm= DNA methylation

Table S6: *Interactive effects on suicide risk*

		PRC suicide attempt in ideators (N=79)			PRC Intent to die among suicide attempters (N= 48)	
Model Terms	**β value**	**Error**	**P value**	**β value**	**Error**	**P value**
DNAm	-0.0034	0.003	0.26	-0.0026	0.0057	0.64
C/T	-0.0064	0.16	0.97	-0.51	0.31	0.11
C/C	0.34	0.26	0.19	0.20	0.46	0.67
Anx	-0.54	0.29	0.064	-0.94	0.89	0.30
Age	-0.0094	0.024	0.7	-0.032	0.047	0.51
Sex	0.07	0.12	0.55	0.11	0.22	0.64
DNAm X Anx	0.017	0.0084	0.053	0.026	0.015	0.08
C/T X Anx	-0.23	0.50	0.63	0.098	0.83	0.90
C/C X Anx	-1.56	0.87	0.078	na	na	na
F	0.97			2		
DF	13/65			10/37		
Model R^2	0.16		0.49	0.353		0.061
		GenRED Waking Cortisol (N= 22)			**GenRED Cortisol Suppression (N= 22)**	
Model Terms	**β value**	**Error**	**P value**	**β value**	**Error**	**P value**
DNAm	0.12	0.035	0.0037	-0.01	0.012	0.41
C/T	-4.7	1.5	0.0068	0.2	0.48	0.69
C/C	-11	3.2	0.004	1.1	1.1	0.34
Age	-0.0094	0.019	0.62	-0.017	0.004	0.00
Sex	0.037	0.1	0.72	-0.06	0.023	0.03
Cort				-0.094	0.54	0.86
DNAm X Cort				-0.11	0.02	0.00
C/T X Cort				5.6	1	$4.1x10^{-4}$
C/C X Cort				10	1.9	$5.5x10^{-5}$
F	5.2			27		
DF	5/13			9/9		
Model R^2	0.67		0.0075	0.96		$1.8x10^{-5}$

DNAm= DNA methylation
C/T= rs7208505 heterozygotes
C/C= rs7208505 alternative homozygotes
Anx = anxiety
Cort= waking cortisol
X denotes an interaction

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