Suppl. Table 1.1 Overview of candidate genes studies associated with psychological stress during prenatal

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| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| NR3C1  (exons 1F)  13 CpGs | Prenatal depressions  /anxious | 33 infants of depressed mothers treated ;  13 infants of depressed non-treated mothers ;  36 infants of non-depressed mother | cord blood  mononuclear cells | Oberlander  et al.(2008) | Prenatal exposure to maternal depressed/ anxious during the 2nd and 3rd trimester was associated with NR3C1 methylation↑ | Maternal medication | √ | η′2:0.081~0.065  Β=0.312  Large power | [18536531](https://www.ncbi.nlm.nih.gov/pubmed/18536531" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1(exons 1F)  Mean 10 CpG  BDNF (exton IV) | Prenatal depression | 20 depressed mother and their new-babies  37 control mother and new-babies | Buccal | Braithwaite  et al.(2015) | Prenatal depression significantly predicted NR3C1 1F methylation↑ (only male) and BDNF IV methylation ↓ in both gender infants | Maternal depression after delivery | √ | Β=0.350,  P=0.017  Large power | [25875334](https://www.ncbi.nlm.nih.gov/pubmed/25875334" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1  (exons 1F, 1B , 1D)  Multiple loci | Prenatal anxiety | 83 pair of Pregnant women and new-baby | umbilical cord blood | Hompes  et al (2013) | Maternal anxiety each trimester best predict DNA methylation at several CpG sites within NR3C1 exons 1 D,1 F.(↑) | Gestational age, sex of baby, maternal weight/age, smoking/ substance use, education | √ | pregnancy anxiety account 7.8% of variance  Power: 69% | 23566423\* |
| NR3C1  (exon 1F)  29 loci | Prenatal/postnatal depression | 1233 mothers and the babies | saliva | Murgatroyd et al.(2015) | Infants’ NR3C1 1-F methylation↑ with the increased of maternal prenatal/postnatal depression. | mothers’ age, years of education, maternal smoking and depression score | √ | Pre depression:  coefficient:0.348  Post depression:  coefficient:0.574  (large power) | [25942041](https://www.ncbi.nlm.nih.gov/pubmed/25942041" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1 (exon 1F, 3 CpG)  11β-HSD2 | Prenatal depression | 128 infants | buccal | Conradt  et al. (2016) | No significant correlations between maternal prenatal stress and infant NR3C1 methylation and 11β-HSD-2. | birth weight, gestational age, ethnicity, sex. | × | b =0 .23,  low power | [26822444](https://www.ncbi.nlm.nih.gov/pubmed/26822444" \t "https://www.geenmedical.com/_blank) |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| NR3C1  (exon 1F)  4 CpG loci  & mean DANm | Prenatal depression  /anxiety | 481 neonate | cord blood | Mansell et al. (2016). | Maternal psychological distress and anxiety  associated with small increase in neonate NR3C1 methylation at specific CpG sites  But No significant after multiple correction. | maternal: age, smoking status, antidepressant use, folate levels, infant sex, birth weight, cell composition | √ | CpG 1.2; r=0.11  large power | [27040859](https://www.ncbi.nlm.nih.gov/pubmed/27040859" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1  (exon 1F)  13 CpGs  11β-HSD2 | Prenatal depression  /anxiety | 482 pregnant women  & new babies  398 control women & babies | placenta | Conradt  et al. (2013) | Methylation of NR3C1 CpG2 is↑for higher prenatal depression exposure infants. methylation of 11β-HSD-2 CpG4 ↑for infants whose mothers reported anxiety during pregnancy. | infant sex, birth weight, maternal age  maternal tobacco, ethnicity, maternal depression/anxiety | √ | NR3C1:  ρ=0.10,P=0.03  11β-HSD-2:  ρ=0.10, P=0.04  (medium power) | [24135662](https://www.ncbi.nlm.nih.gov/pubmed/24135662" \t "https://www.geenmedical.com/_blank) |
| NR3C1  (exon 1F) | Maternal and Paternal PTSD during pregnancy | 80 Adult Holocaust Survivor offspring  15 control offspring without Parental PTSD | blood | Yehuda  et al.(2014) | In the absence of maternal PTSD, offspring with paternal PTSD showed ↑GR-1F promoter methylation; offspring with both maternal and paternal PTSD showed ↓ methylation. | Presence of parent’s Holocaust exposure, age, gender, cell type, lifetime smoking | √ | P=0.05  large power | 24832930\* |
| NR3C1  (promoter)  NR3C2, SLC6A4  BDNF | Prenatal depression | 167 children（6~9 years）  (Longitudinal) | buccal | Stonawski  et al.(2018) | Prenatal depression associated with ↑ DNAm of NR3C1, ↓NR3C2 DNAm. ↑ DNAm of SLC6A4 cg18584905. An interactive effect of depression and sex on DNAm of cg2674128 . No DNAm change of BDNF, CRHR1, FKBP5 | Postpartum/current maternal depressive symptoms,Children’s antibiotic intake, Apgar score | × | NR3C1:P=0.032  η2 = 0.03  SLC6A4:  η2=0.03  small power | 29606180 |
| 16 genes  NR3C1(34 promoter) | Prenatal depression | 22 3–7-year-old children | buccal | Bleker et al. (2019) | No differences in mean DNAm between children born to women with severe depression/anxiety compared to children born to women with mild depression/anxiety. | birth weight, sex, age, and allocation | √ | Low power | 30717815 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| NR3C 1F promoter  CpG22, 23)  Ave DNAm | prenatal and postnatal depression | 176 mother and their offspring | Saliva | Hill et al.  (2019) | In girls, NR3C1 methylation mediated the association between maternal depression and child anxious-depressed symptoms sex depended sex specific analysis | Partner psychological abuse, Maternal age, marital status, socioeconomic status | × | Low power | 31438539 |
| NR3C1  4 CpG sites  Mean DANm | Prenatal anxiety and depression | 163 mother infants pairs | cord blood | Dereix, et al. (2020) | DNAm of CpG 1 higher in infants born to women with high pregnancy anxiety. No association with prenatal depression. | maternal age, race, education, BMI, antianxiety or antidepressant medications taken etc. | / | Anxiety: β=2.54, 95% CI: 0.49-4.58)  Large power | 33215541\* |
| NR3C1  (promoter)  NR3C2 | Prenatal depression  SCID-IV+  EPDS | 236 pregnant women and infants | placental and infant’s buccal | Galbally et al.  (2020) | Early pregnancy depressive symptoms were positively associated with NR3C1 placental methylation at CpGs 10\_11 (r=0.16) and 20\_21 (r= 0.16), and with NR3C2 placental methylation at CpG 24 = 0.15. | maternal age, ethnicity, educational attainment,employment status, relationship status, and smoking | √ | NR3C1: r=0.16  NR3C2: r=0.15  Large power | 32087522\* |
| SLC6A4  (promoter)  BDNF  CpG1-CpG10 | Prenatal depression | 82 pregnant women and their infant | Umbilical cord leukocytes | Devlin et al.  (2010) | Increased (2nd) trimester maternal depressed mood was associated with↓ methylationbut at promoter of SLC6A4 both in maternal and infant instead of late pregnancy. While had no effect on BDNF promoter methylation. | MTHFRC 677T genotype marternal medication | √ | p=0.029~0.039  η2 = 0.070~0.06  low power | [20808944](https://www.ncbi.nlm.nih.gov/pubmed/20808944" \t "https://www.geenmedical.com/_blank) |
| SLC6A4  (promoter) | Perinatal depression | 40 depress mother- offspring;  20 control mother- offspring | Buccal | Mendonca  et al.(2010) | DNAm of SLC6A4 ↓ in mother and child were both diagnosed with depression | / | / | (not provided) | [30447571](https://www.ncbi.nlm.nih.gov/pubmed/30447571" \t "https://www.geenmedical.com/_blank) |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| OXTR  (exon 3) | Perinatal depression | 218 mothers and their children (Longitudinal) | saliva | King et al. (2017) | No DNAm of OXTR for offspring. | Gender of offspring mother’s education | **√** | persistent PDS:  p< 0.001 | 28918249 |
| OXTR  (exton 3) | Prenatal stress/  depression | 39 [neonate](https://fanyi.so.com/?src=onebox" \l " neonate" \t "https://www.so.com/_blank) | umbilical cord blood | Unternaehrer  et al. (2016) | A number of stressful life event, prenatal and chronic stress all can predict ↓ DNA methylation of OXTR in new-babies. | sociodemographic  data, characteristics and birth outcome | √ | 7.183 for depression  Large power | 27107296\* |
| FKBP5  intron 5 | Prenatal maternal affective disorders | 60 infant from the Boston Birth Cohort | cord blood | Duis et al. (2018) | FKBP5 TT carriers associated with increased methylation at multiple CpGs in FKBP5,these findings enhanced among cases exposed to maternal affective disorders | Gestational age, maternal BMI birthweight, preterm delivery, and ancestry | **×** | p = 0.02 | 30619472 |
| IGF2  H19  Multiple loci | Prenatal  Depression/  anxiety | 576 pregnant women and infants | cord blood  mononuclear cells | Mansel  et al. (2016) | Maternal anxiety associated with ↓ methylation in average IGF2/H19 and across six CpG units.(Especially female) | Maternal age, smoking folate intake, cell type | √  (gender) | Δ= − 2.23%  Δ=− 3.70% (F)  Small power | [27023171](https://www.ncbi.nlm.nih.gov/pubmed/27023171" \t "https://www.geenmedical.com/_blank) |
| Imprint genes:  IGF2, MEG3, PEG3,MEST  IG, NNAT etc | Perinatal depression | 508 infants | cord blood | Liu et al. (2012) | infants born to severe depressed women had a 2.4% higher MEG3 methylation. Differences is larger in female infants and those born to black women. Sex and race specific analysis | education, smoking, delivery mode, folic acid use and preterm birth, maternal DNAm | √ | Female : 3.6%,  Black:2.3%,  Medium-large power:61% | [22677950](https://www.ncbi.nlm.nih.gov/pubmed/22677950" \t "https://www.geenmedical.com/_blank)\* |
| IGF2,  H19 | Maternal  depression | 356 infants (IGF2)  411 infants (H19)  (Half was AA) | umbilical  cord blood | Soubry A,  et al (2011) | No association between DNA methylation and maternal depression. | age, race, education, smoking during pregnancy |  | IGF2 : β=0.72  Large power | [22414206](https://www.ncbi.nlm.nih.gov/pubmed/22414206" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1  (exon 1F) | Prenatal SLE | 84 infants | buccal | Ostlund, et al. (2016) | No significant correlations between maternal prenatal stress and infant NR3C1 methylation. For female infants: prenatal stress associated with ↑methylation of NR3C1. sex-specific analysis | maternal age, maternal ethnicity, gestational age, birth weight, infant age | √ | t =−2.01(female)  p=0.057  Large power | [27462209](https://www.ncbi.nlm.nih.gov/pubmed/27462209" \t "https://www.geenmedical.com/_blank)\* |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| NR3C1  (exon 1F, 41 CpG)  11β-HSD2  FKBP5 | maternal  perceived stress  (fetal move) | 61 women (24-27 GW)and their fetal ( 34-37 weeks) | saliva  (mother)  Placental  (infant) | Monk et al. (2016） | Higher maternal perceived stress was associated with ↑ DNAm of NR3C1, 11βHSD2 and FKBP5 in mother, and results were validated among infants. | Infant’s sex, gestational birth weight, C-section status | × | r=0.27–0.41  Large power | [27013342](https://www.ncbi.nlm.nih.gov/pubmed/27013342" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1 (exon 1F)  NR3C2 | Genocide  exposure during pregnancy | 25 women exposed to the genocide and children  25  control women and their children | peripheral blood leukocytes | Perrod  et al.(2014) | Exposed mothers had ↑ DNAm of NR3C1 exon 1F and ↑  CpGs located within NR3C2 coding sequence, not for offspring. | / | / | NR3C1  For offspring:  β=1.18 | 24690014\* |
| NR3C1  (exon1F, mean DNAm)  SLC6A4,  (8 CpG)  SCG5 | Maternal psychological stress | 53 Pregnant mothers and their infants | buccal cells | DeLano  (2020) | No significant associations were identified between maternal community deprivation and methylation of NR3C1. Higher mean methylation across 8 CpG sites in SLC6A4. | household income,  mother’s age, self-identified race, and ACE score | × | SLC6A4:  β=2.81, p= 0.03  Girl: β= 3.69  Large power | 33330307\* |
| NR3C1 exon1F  CpG 35-39 | Several form of prenatal stress | 977 individuals  **(**Meta analysis across 7 studies) | placenta,Cord blood, Saliva, buccal | Palma-Gudielv et al (2015) | From the CpG 35-39, only methylation of CpG 36 ↑ after prenatal stress exposure | gender, methylation at other gene | × | r = 0.14, 95% CI: 0.05–0.23  Large power | [26327302](https://www.ncbi.nlm.nih.gov/pubmed/26327302" \t "https://www.geenmedical.com/_blank)\* |
| NR3C1  (exon IF) | Intimate partner violence during pregnancy | 29 mothers and their adolescents offspring | whole blood | Radtke  et al.(2011) | Mean percentage of methylated clones among adolescent is ↑ after mother's experience of IPV, mother’s GR mehtylation did not affected. | Maternal age, ethnity, marriage status | / | Offspring:  U=30.5,P=0.015  Large power | [22832523](https://www.ncbi.nlm.nih.gov/pubmed/22832523" \t "https://www.geenmedical.com/_blank)\* |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| NR3C1  (promoter) | Prenatal exposure to war stress | 25 pairs of mother-child | umbilical cord blood | Mulligan  et al(2012) | Prenatal exposure to war stress predicted ↑DNA methylation of NR3C1 promoter only infants (roughly 35%), not mother. | Maternal methylation  Birth weight | / | corr =0.565  P=0.0032  Large power | 22810058\* |
| SLC6A4  (83 CpG around promoter) | prenatal, early and recent stress/trauma | 133 healthy young adults | whole blood | Wankerl et al. (2014) | The positive relationship between two site (CpG9,CpG30) and prenatal stress. No significant effect of early/recent life stress/trauma on the mean or site-specific SLC6A4 methylation levels.  Consider the effect of 5-HTTLPR genotype | sex, age, body mass index and smoking status, [contraceptive](https://fanyi.so.com/?src=onebox" \l "contraceptive pill/drug" \t "https://www.so.com/_blank) medication | **√** | η2=0.09 for CpG9  η2=0.16 for CpG30  (small-medium power) | [24937096](https://www.ncbi.nlm.nih.gov/pubmed/24937096" \t "https://www.geenmedical.com/_blank) |
| SLC6A4  (4CpG in promoter)  Loci specific & mean | Prenatal depression/ anxiety, psychological  Stress, SES | 45 high stress neonate  45 low stress neonate | umbilical cord blood | Dukal et al. (2015) | No significant associations between several types of prenatal stress and infant SLC6A4 methylation patterns across four CpG sites. Females display higher DANm.  sex-specific analysis | plate effects | × | female vs.male:  p< 0.001  Prenatal stress;  For CpG1~4:  0.000~0.004  Low power | [26401310](https://www.ncbi.nlm.nih.gov/pubmed/26401310" \t "https://www.geenmedical.com/_blank) |
| OXTR  (CpG island) | Prenatal psychological stress | 743 children | umbilical cord blood | Rijlaarsdam et al (2017) | Prenatal stress did not associate with the methylation of OXTR of offspring. | child sex, age, maternal smoking, array number and position, cell type | × | p = 0.940  large power | 27520745\* |
| OXTR  (CpG island) | parent’s psychopathology, criminal  involvement etc | 84 youth with conduct problems  (longitudinal) | cord blood (birth)  peripheral blood (age 7, 9) | Cecil et al. (2014) | Prenatal maternal risks were associated with ↑ infant DNAm within a CpG island of OXTR, which impact transcription.  Impact of genetic variation on DNAm | Sex, previous and subsequent measure of environment exposure and DNAm of OXT | **×** | r=0.40 for INT-  r=0.32 for INT+  large power | [25199917](https://www.ncbi.nlm.nih.gov/pubmed/25199917" \t "https://www.geenmedical.com/_blank)\* |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| IGF2  GNASXL | prenatal maternal stress | 80 pair of mother-offspring | umbilical cord blood | Vangeel  et al (2015) | DNAm of IGF2 CpG5, CpG33 ↓ GNASXL CpGs ↑for newbabies whose mother suffer prenatal anxiety/ depression | / | √ | IGF2:P <0.0001  GNASXL:P=0.001  IGF2AS:P=0.0003 | 26333472 |
| FKBP5  (intron 7) | Holocaust Exposure  During prenatal | 32 Holocaust survivors and their 22 adult offspring  8 control parent  and 9 offspring | whole blood | Yehuda  et al (2015) | DNAm at bin 3/site 6 of FKBP5 was ↑ among holocaust survivors. Holocaust offspring, DNAm of FKBP5 was lower. Offspring DNAm at bin 2 associated with childhood physical/sexual abuse. | offspring’s PTSD symptom,  children trauma | / | Survivors:  p =0 .046  offspring:  p =0 .034 | 26410355 |
| genes in NF-κB pathway | Prenatal maternal stress | 34 children exposure to ice strom during utero (13.5 yrs) | whole blood T cell | Cao LL et al.(2016) | 6 NF-κB signaling genes (PIK3CD, PIK3R2, NFKBIA, TRAF5, TNFRSF1B, and LTBR) negative mediated the f objective PNMS on IFN-γ secretion. | objective PNMS, DNAm | √ | Not provided | 27182285 |
| DAT,MAOA BDNF  SLC6A4  (global DNAm) | Perceived Stress Scale (PSS) | 18 mothers, 13 fathers and their infants  longitudinally | buccal  cell | Pellicano  Et al(2020) | newborns’ 5-mC was negatively associated with maternal psychopathological symptoms at 48 hr after childbirth. | EPDS | × | p=.026; η2 = 0.27 | 33350469 |
| BDNF  67 CpG | Prenatal war exposure | 24 mothers and newborns  (Democratic Republic of Congo) | umbilical cord blood, placental  maternal venous blood. | Kertes et al.  (2017) | War trauma predicted DNAm at 16 sites of BDNF. Chronic stress predicted methylation at six sites, explaining 13–26% of variance. Associations of maternal stress and BDNF methylation showed high tissue specificity | Infant sex | √ | Regression  coefficient:  2.08~–3.13 | 28680507 |
| CRH, CRHBP, NR3C1, FKBP5 | chronic stress and war exposure | 24 mother-newborn dyads | cord blood, placenta and  maternal blood | Kertes et al. (2016) | Chronic stress or war stress associated with both unique and overlap DNAm changes. Methylation of FKBP5 in placenta and DNAm of CRH and NR3C in cord blood significantly increased. | infant sex | √ | chronic stress:  CRH & NR3C1  R2:16%–25%  War trauma:  4genes:13%–35% | [26822443](https://www.ncbi.nlm.nih.gov/pubmed/26822443" \t "https://www.geenmedical.com/_blank) |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| 11β-HSD2 | SES during pregnancy | 444 healthy term newborn infants | Placenta | Appleton  et al. (2013) | DNAm of 11β-HSD2 ↓8.8% decrease for infants suffered prenatal socioeconomic adversity (especially for male). | maternal age, BMI race, infant sex and birth weight | √ | P<0.0.05 | [24040322](https://www.ncbi.nlm.nih.gov/pubmed/24040322" \t "https://www.geenmedical.com/_blank) |
| LINE-1 | Maternal SES | 241 maternal-infant pair | cord blood | Coker et al.  (2018) | The lowest SES was associated with higher cord blood LINE-1 methylation | maternal age at delivery, number of years living in USA | × | adjusted β = 0.78  Large power | 29760810 |
| INSIGF  IGF2 DMR | prenatal SES | 120 children at 17 months | white blood cell | Obermann  et al. (2012) | Prenatal low education was associated with INSIGF methylation increase | intake of the folic acid  gestational age | × | 11.6%;  P= 0.021 | 25102259 |
| IGF2/H19,DLK1/MEG3NNAT, PLAGL1 | Prenatal SES | 619 pregnant mother-infants pairs | umbilical cord blood leucocyte | King et al (2014) | Unadjusted race/ethnic differences only were evident for DMRs regulating MEG3 and IGF2; race/ethnic differences persisted in IGF2/H19 and NNAT after accounting for income and education. | income and education | × |  | 25678712 |

Note: \* refers to the studies with power>60%.

Suppl. Table1.2 Overview of candidate genes studies associated with stress during postnatal development

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1  (exon 1F)  Mean/loci specific (27) | Child maltreatment  (self-reported, SCID) | 260 preschoolers  (Longitudinal) | saliva | Parent et al. (2017) | methylation of NR3C1exons 1D and 1F ↑ during the early period for maltreated children, and gradually ↓ among follow-up 6 month, and which lower than control group. | age, gender follow days | √ | NR3C1 mean 1F: β=0.07  1F 27-29: β=0.11  Large power | 29162170✱ |
| NR3C1  (exon 1F)  3 loci | Child maltreatment | 534 children  (53.4% abused） | saliva | Cicchetti et al. (2017) | More maltreatment associates with higher methylation of NR3C1 | age, gender, ethnic, genotype | × | Over methylation scores：*F*=5.58  Large power | 29162187✱ |
| NR3C1  (exon 1F,  1D, 1H) | Child maltreat ment; early adversity | 184 children  (74 have moderate -severe trauma) | saliva | Tyrka et al. (2015) | The methylation at exons 1D and 1F in the promoter of NR3C1 ↑ for those suffered children adversity | gender | × | adversity:  CpG1:r=-0 .23  Child maltreatment  CpG3: r=0 .23  Large power | 25997773✱ |
| NR3C1  (exon 1F) | Child abuse | 295 black women | PBMC | Shields et al (2016) | Women reporting childhood abuse victimization exhibited ↑ mean NR3C1 and a CpG site methylation levels | age parent’s education level | / | β= 1.02  Large power | 27620456✱ |
| NR3C1  (exon 1F)  39 loci | Child abuse  TSST | 98 abused adults  102 healthy control | PBMC | Alexander et al. (2018) | NO association between NR3C1methylation with child abuse. Methylation of NR3C1 CpG12 mediated child and cortisol secreation. Individuals with high DNAm showed 62% higher cortisol following TSS. | age, sex, gender, smoking status, BMI, baseline cortisol, use of oral contraceptives | √ | CpG12 : r=-0.05  F: 1.9~0.3  (large power) | 29433075✱ |
| NR3C1  (exon 1F) | Child maltreatment | 281 BPD patients (239 female, 29.4 years) | PBMC | Martin-Blanco et al. (2014) | The more child trauma experience, the ↑ methylation level of NR3C1 promoter 1F for BPD patients | / | / | PA:β=0.06 p=0.009  EN: 0.04 P=0.08  large power | 25048180✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1  (8 loci including exon 1F) | Childhood maltreatment | 101 BPD with severe maltreat,  99 MDD with low maltreatment | peripheral blood | Perroud et al.  (2011) | maltreatment associated with ↑ methylation NR3C1, with the increasing of SA, the methylation of NR3C1 increased significantly. | Gender, past/current alcohol/substance use, past/current PTSD, suicide history, etc | × | Maltreatment vs non-maltreatment:  0.138 vs.0.103  Large power | [22832351](https://www.ncbi.nlm.nih.gov/pubmed/22832351" \t "https://www.geenmedical.com/_blank)✱ |
| 6.5 Mb around NR3C1 intron | Child abuse | 12 male suicide (severe child abuse) 12 control | hippocampus | Suderman  et al. (2012) | For maltreated suicide completers: methylation↓ at 2 DMRs upstream NR3C1,methylation↑at 4 DMRs introns 1, 2 and one DMR downstream of NR3C1 compared with control. | / | / | No data provided | [23045659](https://www.ncbi.nlm.nih.gov/pubmed/23045659" \t "https://www.geenmedical.com/_blank) **Δ** |
| NR3C1  1B, 1C,1H  (different loci） | Childhood Abuse | 12 abused suicides  12 no abuse control | hippocampus | Labonte et al. (2012) | No differences in average methylation across groups, child abuse associated with methylation at GR1B and 1C promoter. SA associated with hypomethylation of CpG13, CpG3, CpG7, CpG10 and hypermethylation of CpG8 (GR1C). | age, pH, PMI, psychiatric medication status | √ | GR1B: p<0.0001  GR 1C: CpG8 p<0.0001 | [22444201](https://www.ncbi.nlm.nih.gov/pubmed/22444201" \t "https://www.geenmedical.com/_blank)**Δ** |
| NR3C1  (exon 1F) | Emotional abuse | 33 MDD  34 healthy control | whole blood | Farrell et al. (2018) | Increased emotional abuse associated ↑ methylaion of NR3C1 exon 1F CG38 among depression patients | Smoking, education years | / | CG37, r=-.53  CG38, r=-.43  Enough power | 29793048✱ |
| NR3C1  (7 loci around exon 1F) | Childhood  sexual abuse and physical trauma | 30 female  with mod-severe child trauma vs. 46 control , 19 HC | blood | Vangeel  et al. (2015) | No significant difference in NR3C1-1F mean methylation between traumatized and nontraumatized CFS patients. | / | √ | Not provided effect size | [26230484](https://www.ncbi.nlm.nih.gov/pubmed/26230484" \t "https://www.geenmedical.com/_blank) |
| NR3C1  (13 CpG in promoter) | Child maltreatment | 152 adult  (94 female) (Longitudinal) | PBMC | Bustamante  et al (2016) | Child maltreatment associated with ↑ methylation of NR3C1 CpG1–4 | age, gender, ethnity，blood number, anti  depression medication | √ | β=0.038  Medium power (66%) | 27475889 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1  (exon 1F)  12,13,30,31,32 | Childhood maltreatment | 12 abused suicide victims,12 control suicide, 12 control | hippocampus | McGowan  et al.(2009) | Hyper percentage of methylated clone of NR3C1 among suicide victims with child maltreatment compared to control. No difference between suicide victims with low abuse and control | mood disorders, substance abuse disorders | / | *F* = 3.47  P<0.05  Large power | [19234457](https://www.ncbi.nlm.nih.gov/pubmed/19234457" \t "https://www.geenmedical.com/_blank)✱ |
| NR3C1  (exon 1F)  52 CpGs | Childhood trauma | 241 individuals (SCZ, BP, siblings) | whole blood  Saliva | Sch¨ur et al. (2018) | GR-1F methylation was not associated with childhood trauma | age, sex, cohort, group  status | √ | low power | 30036796 |
| NR3C1  exon -1F  (10 CpG) | Childhood trauma | 80 female CFS  (chronic fatigue syndrome) patients, 91 female controls | peripheral blood | Vangeel,et al.(2018) | NR3C1-1F DNA hypomethylation at several CpG sites in CFS patients as compared to controls  Emotional abuse was correlated with DNAm at CpG\_3 and CpG\_47. | / | √ | CpG3:  Rho=0.26  CpG47: Rho=−0.239. Large power | 29275786✱ |
| FKBP5  (in intron 7) | Child abuse & other stressors | 231 preschooler (123 with moderate -severe trauma) | saliva | Parade et al. (2017) | Child maltreat associated with ↓ methylation of FKBP5 at baseline, but did not predict change in DNAm at CpG 1 or CpG 2 of FKBP5 over time. | genetic  ancestry, length of time | / | CpG1:β= -1.09  CpG2:β= -1.24  Large power | [29162173](https://www.ncbi.nlm.nih.gov/pubmed/29162173" \t "https://www.geenmedical.com/_blank)✱ |
| FKBP5  (intron 7)  NR3C1  (exon 1D/H) | Child maltreat and stress | 174 children  (69 severe maltreatment) | saliva | Tyrka et al (2015) | Two CpG sites of FKBP5 intron 7 is ↓among abuse children; Stress lead to methylation of FKBP5↓  consider the effect of FKBP5 genotype | age, gender, ehtnity | × | CpG1,t=3.16, CpG2, t=2.29  Large power | 26535949✱ |
| FKBP5  (intron 7) | Child trauma | 30 AA with child trauma  46 control | Peripheral blood | Klenger  et al.(2013) | Early life stress cause ↓ DNAm of GRE for A carriers of FKBP. An interactive effect between genotype and early stress on DANm level of FKBP5.  consider the effect of FKBP5 genotype | age, gender | √ | Early life Stress:  F= 8.2, P=0.006  Interactive effect:  F=31.01  large power | 23201972✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| FKBP5  (intron 7) | Emotional abuse | 33 MDD  34 healthy control | whole blood | Farrell et al. (2018) | No association between emotional abuse and FKBP5 methylation level. | smoking, education years | / | data not provided | 29793048 |
| FKBP5  (TSST, intron7, intron 2) | Childhood maltreatment | 112 adults | whole blood | Bustamante et al. (2017) | Childhood maltreatment did not significantly associate with methylation in any of the four loci of FKBP5. DNA methylation does not mediate childhood maltreatment-depression association. | age, sex, self-reported race, PBMC, anti- depressant medication | √ | data not provided | [28961425](https://www.ncbi.nlm.nih.gov/pubmed/28961425" \t "https://www.geenmedical.com/_blank) |
| FKBP5  (intron 7) | Child maltreatment | 190 subjects (87 MDD,61BD, 42HC) | whole blood | Saitoa et al. (2020) | Emotional abuse/neglect related to lower mean DNAm of FKBP5 intron 7 interacting with rs1360780 in the BD patients. No significant results in MDD and HC. | age and sex | × | ρ=−0.25  Large power | 32553385✱ |
| FKBP5  4CpG | Child maltreatment | 85 patients with psychotic disorder  56 HC | peripheral blood leukocytes | Misiak et al. (2020) | Sexual abuse associated with low FKBP5 CpG4 site methylation level. | ACEs. BMI, age, sex and cortisol levels, smoking | × | F= 5.994, p = 0.003  Large power | 33255215✱ |
| FKBP5  (intron 7, 5 CpG sites | Childhood  maltreatment | 3965 subjects from SHIP | whole blood | Klinger-Konig,et al.(2019) | Reduced methylation in TT allele carriers of rs1360780; childhood maltreatment did not associate with methylation in 5 sites of FKBP5.  consider the effect of FKBP5 genotype | age, gender, cohort  smoking, waist circumference, blood cell counts | √ | Not provided | [30700816](https://www.ncbi.nlm.nih.gov/pubmed/30700816" \t "https://www.geenmedical.com/_blank) |
| FKBP5  (intron 7)  Average DNAm for CpG 1, 2, 3) | Trauma exposure + TSST | 200 adults | whole blood | Alexander  et al. (2020) | Child trauma doesn’t associate with methylation change of FKBP5 intron 7; the latter doesn’t associate with acute /chronic cortisol concentration  consider the effect of FKBP5 genotype | age, gender, education years, BMI, smoking | √ | child trauma；  F=0.071 (average)  Large power: 82% | 32488091✱ |
| SLC6A4  (promoter) | Child sexual abuse | 26 abused female  132 control female  (Iowa Adoption Studies) | lymphoblast | Vijayendran,et al. (2012) | SA influenced higher methylation of cg22584138 and cg05016953. Methylation effects on transcription may vary as a function of gene motif and splice variant. | genotype, ethnicity | × | not provided | 22707942 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| SLC6A4  (Upstream of promoter) | Childhood trauma and physical abuse | 33 MDD (23 F)  36 controls (21 F) | hippocampus | Booij et al.  (2015) | Childhood trauma (physical abuse) were associated with ↑ methylation of SLC6A4 CpGs 5-15(LL carriers), linked to smaller hippocampal volume. | age, gender, MDD dignostic, hippocamps volume | × | Child trauma: β=0.27, p=0.029  PA: r=0.33,  Large power | [25781010](https://www.ncbi.nlm.nih.gov/pubmed/25781010" \t "https://www.geenmedical.com/_blank)✱ |
| SLC6A4  (promoter) | Child sexual abuse | 155 women from Iowa Adoption Studies) (41.1 yrs) | lymphoblast cell lines | Beach et al. (2013) | child sexual abuse associated with SLC6A4 promoter methylation. Sexual abuse and parental psychopathology interacted to predict SLC6A4 methylation levels. | substance use | / | Sexual abuse:  β= 0.311, p < .001  Large power | [23421829](https://www.ncbi.nlm.nih.gov/pubmed/23421829" \t "https://www.geenmedical.com/_blank)✱ |
| SLC6A4  (7 loci around promoter) | Physical abuse sexual abuse, finance hardship parental loss | 108 MDD  (from birth to 16 yrs), Korea  (Longitudinal) | peripheral blood | Kang et al. (2013) | PA and SA both associated with↑ methylation of SLC6A4 after multiple comparisons (parental loss: higher CpG2, other adversities with higher methylation of CpG7). SEP: SLC6A4: no association | **/** | √ | Large power  From 87.3%~99% | 23333376✱ |
| SLC6A4  (promoter)  71 CpG | Child sexual abuse | 155 female from Iowa Adoptee Study | lymphoblast cell lines | Beach SRH et al. (2011) | Significant positive effect of childhood sex abuse on overall methylation of the 5HTT promoter region | **/** | × | β= 0.856  Large power | 20947778✱ |
| BDNF  (promoter) | Child abuse | 64 BN women vs.  32 control women | blood  lymphocyte | Thaler et al. (2014) | Bulimia nervosa patients exposed to child abuse and/or coupled with BPD had higher DNAm at specific CpG sites of BDNF compared with BN without child abuse experience. | BN vs. noneating disorder  BN with PA vs non-PA | × | Sexual abuse:  ERR= 1.55  Large power | [24801751](https://www.ncbi.nlm.nih.gov/pubmed/24801751" \t "https://www.geenmedical.com/_blank)✱ |
| BDNF  (promoter) | Childhood trauma (PA, SA, EA, trauma) | 115 BPD vs.  52 controls | peripheral blood leukocytes | Perroud et al. (2013) | Childhood abuse severity predicted higher levels of BDNF methylation among BPD patients | age, gender | √ | Β= 0.61 (exon IV )  Β= 0.66 ( exon I)  Large power | [23422958](https://www.ncbi.nlm.nih.gov/pubmed/23422958" \t "https://www.geenmedical.com/_blank)✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| BDNF  (Promoter)  NR3C1(9 site)  SLC6A4,  MAOA | Childhood Trauma | 119 MZ twin pairs (84 male pairs, 55 yrs, 35 female pairs 36 yrs) | peripheral blood, leukocytes | Peng et al. (2018) | Child maltreatment associated with ↑ methylation of two CpG sites at BDNF, but it did not survive multiple correction. No any association between childhood maltreatment and MAOA methylation. | twin age, family income, pack-year, physical activity, alcohol consume, BMI, history of PTSD | √ | Large power | [29781947](https://www.ncbi.nlm.nih.gov/pubmed/29781947" \t "https://www.geenmedical.com/_blank)✱ |
| MAOA | Physical abuse  sexual abuse | 114 Swedish women | saliva | Checknita et al. (2018) | Sexual abuse associated with hypermethylation of MAOA exon I region in female samples | age, Lifetime diagnoses, current diagnoses. | √ | F= 12.693  P< 0.001 large power | [29600412](https://www.ncbi.nlm.nih.gov/pubmed/29600412" \t "https://www.geenmedical.com/_blank)✱ |
| MAOA  (first exon intron)16CpGs | Sexual abuse | 252 women and 157 men (14-73 yrs) | saliva | Checknita D, et al.(2021) | Methylation levels were higher among women who  experienced sexual abuse than women who did not.  Stratified sex analysis | lifetime diagnoses of substance dependence | × | p=0.017  Low power | 34424394 |
| OXTR  (promoter, intron,enhancer) | Child maltreatment | 44 abused children  41 control children | saliva | Fujisawa  et al. (2019) | The methylation of OXTR CpG 5,6↑ among abused children | age, gender, IQ, | √ | β= 0.65  Large power | 31071720✱ |
| OXTR  (18CpG around exton 3) | Child maltreatment | 393 African American  (mean ages: 41) | whole blood | Smearman  et al (2016) | Methylation of 4 CpGs located in OXTR exton 3 ↑ after exposing to children maltreatment，but none after multiple correction. OXTR genotypes | age, gender, cell types, batch effect | √ | 0.011 <p< 0.017  after multiple testing: p>0.05 | 26822448 |
| OXTR  Intron 1  14 CpG | Child maltreatment  socioeconomic | 309 African American  (Longitudinal) | saliva | Kogan et al. (2019) | Childhood adversity was not associated with OXTR methylation. Child socioeconomic instability predicted elevated methylation. | Cellular heterogeneity  age, educational attainment, cohabitation  smoking frequency | × | SES with DNAm r=0.16  Large power | 31318641✱ |
| OXTR  (promoter region) | Childhood trauma | 358 young African  American men  (Longitudinal) | saliva | Kogan et al. (2018) | From late adolescent into early adulthood  (19 yrs at baseline, 20.5, 22 years separately)  Significant indirect effect of childhood trauma on OXTR methylation via prosocial ties. | educational level  age, economic distress | / | B=0.04  Large power | [30308385](https://www.ncbi.nlm.nih.gov/pubmed/30308385" \t "https://www.geenmedical.com/_blank)✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| 1. HTR3A   (8CpGs) | Child maltreatment | 346 bipolar, BPD, ADHD | blood | Perroud N, et al. (2016) | CC carriers had higher methylation status at one CpG located 1 bp upstream of 5-HTR3A.  Effect of genetic background | age, gender, category of diagnosis | √ | CpG3 II: b=0.18, CpG2III: b = 0.19  CpG5 III: b=−0.19 | 26350166 |
| DRD2 | child abuse | 52 women with a BSD | blood | Groleau et al. (2014) | childhood sexual abuse associated with marginally significant DRD2 | **/** | × | F =2.687; p= 0.075 | 24157248 |
| ESR | Child maltreatment | 103 healthy female  (40~73years) | PBMC | Fiacco et al. (2019) | No association between child maltreatment and DNAm of NR3C1promoter, EA and more adversity lead to ↑ methylation of ESRαshore | age, BMI, soci-economic, smoking status | × | ESR: p=0.001. | 31708823 |
| rRNA | Early childhood neglect/abuse | 18 male Suicide  12 male control | hippocampus | McGowan  et al. (2008) | rRNA was significantly hypermethylated throughout the promoter and 5' regulatory region in the brain of suicide subjects suffer child neglect/abuse | **/** | √ | p<0.0001 | [18461137](https://www.ncbi.nlm.nih.gov/pubmed/18461137" \t "https://www.geenmedical.com/_blank) |
| IL-6 promoter | Childhood trauma+exposure to violence | 34 AAM (African American men, 18-25 yrs) | blood | Janusek et al. (2016) | Increased exposure to childhood trauma was related to reduced methylation of IL6 promoter and greater TSST induced IL-6 levels | paternal education, indirect violence,  negative affection | / | b = 0.029843  p = 0.013 | 27765646 |
| NR3C1  (exon 1F) | Early life stress | 46 adolescents  (mean age 15years) | PBMC | Radtke  et al. (2015) | The methylation of NR3C1exon1F ↑ for adolescents suffered children maltreatment | / | √ | r:0.30~0.5  Medium power | 26080088 |
| NR3C1  (exon 1F) | Early life stress | 56 children (11~14 years) | whole blood | Romens  et al. (2015) | Children exposed to physical maltreatment had ↑ methylation within exon 1F of NR3C1 promoter region  compared to non-maltreated children, which varied depended on CpG site | age, gender, ethnic soci economic | × | CpG site 3：d = 0.79  CpG site 6：d = 0.96  CpG site 7：d = 0.96  Large power | 25056599✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1 (exon 1D/1F/1H) | Life adversity:  (Stress+child maltreatment+ trauma event) | 171 preschoolers  with early adversity | saliva | Parade et al. (2016) | Early composite adversity associated with hypermethylation of NR3C1 1st exon, which mediated effects of early adversity on internalizing behavior problems. | age, sex, externalizing/  internalizing behaviors | √ | 1F: r=0.16,  p =0 .043  large power | [26822445](https://www.ncbi.nlm.nih.gov/pubmed/26822445" \t "https://www.geenmedical.com/_blank)✱ |
| NR3C1  (exon 1F) | Psychological stress | 1149 adolescents  (13~14years） | saliva | Efstathopoulos et al. (2019) | the methylation of NR3C11F ↑ significantly for adolescents been bullied and lacking of friends | smoking, alcohol use | x | Being bullied: OR=1.89,  Loss friend：OR=2.30  large power | 29921868✱ |
| NR3C1  (exon 1D) | Stressful life events and trauma | 468 adolescents  (mean age 16 years) | peripheral blood | van derKnaap  et al.(2014) | After stressful life events or traumatic experiences, NR3C1 exon 1D methylation↑. No change with prenatal stress exposure. | age, gender smoking | √ | P<0.01~0.001 | [24713862](https://www.ncbi.nlm.nih.gov/pubmed/24713862" \t "https://www.geenmedical.com/_blank)**Δ** |
| NR3C1  (exon 1F) | Genocide survivors  (war trauma) | 69 females,  83 males  (30–41 years) | saliva | Vukojevic V  et al (2014) | Increased DNA methylation in males  Sex-stratified analysis | PTSD symptom duster score | √ | ρ=-0.355,  Pcor= 0.008  large power | [25080589](https://www.ncbi.nlm.nih.gov/pubmed/25080589" \t "https://www.geenmedical.com/_blank)✱ |
| NR3C1  (exon 1F)  MAOA | Child adversity+  +Childhood SEP | 392 depression  1276 controls, Sweden  (F: 993, M: 675) | saliva | Melas et al (2013) | Early parental death associated with hypermethylation of NR3C1 (CpGs 10.11 and 35);  SEP: NR3C1: No association,  MAOA: No association | Age, smoking, MAOA u-VNTR genotype | × | Δβ for CpG35: 5.4%  Δβ for CpG:10: 8%  large power | [23449091](https://www.ncbi.nlm.nih.gov/pubmed/23449091" \t "https://www.geenmedical.com/_blank)✱ |
| NR3C1  (promoter) | Childhood adversity | 340 healthy adult participants | blood leukocyte | Tyrka et al.  (2016) | Childhood adversity and a history of past or current psychiatric disorder associated with **↓** methylation of NR3C1 promoter across the region and specific loci. | Age, gender | x | correlation:  P=0.018,  power>80% | [27378548](https://www.ncbi.nlm.nih.gov/pubmed/27378548" \t "https://www.geenmedical.com/_blank)✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1  promoter | Childhood adversity | 99 healthy adults. | PBMC | Tyrka et al.  (2012) | parental loss, childhood maltreatment, parental care associated with ↑ methylation of NR3C1 | age gender, medication | √ | CpG 1: r = 2.23  Large power | 22295073✱ |
| NR3C1  BDNF, FKBP5 | Discrimination exposure | 147 Latina women  (longitudinal) | blood | Santos et al. (2018) | Discrimination was negatively associated with methylation at CpG sites within NR3C1 and BDNF, FKBP5 (only time1). | maternal age, marital status, education, household income, ethnicity, infant’ sex | √ | NR3C1:RR= 0.85  BDNF: RR=0.86  FKBP5: RR=0.85  Low power | 30144780 |
| FKBP5  (intron7/5/2,  promoter) | Child and adult life stress | 29 high stress  25 low stress children (Longitudinal) | saliva | Harms et al. (2017) | With the increase of early life stress, the methylation of FKBP (intron 5/intron2) ↑. Stress exposure during adult significantly correlated with methylation of intron 7.(-) | / | √ | intron5cg8: r=0.37  intron2cg1:r=0.36 meditation::p=0.08  Large power | 29162190✱ |
| FKBP5  (intron 7) | Childhood adversity | 56 MDD adults  50 controls | whole blood | Tozzi et al. (2018) | Childhood adversity predicted ↓methylation of rs1360780 for MDD patients carrying risk allele Genetic effect | sex,age, rs1360780  genotype | √ | F=4.95  Large power | [29182159](https://www.ncbi.nlm.nih.gov/pubmed/29182159" \t "https://www.geenmedical.com/_blank)✱ |
| FKBP5 SLC6A4  (promoter ) | Early life stress  (institution) | 136 children  72 control raised children. Romanian  (longitudinal) | buccal epithelial cells | Non et al. (2016) | More time spent in institutional care was associated with lower DNA methylation at specific CpG sites within both genes. | Age of buccal swab  Collection, sex, ethnicity, pubertal status | √ | SLC6A4: r=-0.19  FKBP5: CpG1  r=-0.21  Large power | 27218411✱ |
| SLC6A4  promoter | Recent life stress/trauma | 133 healthy young adults | blood | Wankerl et al (2014) | No association between prenatal stress or early or recent life stress and DNA methylation. | oral contraceptives | √ | early life stress:  F=0.03,Recent stress: F=0.73, P=0.39.large power | [24937096](https://www.ncbi.nlm.nih.gov/pubmed/24937096" \t "https://www.geenmedical.com/_blank)✱ |
| SLC6A4  promoter  (12 sites) | Exposed to bullying | 28 bullied children  28 non-bullied monozygotic twins  (10 years ) | buccal | Ouellet-Morin et al. (2013) | Methylation of CpG 8 and overall average of SLC6A4 ↑ in bullied children compared to non-bullied twins, which significantly correlated with the blunted cortisol response to the stressful task. | Family warth, birth weight, IQ, intro/extroversion problem, methylation before being bullied | √ | Bullied: t = 2.49,  From 5~12 years:  p=0.006  large power | 23217646✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| SLC6A4  (intron I and exon I) | A wide range of traumatic events (abuse, loss of friend, any kind of serious injury | 77 trauma exposed/ no PTSD individuals  23 PTSD individuals | whole blood | Koenen et al., 2011 | traumatic events associated with ↑ methylaion of cg22584138of SLC6A4. Association between the number of traumatic events and PTSD symptoms was stronger at low methylation of SLC6A4.Genetic effect, sex difference | age, PBMC count, number of trauma events, methylation -values | **×** | Data not provided | [21608084](https://www.ncbi.nlm.nih.gov/pubmed/21608084" \t "https://www.geenmedical.com/_blank) |
| SLC6A4  (exon 1)  (differ loci) | Adversity during child and adolescents | 939 adolescents  (16.2 years) | whole  blood | van der Knaap et al (2015) | More life adversity associated with ↑ methylation of SLC6A4, independently of childhood exposure, especially for carriers of LL carriers. | perinatal adversities, childhood trauma, Stress during child and adolescents | **×** | r=0.011(SLE)  p=0.004 (adolescent SLE)  Large power | 25849128✱ |
| SLC6A4  (promoter) | Early adversity  (both prenatal and postnatal | 50 children of alcoholics (COA)  50HC India | saliva | Timothy et al. (2021) | SLC6A4 methylation was higher in COA, and correlated with early adversity. | / | √ | β =-0.366.  P<0.001  Large power | 31082414✱ |
| BDNF  (exons VI) | Maternal care during childhood | 47 high stress adults  42 low stress adults | blood | Unternaehrer et al. (2015) | low maternal care group associated with ↑DNA methylation of BDNF | age, sex, batch number | / | Likelihood-Ratio:  4.47 | [26061800](https://www.ncbi.nlm.nih.gov/pubmed/26061800" \t "https://www.geenmedical.com/_blank) |
| BDNF  (exon IV)  (4 CpG) | Exposure to child violence | 54 mothers with IPV-PTSD  Switzerland | saliva | Moser DA, et al. (2015) | Maternal exposure to domestic violence as a child was significantly correlated with the degree of methylation at the CpG3 site | / | √ | rs = .421, p = .002  Large power | 26649946 |
| OXTR  (covering exon 1~ exon III) | Maternal care during childhood | 47 high stress adults (36 women)   42 low stress adults (35 women) | blood | Unternaehrer et al. (2015) | CT associated with hypermethylation of one OXTR target sequence(1), but not the second OXTR target sequence(2).This results couldn’t be explained by different blood cell counts. | age, sex, batch number | × | Likelihood-Ratio: 4.33  Large power | [26061800](https://www.ncbi.nlm.nih.gov/pubmed/26061800" \t "https://www.geenmedical.com/_blank)✱ |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| OXT  promoter | sstress life event | 146 MDD  Germany | peripheral blood | Sanwald et al. (2019) | Stressful life events negatively associated with mean methylation status as well as with single CpG in the promoter of OXT. Significant sex differences in DNAm. | Sex, age, substance use, antidepressive BMI, medication | √ | b =0.0008, p=0.021  Low power | 31768943 |
| HPA axis genes | Harsh Parenting | 96 MZ twins  (multi ethnicity)  (Longitudinal) | buccal | Lewis et al. (2020) | harsh parenting significantly predicted methylation of several HPA axis genes, including NR3C1, AVPRB1, CRHR1, CRHR2, and MC2R | twin interdependence  Sex, array, cellular heterogeneity, SES | √ | NR3C1:β=0.295  AVPBR1:β=−0.224  POMC: β=−0.323 | 32472381 |
| MTHFR | Perceived Stress (PSS) | 78 healthy participants (mean age: 20.9 years) | PBMC | Jiménez et al. (2018) | A significant inverse correlation between MTHFR methylation levels and perceived stress, even after adjusted for covariant. | Age, gender, depression symptom | × | P=5.9×10−5 | 29595559 |
| OPRL1 | Psycho-social stress | 660 adolescents  (14 years) | whole blood | Ruggeri et al. (2018) | Methylation of OPRL1 intron 1 is ↓ under higher psycho-social stress and involved in drinking behavior | gender | √ | p=0.013 | 29197086 |
| TPH2 | Early life stress | 291 MDD patients and 100HC (China) | peripheral blood | Shen et. al (2020) | High child maltreatment predicted DNA hypomethylation at CpG-site TPH2-8-237 in males. | age and baseline HAMD score | √ | r: -0.213  FDR=0.038 | 32738671 |
| differ species | Early-life stress | 30 MDD, 28 cocaine use disorder, 32 HC | PBMCs | Catale et al. (2020) | A significant effect of the mental health diagnosis on global methylation levels was observed. No effect of either childhood abuse or neglect was detected | / | × | child abuse, b= 0.04. child neglect, b =0.017, P = 0.89 | 33344704 |
| COMT | lifetime stress | 84Healthy subjects (32 males） | PBMCs | Ursini, et al. (2011) | For Val/Val carriers of COMT greater stress are related to and lower methylation. | / | × | F(2,20)=4.1  p=0.03 | 21543598 |
| MORC1  promoter | Early life stress (ELS)  CTQ scores | 151adult cohort  (presence with depression and child maltreatment)  Germany | whole  blood | Thomas et al. (2019) | MORC1 DNAm in adult was not associated with child maltreatment, which were validated among two additional cohorts(N=299, N=310) separately. Association between DNAm with depressive symptoms was present in all cohorts. | Sex, age and smoking behavior, first two axes of PCs | √ | Not provided | 31683097 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| CYP2E1 | Exposed to severe adversity | 49 adolescents (15years) high stress vs. low stress | buccal | Kumsta et al. (2016) | One DMR in the promotor of the CYP2E1 was identified methylation↑ associated with deprivation and impaired social cognition. | gender | √ | p=2.98×10−5 | [27271856](https://www.ncbi.nlm.nih.gov/pubmed/27271856" \t "https://www.geenmedical.com/_blank) |
| DDR1  43 CpG | Psychological stress | 60 patients with psychosis, 40 HC  Spain | blood | Garcia-Ruiz et al.(2020) | leukocyte DDR1 hypermethylation in patients with psychosis is associated with psychological stress, | Antipsychotic, age  biperidene doses, coffee, alcohol consume | √ | r =-0.202, p=0.038 | 31920096 |
| KITLG | Childhood Adversity | 60 healthy adults  (39~ 60 yrs) German | CD14+ monocytes | Frach et al. (2020) | neither replicate the association between KITLG DNA methylation with childhood adversity. | Age and sex | / | β = −0.032,  p = 0.817 | 32203862 |
| GRIN2B 4CpG | Childhood adversity | 186 individuals  Swedish | saliva | Engdahl, et al. (2021) | childhood adversity is associated with increased methylation levels of GRIN2B in adulthood for three of CpGs (p = 0.007, 0.006 and 5 × 10− 14). | age, sex, smoking nor alcohol intake, level of education, occupational status, financial stability | × | CpG1: β=0.95  CpG3: β = 2.12 | 33038564 |
| HSD11B2 | Early childhood adversity | 100 children | saliva | Oni-Orisan  (2020) | Early childhood adversity were associated with greater DNA methylation of HSD11B2 at the CpG2 site. | gestational age at birth, self-reported use of tobacco/alcohol/marijuana | × | B=0.11, P < 0.01 | 32663835 |
| SLC6A4  (Promoter) | Childhood  cumulative SES | 388 African American (19 yrs, F: 213) | Blood | Beach et al. (2014) | SLC6A4: Women- 2 cg sites differentially methylated  Men- no association. Sex-stratified analysis | sex | √ | Effect size:0.011  Low power | [24192273](https://www.ncbi.nlm.nih.gov/pubmed/24192273" \t "https://www.geenmedical.com/_blank) |
| LINE-M1  Sat2-M1, Alu-M2 | Child SES  Adult SES | 89 Women (43yrs)  USA  (longitudinal) | blood white cell | Tehranifar  et al.(2013) | Low family income at birth associated with ↑Sat2 methylation, single parent family was associated with ↑Alu methylation. Lower adult education was associated with ↓Sat2 methylation. | race/ ethnicity, maternal age at pregnancy,  maternal smoking in pregnancy, birth order | / | Sat2: β= 19.7,  95% CI: 0.4-39.0  Alu-M2:β= 23.5, 95% CI: 2.6-44.4 | 23196856 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| HTR2A | CM+Child adversities +  Childhood SEP | 119 children with severe trauma  109 control child USA | saliva | Parade et al. (2017) | The methylation of 1420 loci↑ with the rise of stress for HTR2A“AA”carriers, but for GG carriers the methylation↓ | ethnicity age, HTR2A genotype | × | stress-methylation:  “AA”: r=0.21  “GG”: r =−0.28 | 29162169 |
| OXTR  (promoter & intron, enhancer) | Child adversity+SES + child trauma | 24 high ELA adults  22 low ELA control (27 years, 23 F)  Canada | PBMC | Gouin  et al.(2017) | No significant global difference (16 CpG) between high/low ELA groups. Methylation of CpG7 is ↑ among high stress group, none after multi-correction. OXTR promoter: CpG 5 associated with childhood stressor exposure in females. | / | √ | High/low ELA groups: p=0.46  Female：  Cohen’s d > 0.80 | 28785027 |
| SLC6A4 | Child adversities + child SEP | 182 Adolescent  USA | saliva | Swartz et al. (2017) | SLC6A4: Lower SES at wave one predicts greater increases of promoter methylation at Wave 2 | age, time between waves, gender, anxiety, risk factors | × | β=−0.24  Large power | [27217150](https://www.ncbi.nlm.nih.gov/pubmed/27217150" \t "https://www.geenmedical.com/_blank)✱ |
| NR3C1, LEP, ABAC1, INS-IGF2 HSD11B2, | Childhood  socioeconomic  position | 613 adult (F:63) Israel | whole Blood | Huang et al. (2015) | High SEP associated with:↑methylation of ABAC1, INS-IGF2, LEP, and↓methylation of NR3C1. Higher maternal education was associated with ↑HSD11B2 methylation | age, birthweight | × | β = 0.5 | [27651384](https://www.ncbi.nlm.nih.gov/pubmed/27651384" \t "https://www.geenmedical.com/_blank) |
| LINE-1  Alu: | Child  socioeconomic  position | 988 Adult( Female:  52 %), USA  Multi-race/ethnicity | blood  leukocytes | Subramanyam et al. (2013) | African-Americans had 0.27% lower Alu, 0.41% higher LINE-1 than whites. Hispanics had 0.20% lower Alu, 0.39% higher LINE-1 methylation than whites. | age, gender, race/ ethnicity, income, wealth, education | × | Alu: △β= 0.27%  LINE-1: △β=0.41% for AA. | [23320117](https://www.ncbi.nlm.nih.gov/pubmed/23320117" \t "https://www.geenmedical.com/_blank) |
| NR3C1,DRD4BDNF, 5-HTT, COMT, DAT1 | Child  adversities +  Childhood SEP | 109 Child  (Female: 60, M: 49)  USA | buccal | Essex et al. (2013) | NR3C1, DRD4, BDNF, 5 HTT, COMT, DAT1 (no associations for any of these) | / | √ | Rho: −0.39 to0 .26  Large power | 21883162✱ |
| BDNF  IV promoter | Childhood SEP | 33 Adolescent  (Australia) | buccal | Wrigglesworth et al.(2019) | Neighbourhood disadvantage negatively associated with BDNF methylation exon IV. Promoter. | Age and Sex | × | ß = 0.011  Low power | [30771753](https://www.ncbi.nlm.nih.gov/pubmed/30771753" \t "https://www.geenmedical.com/_blank) |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | **Covariate** | **Multiple testing** | **Effect size/Power** | **PMID** |
| NR3C1 | Childhood  adversities +  Childhood SEP | 468 Adolescent (Female: 50.4 %)  Netherlands | whole blood | van der Knaap  e al. (2014) | NR3C1: Hypermethylation exposure to SLE (age 0−15) at amplicon 1 and Hypomethylation- repeated  exposure to other traumatic youth experiences at  amplicon 3，but not exposure to perinatal stress. | age, daily smoking,  oral contraceptive,  medication, pubertal  status, acute infection | × | B=0.44,  B=−0.26 | [24713862](https://www.ncbi.nlm.nih.gov/pubmed/24713862" \t "https://www.geenmedical.com/_blank)\* |
| 18 genes related to stress/inflammation | Childhood  SEP (education) | 1231USA Adults  Multi-race/ethnity | blood  monocytes | Needham et al.  (2015) | AVP- increased methylation; FKBP5:increased DNAm  OXTR:increased DNAm ;CCL1:increased DNAm in promoter sites; CD1D:increased DNAm in promoter sites | age, sex, race/ ethnicity, enrichment scores for neutrophils, B cells, T cells and NK cells) | √ | AVP: q=0.17  FKBP5:q=0.13 OXTR: q=0.10  CCL1: q=0.07  CD1D: q=0.02 | 26295359 |
| 18 genes related to stress/inflammation | life-course SES | 857 individual from Italy prospective cohort study (EPIC) Italy | blood  leukocytes | Stringhini et al.  (2015) | NFATC1,IL1A, GPR132 and genes belonging to the MAPK family was less methylated, CXCL2 and PTGS2 more methylated in individuals with low vs high SES. | age, sex, disease status, smoking status, alcohol consumption, diet, physical activity, BMI | √ | household’s highest occupational △β=0.67,  father’s occupation: △β= 0.52  large power | 2588903✱ |

Note: \* refers to the studies with power>60% for evaluating the reproduicibility, ∆ means studies exclude d owing to some less-common loci examined in it.

Suppl. Table 1.3 Overview of candidate genes studies associated with chronic stress during adulthood

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| SCL6A4  promoter | shift-working | 24 high work stress nurses;  25 low work stress nurses | peripheral blood leucocytes | Alasaari  et al.(2012) | Nurses in the high stress environment had significantly lower promoter methylation levels at all five CpG of SLC6A4(p<0.01). Burnout and work-related stress were associated with an decrease SLC6A4 methylation. | | 5-HTT genotype | / | Cohen’s d: 1.2  p=7.10E–06(CpG5)  p=2.50E–05(CpG4)  p=0.000292(CpG3) | 23029256 |
| BDNF | Chronic Job-stress | 774 Japanese workers stratified into quartiles  (9% female) | saliva | Song et al.  (2014) | The methhylation of BDNF is slighlty ↑ among high stress  Workers(22 CpG sites:↑, 28 CpG sites:↓)，but no significant difference of methylation of BDNF between high stress and low stress workers. | | / | × | P=0.045  5.6% vs. 5.7%  Small power | [24801253](https://www.ncbi.nlm.nih.gov/pubmed/24801253" \t "https://www.geenmedical.com/_blank) |
| TH | Occupational Stress | 90 high vs. 90 low job stress workers | saliva leukocyte | Miyaki et al.  (2015) | Subjects with high stress associated with ↑ DNA overall methylation, and ↑ methylation level of 4 CpG TH promoter region | | / | × | Overall methylation：  p=2.48×10-6  Promoter:p=7.14×10-9 | ///. |
| 31 miR-  promoters | night shift | 10 shift workers  10 day workers | blood samples | Shi et al. (2013) | 31 miRNAs (especially miR-219) were differentially methylated in night shiftworkers | | folate intake,  age | × | Small power  ∆=9.3%~2.2% | 23813567 |
| BRCA1 BRCA2   (Promoter) | shift-working | 347 women rotating-shift work  363 women working days | blood leucocytes | Peplonska  et al. (2017) | Current night work and night work history were not associated with methylation status of the promoter sites within BRCA1 and BRCA2 genes | | age, folate intake, other lifestyle characteristics | × | OR=1.08  Small power | 28594926 |
| CLOCK, BMAL1, CRY1,  PER1, PER2 | shift working | 558 female nurses working night shift  (278 breast cancer cases, 280 controls) | saliva | Erdem et al. (2017) | Breast cancer cases, medium exposure to night work, associated with an increase in BMAL1 and PER1 methylation compared with day working cases. | | alcohol, familiar breast cancer, years since cancer and alcohol | × | BMAL1: p=0.003  PER1: p=0.035 | 28928877 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | | **Main results** | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| CLOCK  CRY2 | Shift-work | 117 female | peripheral blood | Zhu et al.  (2011) | The methylation of CLOCK promoter↓and CRY2 promoter ↑ for long-term shift-workers | | age, folate intake | √ | CLOCK:  adjp:0.0009  CRY2: adjp:0.0068 | [22080730](https://www.ncbi.nlm.nih.gov/pubmed/22080730" \t "https://www.geenmedical.com/_blank) |
| GCR, TNF-α, IFN-γ | Shift-work | 155 male workers | peripheral blood | Bollati et al (2010) | For shift-workers, with the rise of working years, the methylation of Alu and IFN-γ ↓(Overall methylation) | | age, BMI,  working years | / | Alu: p=0 .006  IFN-γ: p=0.007 | [20636218](https://www.ncbi.nlm.nih.gov/pubmed/20636218" \t "https://www.geenmedical.com/_blank) |
| MAOA | Shift Working | 3631 Oilfield Workers | peripheral blood | Jiang et al . (2019) | The methylation of CpG loci of MAOA is↓ among workers with higher stress | | / | / | p< 0.05 | 31878203 |
| tumor suppressor genes | Shift working | 46 nurses with night work  51 female with day work | blood | Carugno et al. (2019） | TP53, CDKN2A, BRCA1, BRCA2, ESR1, ESR2, Alu, TL  LINE-1. NS was associated with hypomethylation of ESR1, TP53, and BRCA1. NS-associated markers potentially involved incellular aging, genomic instability, and cancer development | | age, BMI, oral contraceptive use, smoking, marital status/age at marriage | × | ESR1:β=−1.85  TP53: β=−0.93  BRCA1: β=−1.14 | 31261650 |
| PER1,  PER2,  PER3, CRY1, CRY2, CLOCK, NPAS2, BMAL1 | Shift working | 347 women rotating-shift work  363 women working days | blood leucocytes | Reszka, et al.(2019) | Night shift associated with decreased PER2 promoter CpG methylation. A longer lifetime duration of shift work presented a lower status of PER1 methylation  BMAL1: hypomethylation. | | age, current smoking status, folate intake and blood collection time. | × | PER2:P<0.004  PER1:P=0.040  BMAL1:P=0.013 | 29144171 |
| **Gene (loci)** | **Stress type** | **Sample character** | **Tissue** | **Author (year)** | **Main results** | | **Covariate** | **Multiple testing** | **Effect size/power** | **PMID** |
| SCL6A4  promoter | Early stress & recent chronic stress | 105 healthy males  (18~77years) | whole blood | Duman et al.  (2015) | Increased methylation associated with ELS and chronic stress among SLC6A4“SS”,which correlated positively with SLC6A4 expression. | | age global methylation | × | ELS: r=0.45  chronic stress:  r=0.44. large power | 25995833 |
| SLC6A4  (16 loci Promoter) | Marital separation | 47 adults | whole blood | Sbarra et al. (2019) | less subjective separation-related psychological distress associated with greater DNAm of SLC6A4 | | age, SLC6A4 genotype  Separation time | × | b = −211.99 | 31053862 |
| NR3C1 | War trauma exposure | 92 soldiers  (longitudinal) | whole blood | Schür et al.  (2017) | War trauma lead to methylation changes of multi loci of GR-1, while only functional loci methylation associated with later psychopathology symptom | | age, BMI, cell types and number, education level | √ | Overall methylation:  p=0.003；function methylation: p= 0.002 | 28742078 |
| CACNAC1 | Perceived stress | 103 adult males | whole blood | Pennington et al. (2020) | Positive correlation between CpG5 methylation and perceived stress | | age | × | OR=0.1~0.2 for CpG1,CpG11 | 33169621 |
| OXTR  (promoter) | Adverse stress | 100 AA female | whole blood | Simons  et al. (2017) | Adverse stress correlated with 4 CpG (cg08535600, cg09353063, cg17285225, cg23391006) of OXTR. | | child trauma, age, cell types, EWAS | × | B=0.275. R=0.262  Large power | 27323309 |
| NR3C1 mean DNAm  FKBP5 | Perceived daily stress | 51 healthy adults | saliva buccal cell | [Sante](https://www.sciencedirect.com/science/article/abs/pii/S0306453017316438?dgcid=api_sd_search-api-endpoint" \l "!) et al. (2018) | Greater buccal cell- derived NR3C1-1 F methylation was associated with lower perceived daily life demands. | | Sex, tissue-type | × | b=-0.15  N=48, small power | 30059826 |
| 18 genes related to stress/inflammation | Adult SEP  (education) | 1231 Adults  (Non Hispanic white, African American, Hispanic) | blood  monocytes | Needham et al.  (2015) | Adult SES associated with: increased AVP DNAm in shore/shelf sites; increased CD1DDNAm in promoter, decreased in non-promoter sites. F8: decreased DNAm in shore/shelf sites. KLRG1: increased DNAm in non-promoter sites. SLC6A4: (-) | | age, sex, race, enrichment scores for neutrophils, B cells, T cells and NK cells | √ | AVP:q=0.007  CD1D: q=0.03 F8:q=0.0009  KLRG1:q=0.17  NLRP12:q=0.02 | 26295359 |