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DNA methylation in regulatory elements of the *FKBP5* and *NR3C1* gene in mother-child binomials with depression

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ABSTRACT

Background: The *FKBP5* and *NR3C1* genes play an important role in stress response, thus impacting mental health. Stress factor exposure in early life, such as maternal depression, may contribute to epigenetic modifications in stress response genes, increasing the susceptibility to different psychopathologies. The present study aimed to evaluate the DNA methylation profile in maternal-infant depression in regulatory regions of the *FKBP5* gene and the alternative promoter of the *NR3C1* gene.
Methods: We evaluated 60 mother-infant pairs. The levels of DNA methylation were analyzed by the MSRED-qPCR technique.
Results: We observed an increased DNA methylation profile in the *NR3C1* gene promoter in children with depression and children exposed to maternal depression ($p < 0.05$). In addition, we observed a correlation of DNA methylation between mothers and offspring exposed to maternal depression. This correlation shows a possible intergenerational effect of maternal MDD exposure on the offspring. For *FKBP5*, we found a decrease in DNA methylation at intron 7 in children exposed to maternal MDD during pregnancy and a correlation of DNA methylation between mothers and children exposed to maternal MDD ($p < 0.05$).
Limitations: Although the individuals of this study are a rare group, the sample size of the study was small, and we evaluated the DNA methylation of only one CpG site for each region.
Conclusion: These results indicate changes in DNA methylation levels in regulatory regions of *FKBP5* and *NR3C1* in the mother-child MDD context and represent a potential target of studies to understand the depression etiology and how it occurs between generations.

1. Introduction

Major depressive disorder (MDD) is among the most prevalent mental health problems in the world and is one of the main diseases that cause incapacity, by negatively impacting the quality of life. The latest studies report that MDD affects an average of 280 million people worldwide (World Health Organization, 2016). MDD is a complex and heterogeneous disorder. The genetic factors act as strong risk factors for depression development, with an estimated contribution of approximately 35 % (Flint and Kendler, 2014; Otte et al., 2016; Sullivan et al., 2000). Although genetic predisposition influences biochemical and molecular processes in neurophysiology, it is not the only factor

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affecting mental health development (Cattaneo and Riva, 2015).

Furthermore, epigenetics respond to environmental factors, influencing the modulation of transcription of human genes through epigenetic marks. These actions lead to a set of dysfunctions in different systems associated with MDD, such as the serotonergic, dopaminergic, neurotrophic and oxytocin systems, as well as the hypothalamus pituitary adrenal axis (Crespi, 2020; Silva et al., 2021).

Along with the phenotypic and genetic contribution, environmental factors are strong components of the psychopathology process. Environmental factors such as the period of life and time of exposure to trauma/stress are determining factors in MDD (Thapar and Riglin, 2020). MDD can manifest itself differently among individuals throughout life (Kwong et al., 2019). The probability of incidence of psychiatric disorders' developing during the transition from childhood and adolescence to adulthood is greater than in other periods of life. About 75 % of psychiatric disorders are triggered until early adulthood (Kessler et al., 2005; Thapar and Riglin, 2020).

The first stressors experienced in early life may influence biological changes and individuals' development, behavior, and health (Aristizabal et al., 2020). Recurrent exposure to stress episodes, such as maltreatment and neglect during childhood, increases the risk of mental health-related disorders (Erickson et al., 2019; Gilbert et al., 2009; Lane and Dubowitz, 2021; LeMoult et al., 2020). Moreover, individuals with a history of early life stress are twice as likely to develop chronic depression and more frequent and prolonged depressive episodes (Silva et al., 2021).

Persistent stress events implicate long-term epigenetic modifications and may be transmitted with subsequent generations. Epigenetic changes induced by stress events, such as DNA methylation, can be passed down to succeeding generations and contribute to the etiology of brain disorders (Rachdaoui and Sarkar, 2014).

Children exposed to trauma as maternal depression are more susceptible to developing a psychiatric disorder (Goodman et al., 2011). Depression perinatal or maternal depressive symptoms lead to behavioral, emotional, social, and cognitive effects on the offspring. That may trigger changes in the DNA methylation pattern in essential genes related to neurobehavioral and psychiatric disorders (Sawyer et al., 2019). For example, early-life exposure to stressors is associated with

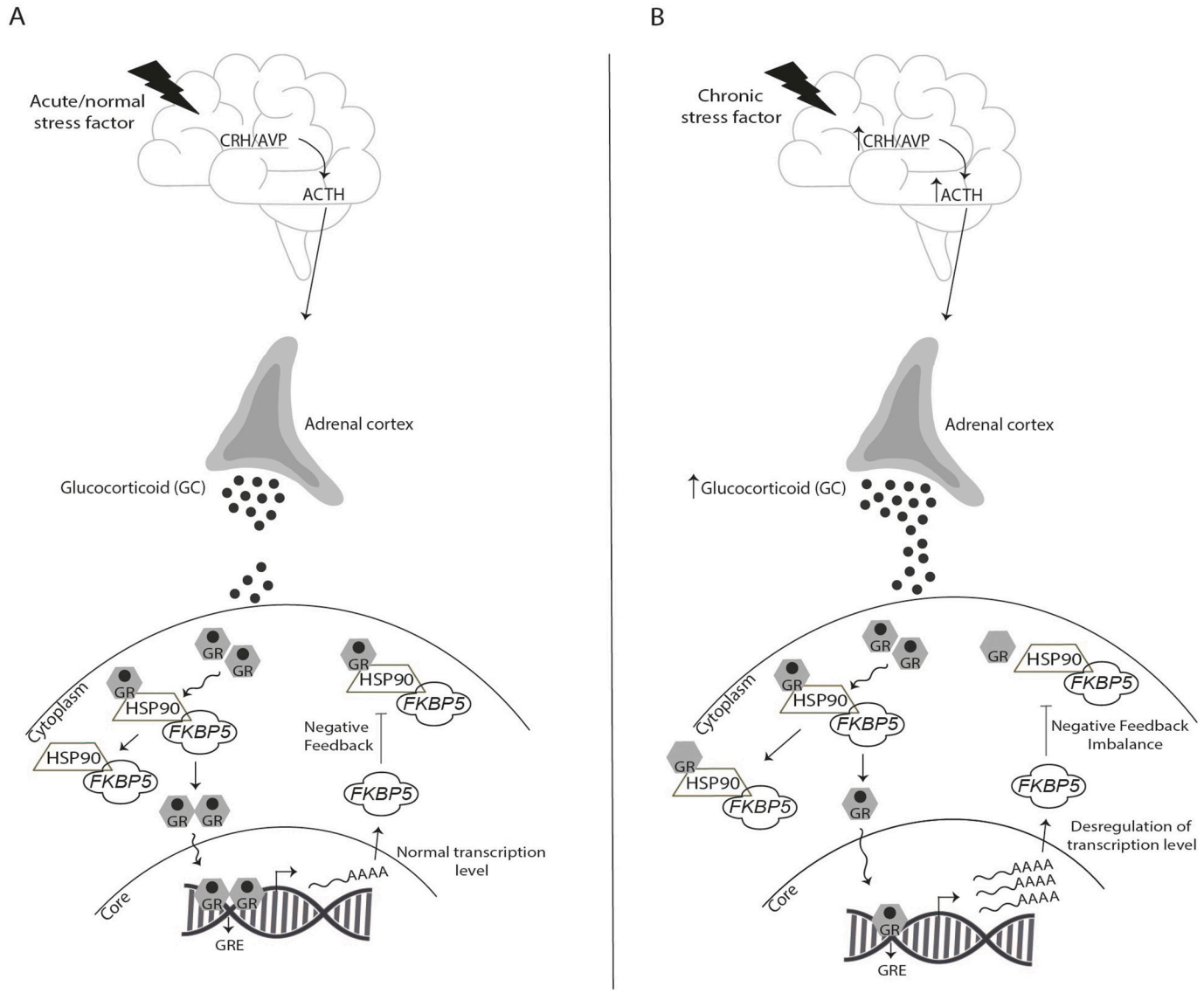

Fig. 1. HPA axis-mediated stress response system. (A) GC signaling under normal conditions. The stress stimulus considered normal or acute leads to normal HPA axis activity, resulting in a good response to GCs. (B) GC signaling under chronic stress conditions. Chronic or continuous stress stimulation leads to dysregulation of HPA axis activity. CRH — corticotrophin-releasing hormone; AVP — arginine vasopressin; ACTH — adrenocorticotropin hormone; GR — glucocorticoid receptor; CG — glucocorticoid; Hsp90 — heat shock protein 90; FKBP5 — FKBP51 binding protein; GRE — glucocorticoid response element.

changes in the expression of genes involved in the Hypothalamic–pituitary–adrenal axis (HPA axis), such as *FKBP5*, *NR3C1*, and *CRHR1*, inducing neurological and behavioral changes in offspring (Conradt et al., 2013; King et al., 2017; Weaver et al., 2004).

Exposure to early life adversity involves not only the diagnosis of mood disorders but also the family context. Family adversities experienced in childhood and maternal care for example have a direct influence on the gene expression, through changes in the pattern of DNA methylation, leading to changes in the gene expression involved in the stress response system and may be associated with the emergence of psychopathologies throughout life (Bierer et al., 2020; McGowan et al., 2009; Oberlander et al., 2008; Weaver et al., 2006).

The HPA axis has a central role between stress response and depression development (Fig. 1). MDD patients show dysfunction of the HPA axis, characterized by failures of negative feedback, associated with receptor glucocorticoid (GR) resistance (Troubat et al., 2021).

The genes encoding the FK506 binding protein 5 (*FKBP5*) and the glucocorticoid receptor (*NR3C1*) have been implicated in the regulation of stress reactivity. The *FKBP5* gene is an important regulator of GR for GC binding (Fig. 2A). This gene is responsible for encoding the FKBP51 binding protein, located on chromosome 6p21.31, and has 4 isoforms due to alternative splicing (Binder, 2009). The FKBP51 protein is a co-chaperone, belonging to the family of immunophilin proteins, which affect the immunoregulation processes and cell processes involving protein folding and traffic. In conjunction with the Hsp90, FKBP52 and p23 proteins, the FKBP51 forming the GR complex acts on GC signaling (Criado-Marrero et al., 2018).

The *NR3C1* gene (nuclear receptor of subfamily 3, group C, member 1) encodes the GR, a member of a large family of nuclear hormone receptors (Fig. 2B) (Arnett et al., 2016). This gene is located on chromosome 5q31.3 and consists of 8 coding and 1 non-coding exon. The 5′ untranslated region of the *NR3C1* gene is composed of several exons, in which 4 exons are located in the distal promoter region (A1–3 and I) and 10 exons are found in the proximal promoter region (D, J, E, B, F, G, C1–3 and H). The proximal promoter comprises a CpG island (Daskalakis and Yehuda, 2014; Radtke et al., 2015).

Among genes involved in the stress response system, the *FKBP5* and *NR3C1* genes are in the midst of those with significant evidence of association with depression. The *FKBP5* gene plays an essential role in regulating the glucocorticoid system as well as the oxytocinergic, serotonergic, and dopaminergic systems (McKenna et al., 2021; Zimmermann et al., 2011). The *NR3C1* gene encodes the GR, playing a primary role in regulating stress and modulating the transcription of genes involved in the HPA axis. (Arnett et al., 2016).

These genes act directly on the negative feedback of the HPA axis. Thus, high intracellular levels of the FKBP51 protein, encoded by the

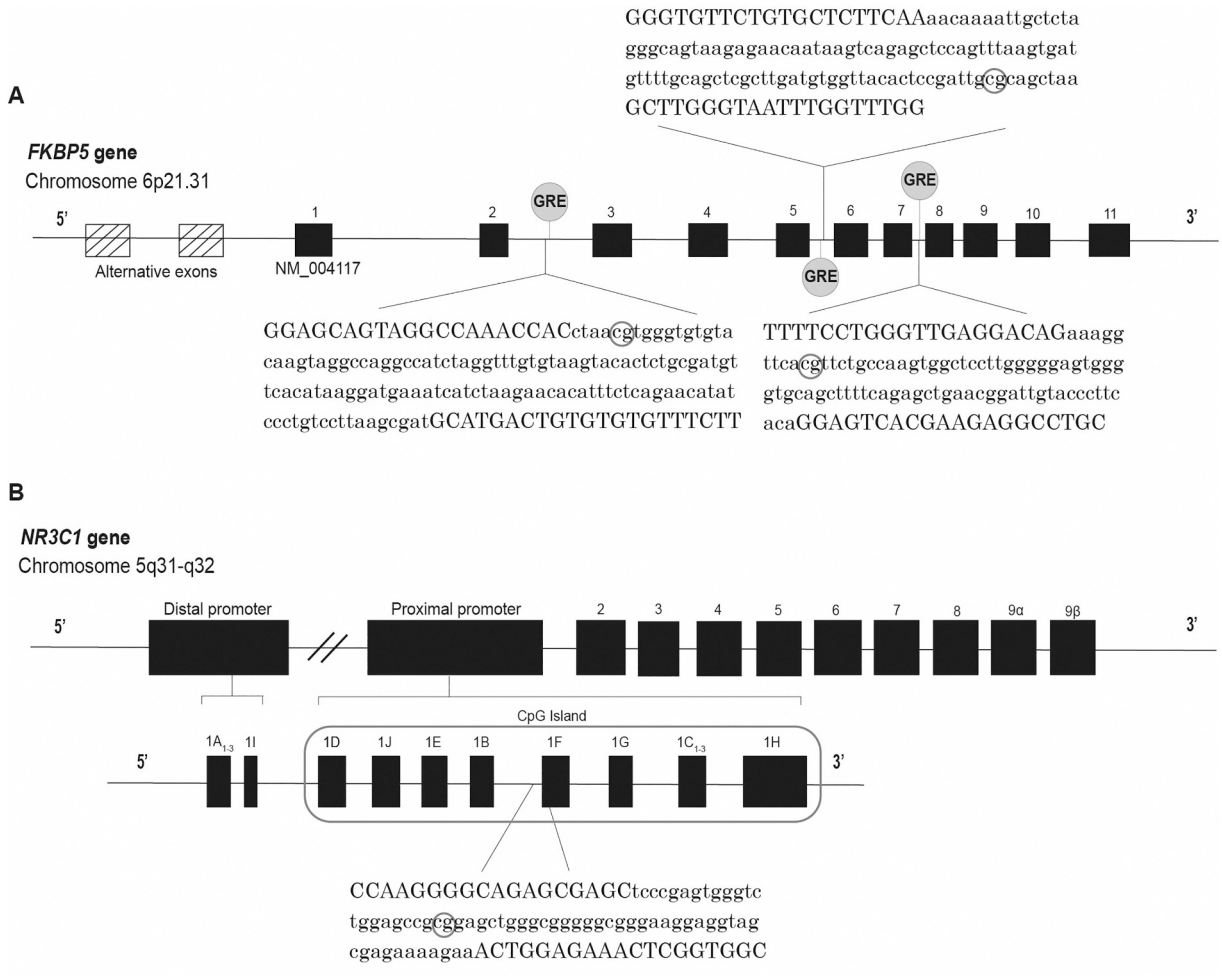

Fig. 2. Schematic representation of the *NR3C1* and *FKBP5* genes and location of the sequences analyzed in this study. (A) Description and location of the *FKBP5* gene and glucocorticoid response elements (GRE). Amplicons for DNA methylation analysis in introns 2, 5, and 7. Description and location of the *NR3C1* gene and CpG island in the promoter region. Amplicon for methylation analysis in the 1F promoter of the *NR3C1* gene. All genomic coordinates were taken from the UCSC Genome Browser Build 2009/hg19. The CpG dinucleotides analyzed in this study are indicated by a circle.

FKBP5 gene, decrease the affinity of GR for GC, and its translocation to the nucleus occurs less efficiently. Dysregulation of the HPA axis, generated by altered levels in the synthesis of GCs, induces a negative feedback imbalance (Arnett et al., 2016; Silva et al., 2021).

In individuals with depression, GR sensitivity is impaired, leading to an alteration in the negative feedback mechanism and, consequently, dysregulation in the synthesis of CRH and ACTH, leading to an increase in the GCs production (Menke, 2019; Troubat et al., 2021).

Thus, the environmental factors, both physical and exposure to adverse events during life, act as HPA axis regulators and induce changes in glucocorticoid response, which may remain stable throughout life. These changes occur due to genetic variants that provide a differential response to the stress factor and/or through epigenetic marks (Buschdorf and Meaney, 2016).

The genetic, epigenetic and environmental factors can cause changes in *FKBP5* and *NR3C1* transcript levels. DNA methylation in the GR gene is associated with psychopathologies. Many studies on the *NR3C1* gene promoter have associated increased DNA methylation with exposure to abuse in childhood, related to greater vulnerability to development of mental health disorders (Labonte et al., 2012; McGowan et al., 2009; Radtke et al., 2015).

Most studies of DNA methylation in the *NR3C1* gene have focused on the exon 1F promoter. Higher levels of DNA methylation in this region have been related to GR transcript reduction, reducing the efficiency of negative feedback and intracellular glucocorticoid accumulation (Tyrka et al., 2016; Zhang et al., 2013). Higher *NR3C1* promoter DNA methylation levels have been associated mainly with reduced GR expression and increased HPA axis reactivity (Cattaneo and Riva, 2015).

GR-induced *FKBP5* transcription is mediated by the binding of GR to glucocorticoid response elements (GREs) located in a region that covers >100 kb and varies from a promoter upstream to introns 2, 5, and 7 of the *FKBP5* gene. Genetic and epigenetic mechanisms moderate the intensity of GC activity in *FKBP5* transcription (Matosin et al., 2021; Zannas et al., 2016).

Studies suggest that maternal care alters the expression of numerous of genes, such as *SLC6A4*, *FKBP5*, *NR3C1*, *BDNF* and *OXTR* (Bierer et al., 2020; Conradt et al., 2013; King et al., 2017; Weaver et al., 2004). In addition, these changes in gene expression patterns correlate with epigenetic changes in gene promoters as well as in intragenic and intergenic regions (Buschdorf and Meaney, 2016; Weaver et al., 2006). In general, epigenetic changes in genes related to the regulation of the HPA axis play an important role in the stress response, involving intensity and duration of response. These changes reflect mood regulation along with emotional and cognitive responses. DNA methylation in these genes has been extensively explored in this area, due to its role in the molecular stress response.

Despite the significant number of studies that have focused on DNA methylation in the *NR3C1* and *FKBP5* genes in response to exposure to early life stress, few studies have evaluated the DNA methylation profile of these genes in patients with depression (Chiarella et al., 2015; Han et al., 2017; Klengel and Binder, 2013; Roy et al., 2017).

The main objective of this study was to evaluate of DNA methylation profile in the mother-child depression context of two HPA regulatory genes, *FKBP5* and *NR3C1*, to determine whether the DNA methylation is associated with stress factors like maternal depression, post-natal depression, and family problems experienced in childhood.

2. Methods

2.1. Study population

One hundred and twenty subjects were included in the study, composed of 60 mother-child pairs. They were split into two groups: G1 (N = 60), counting all mothers with MDD diagnosis (children with or without MDD diagnosis); and G2 (N = 60), a control group (mother and child without MDD diagnosis). For DNA methylation analysis in mothers and children separately, the G1 group was subdivided into G1A (G1A-mother with MDD and G1A-children with MDD) and G1B (G1B-mother with MDD and G1B-children without MDD but exposed to maternal MDD). All participants were selected in a primary care setting in the Basic Health Unit of Uberaba, Minas Gerais, Brazil. The study was approved by the research ethics committee of Uberaba University (UNIUBE) (CAAE: 0039.0.227.000-06), and all participants signed the informed consent form.

The inclusion criteria for mothers were: no pregnancy, with biological children aged between 6 and 12 years, with no apparent physical and/or sensory deficiencies. Women with other psychiatric disorders and those receiving psychological treatment, medications use, or other organic comorbidities were excluded from the study to ensure no interference of variables other than depression.

The inclusion criteria of the children (both genders) were age between 6 and 12 years old and living together with their biological mother. The study excluded children with a history of organic diseases or with apparent sensory deficiencies to avoid confounding variables that might interfere with the child's behavior.

We collected sociodemographic data from all participants (age, gender, socioeconomic level, presence of major maternal depressive disorder (MDD), MDD during pregnancy, postpartum MDD, other disorders of child anxiety and hyperactivity, father's mental disorder, family history of MDD, drug and alcohol use, child's use of medication, medication in pregnancy, child interaction with maternal MDD, and mother's use of medication).

All women were assessed through a screening self-questionnaire for depression, the Patient-Health-Questionnaire (PHQ-9) (Spitzer et al., 1999). The diagnosis of major depressive disorder was clinically confirmed using a semi-structured interview for DSM-IV mental disorder diagnoses (SCID) (First and Pincus, 2002; Williams et al., 1992). We used the Brazilian version (Del-Ben et al., 2001). Moreover, we obtained information on major depressive episodes occurring during pregnancy and/or postpartum through complementary questionnaires. Child depression was assessed through the mother's administration of the DSM-IV-R diagnosis tool for children and teenagers, the Development and Well-Being Assessment (DAWBA), and the Strengths and Difficulties Questionnaire (SDQ) (Goodman et al., 2000). We used the validated Brazilian versions of the DAWBA and SDQ (Fleitlich-Bilyk and Goodman, 2004).

2.2. The regions in the FKBP5 and NR3C1 genes

We analyzed previously reported regulatory regions of the *FKBP5* introns (2, 5 and 7) and an alternative promoter 1F in the *NR3C1* gene, reported to have methylation levels alteration in previous studies with psychiatric patients (Argentieri et al., 2017; Klengel et al., 2013; Yehuda et al., 2014). The genomic coordinates used in the present work were derived from GRCh37/hg19 assembly. We used the UCSC genome browser (http://genome.ucsc.edu/) to characterize the location of these regions, with tracks such as CpG island position and GenEnhancer track, in addition to overlap with transcription factor binding sites (ENCODE regulation tracks — Txn Factor ChIP).

The CpG site analyzed, located on the CpG island of the 1F promoter of the *NR3C1* gene, used as reference the numbering of the CpG sites based on the review by Palma-Gudiel et al. (2015).

Based on the data obtained, we used buccal epithelial cells derived from mother-child pair subjects to perform the analysis to detect major depressive disorder - differentially methylated regions (MDD-DMR). Buccal epithelial cells have been suggested to be the most sensitive cell type when studying *FKBP5* and *NR3C1* methylation in behavioral disorders (di Sante et al., 2018; Smith et al., 2015; Vukojevic et al., 2014). In addition to the facility of obtaining these cells, they derive from the same ectoderm layer as brain cells during development (Lowe et al., 2013; Smith et al., 2015).

2.3. DNA methylation analysis

The DNA samples used in the present study were obtained from the DNA databank of the Department of Neuroscience and Behavioral Science of the Ribeirão Preto School of Medicine, São Paulo, Brazil. The samples were collected at the Basic Health Unit of Uberaba, Minas Gerais. The collection of buccal cell samples for DNA isolation was approved by the ethics committee of Uberaba University (UNIUBE) (CAAE: 0039.0.227.000-06). The DNA was isolated from buccal epithelial cells following the salting-out protocol (Olerup and Zetterquist, 1992). Samples of buccal epithelial cells were treated with 25 mg/μl of proteinase K overnight. Subsequently, the DNA was isolated with a 5 M NaCl solution, and precipitated and purified by 100 % and 70 % alcohol, respectively.

For the MSRED-qPCR (methylation-sensitive restriction enzyme digestion qPCR) assay, 400 ng of DNA sample was digested with 5 U of methylation-sensitive restriction enzymes (New England — Biolabs). The restriction enzymes used were: *Hpy*CH4IV for the regions of introns 2 and 7 of *FKBP5*; *Hha*I for intron 5 of the *FKBP5* gene; and *Bst*UI for the *NR3C1* gene promoter. DNA samples were incubated for 4 h at 37 °C (HpyCH4IV; HhaI) and 60 °C (BstUI) and subsequently submitted to inactivation time and temperature according to the specification for each enzyme. For control, DNA from undigested samples were used.

The quantitative analysis of methylation level at the *NR3C1* alternative promoter and introns 2, 5, and 7 of *FKBP5* was performed by real-time PCR assay using StepOnePlus™ (Applied Biosystems™), following the protocol described by (Gomes et al., 2007). qPCR assays were performed in a final volume of 10 μL [10 μM of each primer pair; 5.0 μL PCR Master Mix — Sybr Green (Applied Biosystem); 0.2 μL 807 Milli-Q water; 4.5 μL of each sample (±10 ng of DNA). Cycling conditions were: 95 °C for 10 min, 40 cycles of 95 °C for 30 s; 60 °C for 30 s; and 72 °C for 30 s. The amplified fragment corresponds to the coordinates chr5:142783579–142783677 (NCBI37/hg19) located in a CpG island at the *NR3C1* 1F alternative promoter. For *FKBP5,* the coordinates comprised intron 2 chr6:35607880–35608046, intron 5 chr6:35569724–35569867, and intron 7 chr6:35558477–35558596.

The percentages of DNA methylation of each sample were calculated with the formula $5mC\% = 100 \times 1/2^{(\Delta Ct)}$ (ΔCt = Ct mean digested sample − Ct mean undigested sample) (Evans, 2007). The methylation level of each sample was analyzed in triplicate.

2.4. Statistical analysis

In the analysis of the 5mC%, we used an unpaired *t*-test with Welch's correction and one-way ANOVA with Tukey's multiple comparisons test and Bonferroni's multiple comparisons test. For the DNA methylation correlation analysis between the mother-child pairs, Kendall's tau correlation test was performed. Data processing and statistical analyses were conducted with GraphPad Prism 5.0 and R version 4.0.5. The level of significance was set at $p \leq 0.05$.

3. Results

3.1. DNA methylation in MDD mother-child dyads

Based on the objectives, at first we evaluated the DNA methylation profile of *FKBP5* and *NR3C1* genes associated with the diagnosis of depression in mother and child, along with the effect of exposure to clinical variables on DNA methylation in these genes in children.

DNA methylation in mothers and children were assessed separately in the risk group (G1 — exposed to trauma) and control group (G2). Thus, we observed the DNA methylation pattern between mothers with MDD (G1 mothers) and mothers without MDD (G2 mothers); and, children with MDD (G1A), children without MDD but who experienced maternal MDD (G1B), and control children (G2C) (Supplementary Table 1).

For the *FKBP5* gene, in the maternal samples we found a significant difference of introns 2 and 5 in mothers with MDD (G1 mothers), and for mothers of the control group (G2 mothers) ($p < 0.05$) (Fig. 3). In the region of intron 2, we found higher levels of 5mC% in G1 (25.75 %) compared to G2 (20.78 %) ($p < 0.05$) (Fig. 3A); while in intron 5 the we observed lower levels of 5mC% in group G1 (70.57 %) compared to group G2 (78.22 %) ($p < 0.05$) (Fig. 3B). In the region of intron 7 of *FKBP5* and the promoter of *NR3C1*, there was no significant difference between groups ($p > 0.05$) (Fig. 3C–D).

In contrast, we found a significant increase in DNA methylation in the *NR3C1* gene promoter in children, both in the G1A and G1B groups, compared to G2 (Fig. 4D). In children from G1A, the average DNA methylation observed in *NR3C1* was 51.89 %, and in G1B it was 57.62 %, while children in G2 showed an average of 30.64 % ($p < 0.05$ and $p < 0.002$, respectively). The mean DNA methylation in the G1A group, where children had been diagnosed with MDD, was approximately 20 % higher than in G2, without a diagnosis of MDD and exposure to maternal MDD. Similarly, in G1B children who did not have MDD but had been exposed to maternal MDD, DNA methylation was on average 27 % higher compared to the average of G2 children. In the analyzed regions of introns 2, 5, and 7 of the *FKBP5* gene, there was no significant relationship of DNA methylation among children from G1A, G1B, and G2 ($p > 0.05$) (Fig. 4A–C). In both regions of the *FKBP5* gene, the average of methylation was similar between the groups.

The results presented demonstrate the occurrence of alterations in DNA methylation detected in a generation- and gene-specific manner, in which mothers with MDD showed significant alterations in the DNA methylation of intron 2 and 5 *FKBP5*, while children exposed to maternal MDD presented *NR3C1* DNA methylation changes.

3.2. Effect of clinical variables in DNA methylation on children

We evaluated the effect of clinical variables, namely the presence of other mental disorders in children (ADHD and anxiety disorder), postpartum depression (PPD), MDD during pregnancy, and family history of depression on the DNA methylation of *FKBP5* and *NR3C1* genes in children.

Introns 2 and 5 of *FKBP5* showed no significant difference in DNA methylation between the presence and absence of clinical variables ($p > 0.05$) (Fig. 5A–H). In intron 7 we found a significant decrease in DNA methylation between the presence of MDD diagnosis during pregnancy (34.68 %) and absence (40.74 %) ($p < 0.05$) (Fig. 5L). As for the clinical variables related to the number of disorders, PPD, and family history of depression, there was no relationship between presence and absence on intron 7.

In the *NR3C1* promoter, we found an association of increased DNA methylation level in the presence of one or more psychiatric disorders (anxiety disorder and ADHD), with an average of 51.33 % compared to 35.26 % without any disorder ($p < 0.05$). The other variables – PPD, MDD during pregnancy, and family history of depression – showed no significant difference in *NR3C1* DNA methylation levels between presence and absence (Fig. 5M–P).

3.3. Correlation of DNA methylation in mother-child dyads

To evaluate the effect of early life stress exposure on DNA methylation patterns of *FKBP5* and *NR3C1* genes, we performed a correlation analysis of DNA methylation in mother-infant pairs in groups G1A, G1B and G2. The correlation of DNA methylation between mother and child was significant in the target regions of the *NR3C1* gene and intron 7 of the *FKBP5* ($p < 0.05$) (Fig. 6E–H). In *NR3C1*, the correlation of DNA methylation levels occurred both in the risk group G1A and in the control group G2 ($\tau = 0.2$; $p < 0.002$ and $\tau = 0.5$; $p < 0.0001$, respectively), in which the G1A group showed a pattern of increased DNA methylation of the *NR3C1* promoter while the control group showed a decrease in DNA methylation levels. In intron 7 of the *FKBP5* gene, we

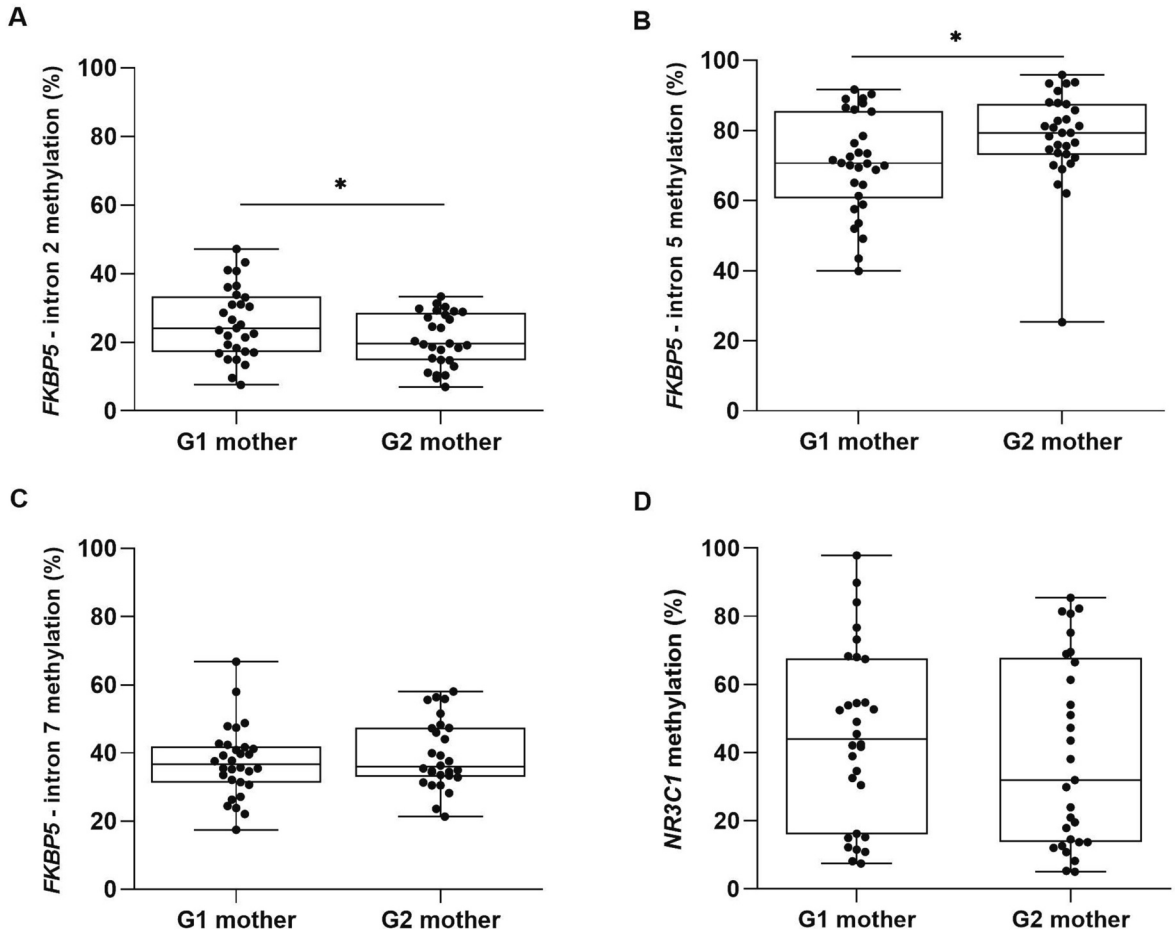

Fig. 3. Mean DNA methylation in *FKBP5* and *NR3C1* genes between mothers with depression (G1) and mothers without depression (G2). (A) % methylation of intron 2 — *FKBP5*. A significant difference in DNA methylation of the G1 group compared to the G2 ($p < 0.05$) was found. (B) % methylation of intron 5 — *FKBP5*. A significant difference in DNA methylation of the G1 group compared to G2 was found ($p < 0.05$). (C) % methylation of intron 7 — *FKBP5*. There was no significant difference in DNA methylation between groups. (D) % methylation of NR3C1. There was no significant difference in DNA methylation between groups (unpaired *t*-test with Welch's correction).

observed a correlation between mother and child only in the G1B risk group ($\tau = 0.4$; $p < 0.05$). In introns 2 and 5 of the *FKBP5* gene, we did not find a significant correlation in DNA methylation between mothers and children ($p > 0.05$).

4. Discussion

In the present study, we aimed to investigate the DNA methylation profile of *NR3C1* and *FKBP5* in mother-child dyads with MDD and the effect on child stressor exposure. According to our results, on the *FKBP5* gene, there was a significant difference in DNA methylation of introns 2 and 5 in mothers with MDD compared to mothers without MDD. In the region of intron 2, there was an increase in DNA methylation in mothers with MDD, while in intron 5 there was a decrease in DNA methylation levels in mothers with MDD compared to mothers in the control group.

To date, no study in the literature has reported changes in the DNA methylation pattern in introns 2 and 5 of the *FKBP5* gene in individuals with MDD, highlighted in the present study in the context of mothers with MDD. There are few studies on *FKBP5* methylation in patients with depression (Chiarella et al., 2020; Han et al., 2017; Höhne et al., 2014; Klinger-König et al., 2019; Saito et al., 2020; Tozzi et al., 2018a). Most of them focus on intron 7 methylation, which has been associated with conformational chromatin change in individuals exposed to early life stress (Klengel et al., 2013). Unlike our findings, some studies have reported lower *FKBP5* methylation in intron 7 in patients with depression (Chiarella et al., 2020; Han et al., 2017; Klinger-König et al., 2019; Tozzi et al., 2018b). However, most of these studies report lower DNA methylation on intron 7 with the risk allele of SNP rs1360780, which we did not evaluate.

In our study, we found no significance of the diagnosis of psychiatric disorders in children, PPD, and maternal depression associated with differences in DNA methylation level at intron 7, except for MDD during pregnancy, in which a significant reduction in intron 7 methylation was observed in relation to children not exposed to MDD during pregnancy. In the same way, Ramo-Fernández et al. (2019) associated a reduction in the methylation average of 79 CpG sites of intron 7 of peripheral blood in women with a history of childhood maltreatment (Ramo-Fernández et al., 2019). However, the average methylation at these CpG sites was higher (~75 %) than observed in the region analyzed in the present study (~40 %). Other researchers have also reported the hypomethylation of intron 7 of the *FKBP5* gene in children exposed to stress factors, such as childhood maltreatment (Klengel et al., 2013; Tyrka et al., 2015). In contrast, Grasso et al. (2020) reported an increase in DNA methylation at 4 CpG sites of intron 7 in infants exposed to maternal stress factors and maternal PTSD symptom severity (Grasso et al., 2020).

The present study is one of the first studies evaluating the methylation of *FKBP5* in introns 2, 5 and 7, and the first to evaluate these regions in parallel in the context of mothers and children with MDD. A previous study reported no significant effect of children's stress exposure on introns 2 and 7 of *FKBP5* (Bustamante et al., 2018). Also, Klengel et al. (2013) evaluated DNA methylation 2, 5, and 7 of individuals that

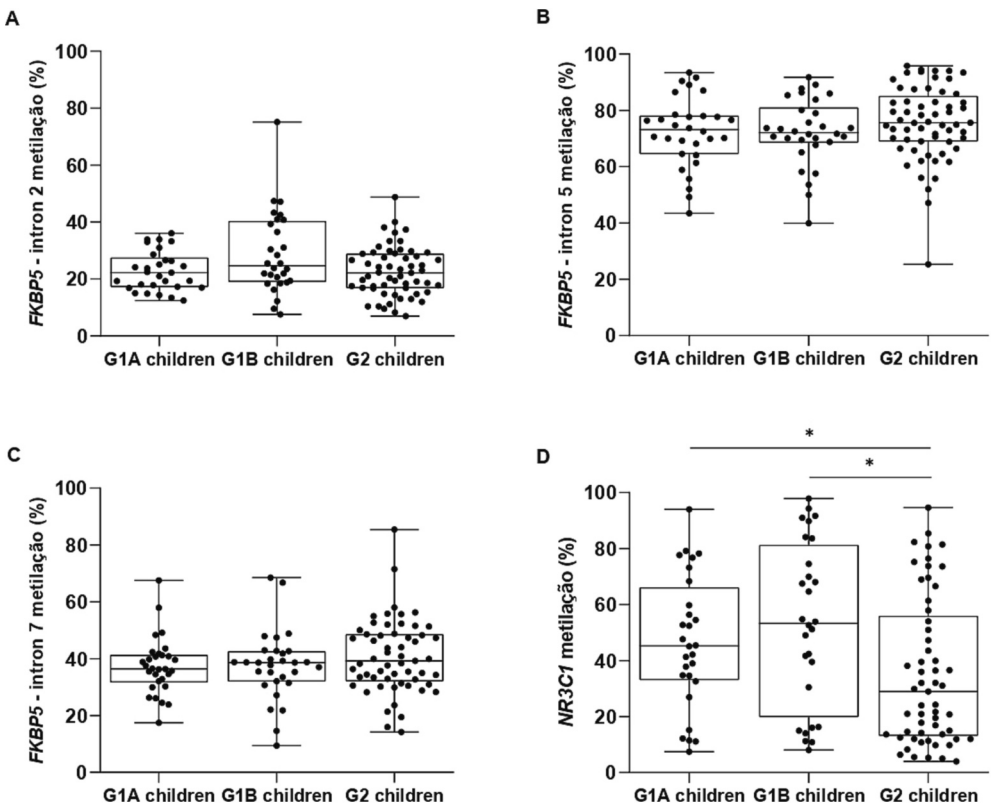

Fig. 4. Mean DNA methylation in *FKBP5* and *NR3C1* genes in children from groups G1A, G1B and G2. (A) % methylation of intron 2 — *FKBP5*. There was no significant difference in DNA methylation between groups. (B) % methylation of intron 5 — *FKBP5*. There was no significant difference in DNA methylation between groups. (C) % methylation of intron 7 — *FKBP5*. There was no significant difference in DNA methylation between groups. (D) % NR3C1 methylation (G1A versus G2 $p < 0.05$; G1B versus G2 $p < 0.002$). (One-way ANOVA — Tukey's multiple comparison test).

suffered childhood physical and sexual abuse and found genotype-dependent DNA methylation associated with trauma in intron 7. For introns 2 and 5, the same study did not find epigenetic alteration and childhood trauma association. Duis et al. (2018) also associated methylation in intron 5 with the presence of the rs1360780 allele, in which exposure to maternal affective disorder was related to the increase in DNA methylation in this region in patients with the homozygous risk allele (Duis et al., 2018). In summary, there are not enough reports in the literature about introns 2 and 5 of the *FKBP5* gene. Our preliminary results in these regions of *FKBP5* gene, indicate a significant association of DNA methylation between mothers with depression compared to mothers without depression, but this was not observed in children.

Regarding DNA methylation in the *NR3C1* gene, our results demonstrate a differential methylation pattern in risk groups (children exposed to maternal MDD), both in the general analysis of mother-child dyads and also separately assessed in children. Our results highlight a profile of DNA methylation gain in *NR3C1* in the risk groups compared to the control group, a significant increase of DNA methylation of about 20 to 27 % in relation with the control group. Our findings corroborate those of studies that have reported DNA methylation increase of *NR3C1* in MDD patients (Bakusic et al., 2020; Nantharat et al., 2015; Roy et al., 2017). The CpG36 dinucleotide analyzed in the present study is close to the site of NGFI-A binding protein, a transcription factor that regulates GR expression. Hypermethylation of DNA in regions overlapping the NGFI-A binding site has been associated with early stress and depression (Bakusic et al., 2020; Liu and Nusslock, 2017; Weaver et al., 2004).

A study that evaluated multiple CpG sites within the CpG island in the *NR3C1* promoter found hypermethylation at the CpG12 and CpG20 sites in patients with depression overlapping regions of the NGFI-A binding site. The average methylation of all analyzed CpGs was also higher and significant compared to the control (Bakusic et al., 2020). Another study evaluated CpG 40–47 on the CpG island in the gene promoter and observed an increase in DNA methylation levels at CpG sites 40, 42, and 46, and CpG of 40–47 in individuals with MDD (Borçoi et al., 2020). In contrast to our results, which indicated a relationship between DNA methylation in the exon 1F region CpG36 and depression, Bakusic et al. (2020) found no significant association at that specific CpG site. Similar to our findings, Roy et al. (2017) and Farrell et al. (2018) reported an increase in DNA methylation levels in depression patients at the CpG 35–37 and CpG 36–39 sites, respectively. In addition, Roy et al. (2017) associated *NR3C1* hypermethylation with lower gene expression. Few studies have reported lower *NR3C1* methylation levels associated with MDD (Bustamante et al., 2016; Na et al., 2014).

Many studies have focused on the *NR3C1* methylation as a mediator of early life stress effect and of the development of psychopathologies (Murgatroyd et al., 2015; Oberlander et al., 2008; Palma-Gudiel et al., 2015; Tyrka et al., 2016). One of the main objectives of our study was to evaluate the effect of maternal MDD, PPD and MDD during pregnancy on DNA methylation in children. Our results showed a higher methylation average in children with depression and other psychiatric disorders (anxiety and ADHD) and those who experienced maternal mental disorders. Bustamante et al. (2016) found an increase in DNA methylation of CpG 35–38 sites due to childhood maltreatment, but a significant decrease in the average methylation of CpG 39–47 sites in patients with depression. The higher average DNA methylation in childhood trauma exposure and adolescent depression corroborates our findings' target region (Bustamante et al., 2016; Efstathopoulos et al., 2018).

Murgatroyd et al. (2015) reported that pre-and postnatal depression exposure is associated with an increase in *NR3C1* 1F promoter methylation in infants, but that this epigenetic change is reversed by maternal care after the first weeks of life. Further, another study reported that maternal depression exposure was associated with increased *NR3C1* methylation at the NGFI-A binding site and increased salivary cortisol levels in the first months of life (Oberlander et al., 2008). Thus, most studies have associated hypermethylation in or near the NGFI-A binding region. It has been suggested that this region is a possible regulatory target for etiology of depression studies.

Whereas the distribution of CpG sites within a gene can vary, it is crucial to assess how the distribution of sites associated with DNA

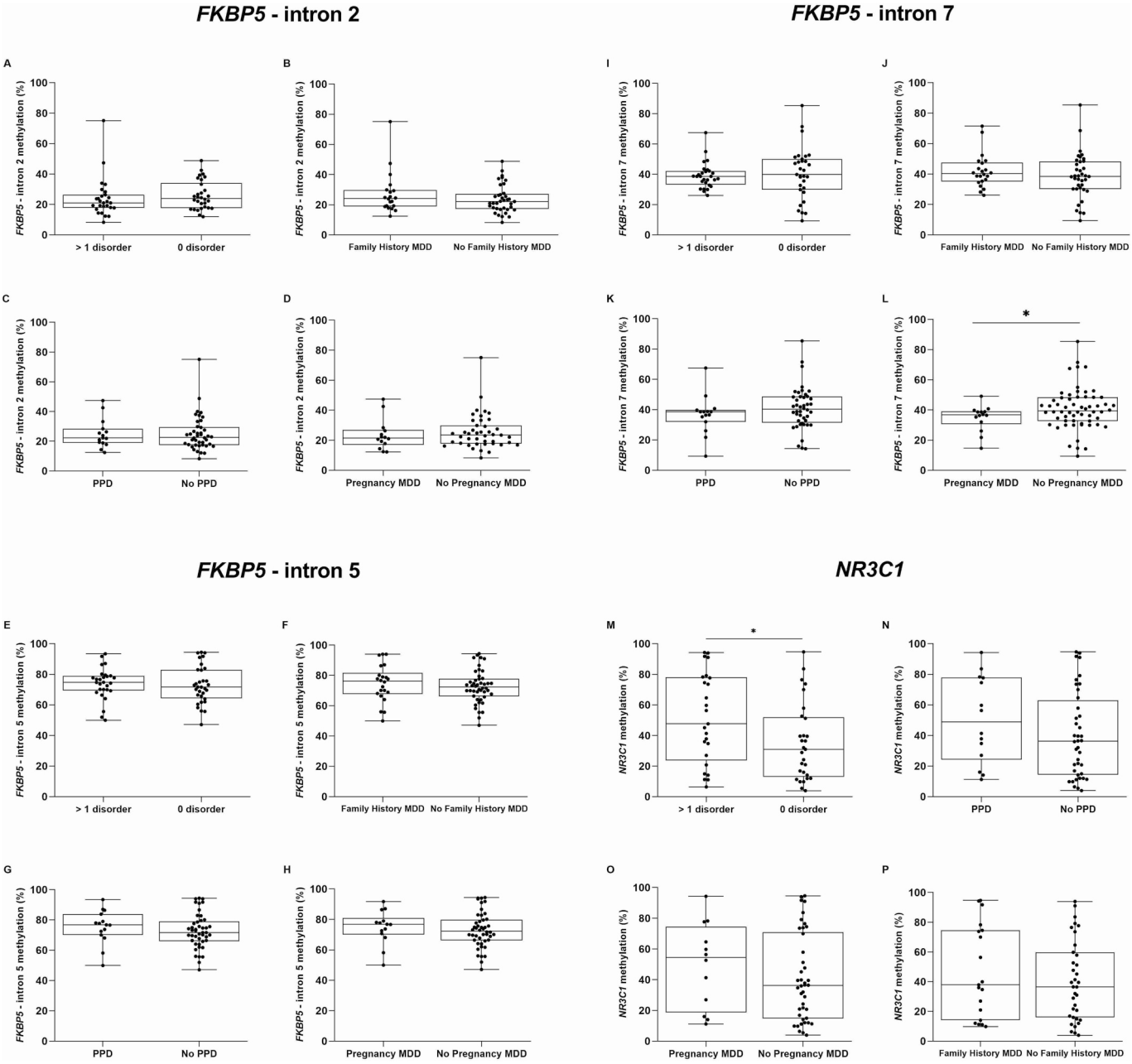

Fig. 5. Relationship of DNA methylation with clinical variables present in children in introns 2, 5 and 7 of the *FKBP5* gene and *NR3C1* gene. (A) % methylation of intron 2 — *FKBP5* associated with the presence of psychiatric disorders. (B) % methylation of intron 2 — *FKBP5* associated with a family history of MDD. (C) % methylation of intron 2 — *FKBP5* associated with maternal PPD. (D) % methylation of intron 2 — *FKBP5* associated with MDD during pregnancy. (E) % methylation of intron 5 — *FKBP5* associated with the presence of psychiatric disorders. (F) % methylation of intron 5 — *FKBP5* associated with a family history of MDD. (G) % methylation of intron 5 — *FKBP5* associated with maternal PPD. (H) % methylation of intron 5 — *FKBP5* associated with MDD during pregnancy. (I) % methylation of intron 7 — *FKBP5* associated with the presence of psychiatric disorders. (J) % methylation of intron 7 — *FKBP5* associated with a family history of MDD. (K) % methylation of intron 7 — *FKBP5* associated with maternal PPD. (L) % methylation of intron 7 — *FKBP5* associated with MDD during pregnancy ($p < 0.05$). (M) % *NR3C1* methylation associated with the presence of psychiatric disorders ($p < 0.05$). (N) % *NR3C1* methylation associated with a family history of MDD. (O) % *NR3C1* methylation associated with maternal PPD. (P) % *NR3C1* methylation associated with MDD during pregnancy (unpaired *t*-test with Welch's correction).

methylation affects gene expression. It is known that the distribution diversity of CpG sites around the promoter regions of genes may influence the degree of clustering of regulatory mechanisms. In the case of the CpG36 site analyzed in the present study is close to the site of NGFI-A binding protein, a transcription factor that acts in regulates GR expression. This may explain why previous studies evaluated different CpG sites in the *NR3C1* gene to determine a DNA methylation profile, associating them with the etiology of depression (Tian et al., 2022).

Another aim of the present study was to investigate the correlation of DNA methylation in these stress response regions on mother-child pairs. Our results demonstrated a significant correlation in the methylation of *NR3C1* in the G1A group, between mothers and children with MDD. Furthermore, we found a correlation in DNA methylation between mother and child at intron 7 of the *FKBP5* gene only in the G1B risk group, in which children live with maternal MDD but do not have MDD. These data suggest that stress factors, such as maternal affective disorders (MDD, MDD during pregnancy, PPD) generate epigenetic changes that can be transmitted to the next generation. Few studies to date have

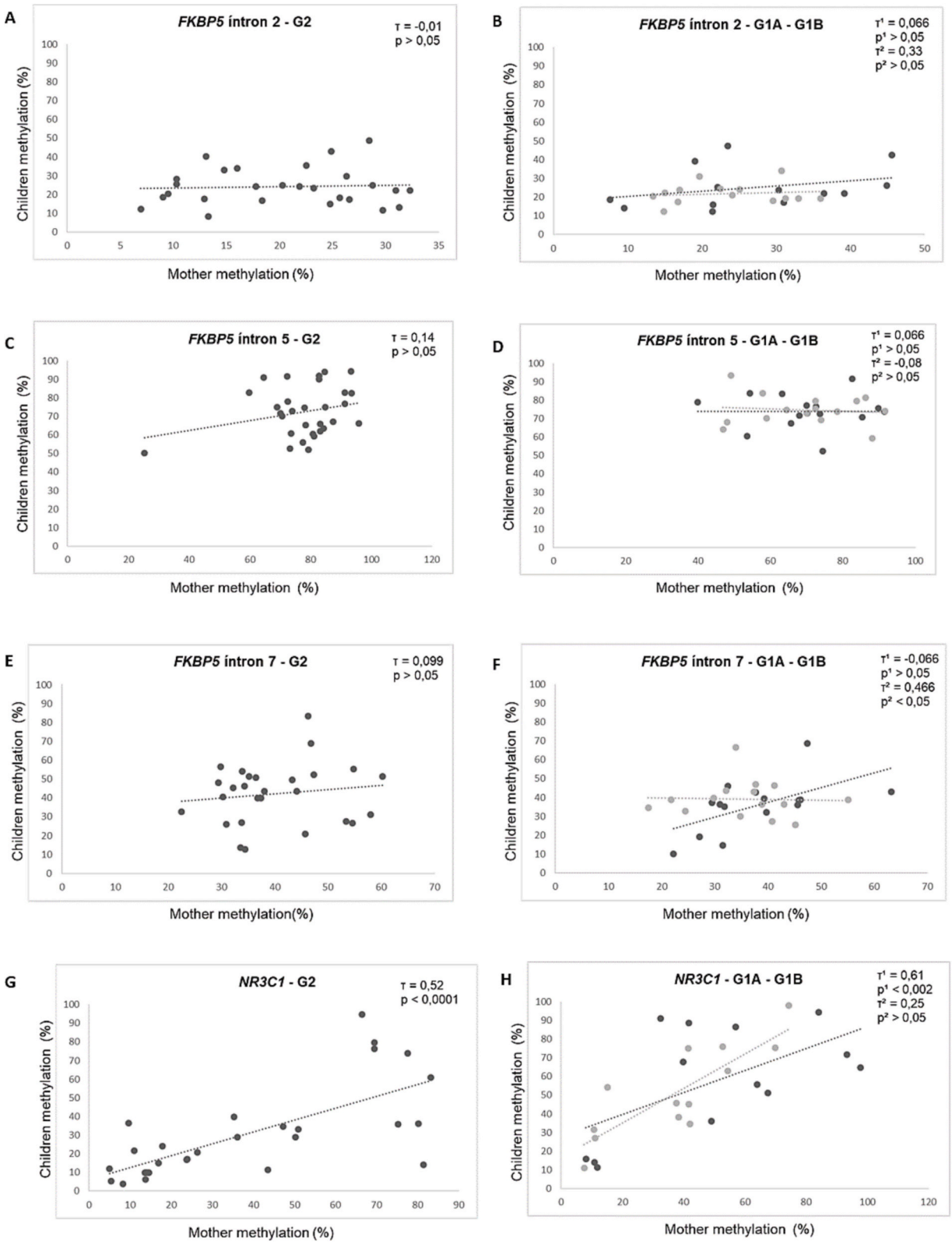

Fig. 6. Correlation of DNA methylation between mother-child pairs of groups G1A, G1B and G2. In the graphs of G1A and G1B, the circle and trend line in black color correspond to the mother-child pairs of G1A; the gray circle and trendline correspond to the G1B mother-child pairs. τ^1 and p^1 correspond to the statistical data of G1A while τ^2 and p^2 correspond to the statistical data of G1B (Kendall's tau correlation test).

reported the correlation of DNA methylation on the *FKBP5* and *NR3C1* genes in mother-child dyads (van Aswegen et al., 2021; Bierer et al., 2020; Bowers and Yehuda, 2015; Ramo-Fernández et al., 2019; Yehuda et al., 2014).

We did not find a correlation of DNA methylation between mothers and children with MDD in intron 7 of the *FKBP5* gene, but there was a correlation in the group of children without MDD but exposed to maternal MDD. Similar to our findings in the intron 7 region, Yehuda et al. (2014, 2015) observed the intergenerational effect of the gene in the region close to the GRE of intron 7 of *FKBP5* in individuals surviving the Holocaust and their adult offspring. However, as in the present study, they reported a significant correlation of the methylation of the *NR3C1* 1F promoter and paternal post-traumatic stress. Ramo-Fernández et al. (2019) did not observe an intergenerational effect on DNA methylation in the *FKBP5* and *NR3C1* genes in peripheral blood and umbilical cord blood cell samples from mothers who suffered childhood maltreatment and infants, respectively. In addition, DNA methylation levels were not correlated with gene expression in these individuals. This is the first study to provide evidence of correlation of DNA methylation in the *NR3C1* gene in mother-child pairs with MDD, suggesting a possible intergenerational effect in this region.

Exposure to adverse events in early life may confer greater susceptibility to mental illness, besides related to greater resilience and adaptation to these factors (Cattaneo and Riva, 2016). The stress-resilience response relationship is complex. Interestingly, our results show a correlation of *FKBP5* intron 7 DNA methylation in children without depression but exposed to maternal depression. (Kang et al., 2020) observed that resilience moderates the effects of the interaction of *FKBP5* genetic polymorphisms related to childhood trauma on depressive symptoms (Kang et al., 2019). In addition, (Serpeloni et al., 2019) compared the DNA methylation profile in the *FKBP5* and *NR3C1* genes in children who experienced maternal intimate partner violence during pregnancy. The authors observed a hypermethylated profile in trauma-exposed children in these genes, resulting in enhanced negative feedback and faster recovery from stress in trauma-exposed children (Serpeloni et al., 2019).

Although 50 % of mothers in the risk group in this study had depression during pregnancy history, it is not possible to suggest the existence of an intergenerational effect on DNA methylation because the average age of the participating children was 6 to 12 years. Despite previous studies exploring the intergenerational effect even in adult and child (8–16 years old) offspring (van Aswegen et al., 2021; Yehuda et al., 2015), DNA methylation may change according to environmental exposure during lifetime. However, our findings corroborate the developmental origins of healthy and disease hypothesis (DoHaD), in which the first years of life are crucial to maintenance of epigenetic regulation in adulthood (Bianco-Miotto et al., 2017). Childhood is the period of greatest vulnerability to environmental exposure. Thus, exposure to affective maternal disorders such as MDD, MDD during pregnancy, and PPD are considered stressors in early life that can trigger future psychiatric disorders.

Another finding to highlight in the present study was the DNA methylation profile in the *NR3C1* gene between mothers and children. Although not significant, in the risk groups we observed that the DNA methylation profile in children was higher compared to mothers, by around 10 %. On the other hand, in the control group, the children had lower levels of DNA methylation compared to the mothers. Variations in DNA methylation of the *NR3C1* gene have been reported in both pre-and postnatal exposure (Chen et al., 2017; Galbally et al., 2020; Kundakovic and Jaric, 2017). Childhood is the period of greatest vulnerability to epigenetic changes (Jiang et al., 2019; Nemoda and Szyf, 2017). Thus, this trend towards higher levels of DNA methylation in children exposed to maternal MDD compared to the mother can be explained by the association of exposure to risk factors in the first years of life with increased levels of DNA methylation at *NR3C1*.

In the mother and child context, this change seems to be generation-specific, since changes in DNA methylation in introns 2 and 5 of *FKBP5* were observed only in mothers with MDD, while in children exposed to maternal MDD, we found a change in methylation in the *NR3C1* gene. However, DNA methylation alterations in the maternal-child context need to be better elucidated, considering the negative feedback regulation of the *FKBP5* and *NR3C1* genes (Arnett et al., 2016).

One of the limitations of our study was the type of tissue used for DNA methylation analysis, derived from buccal cells. Due to the impossibility of assessing DNA methylation in the living human brain, peripheral tissues such as blood and buccal epithelium are predominant in this assessment (Binder, 2009; Klengel et al., 2013; Tyrka et al., 2015; Yehuda et al., 2015). In addition, buccal cells and the brain are derived from the same ectodermal layer during development in the womb, which suggests that epithelial cells are more compatible with brain methylation patterns than peripheral blood cells (Lowe et al., 2013; Smith et al., 2015).

Furthermore, although the individuals evaluated in this study are a rare group, considering the entire clinical survey and the context of psychiatric diagnosis, the sample size of the study was small. Another point that should be highlighted is that our study evaluated the methylation of only one CpG site for each region, but these analyzed regions are located in important regulatory regions of the aforementioned genes and may contribute to new findings regarding children's MDD. Evidence about how and which genes are involved in the etiology of psychiatric disorders is contradictory in the literature. Gene association studies in the context of psychiatric disorders are often complex and discordant due to the clinical heterogeneity of individuals (Hoehe and Morris-Rosendahl, 2018; Sullivan and Geschwind, 2019).

A previous study by our group reported a differential DNA methylation pattern of the *SLC6A4* gene in this same sample group. In the mother-child pairs with MDD, a profile of lower levels of DNA methylation was observed in the group without MDD (Mendonça et al., 2019). These changes, added to the results found in the present study, which demonstrate a profile of DNA methylation gain in mother-child binomials with MDD, suggest that exposure to stress factors, especially in early life, generates an altered pattern of methylation of DNA in a multilocus context. Thus, these results should be considered in new studies aimed at other genes involved in the stress response and the physiology of MDD.

Based on the studies, it is clear there are contradictions associated with depression and DNA methylation in these genes. It is known that the deregulation of the HPA axis, both hyper-regulation and deficiency in the production of GC, may cause damage to human health in several aspects (Juruena et al., 2018; Silva et al., 2021). Thus, both hypo and hypermethylation of stress response genes are associated with maladaptation and alteration of negative feedback, contributing to the development of diseases (Arnett et al., 2016; Lee et al., 2014). The results of the present study suggest that the alteration of DNA methylation in regulatory regions of *FKBP5*, associated with GC binding sites and *NR3C1* methylation represent a possible target for future studies to better understand the etiology and improve the treatment and prognosis of depression.

5. Conclusion

In summary, it was observed that DNA methylation of the *NR3C1* gene is related to higher levels of DNA methylation in children with MDD and children exposed to maternal MDD. The correlation of DNA methylation at the *NR3C1* promoter in mother-child pairs with depression indicates a possible intergenerational effect of maternal MDD exposure in the offspring. Regarding the intronic regions of the *FKBP5* gene, a decrease in DNA methylation at intron 7 was observed in children exposed to maternal MDD during pregnancy, and a correlation of DNA methylation between mothers and children exposed to maternal MDD.

In conclusion, our results demonstrate an alteration in the DNA

methylation pattern in the *FKBP5* and *NR3C1* genes underlying the etiology of MDD in the maternal-infant context, suggesting a possible intergenerational effect of maternal MDD exposure in offspring. This combination of epigenetic alterations in a multi-locus context can be associated with depression development in those exposed to maternal MDD, suggesting a contribution in a clinical approach to the diagnosis of MDD.

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CRediT authorship contribution statement

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Methodology and investigation: Mariana Mendonça, Paula Magnelli, Álvaro Rios.

Original Draft: Mariana Mendonça.

Recruitment of sample and data collection: Ana Mendes, Sônia Loureiro, Rocio Martin-Santos, José Crippa, Jaime Hallack.

Analysis and tabulation of clinical data: Ana Mendes, Sônia Loureiro, Rocio Martin-Santos, Wilson Marques, Silmara de Marco, José Crippa, Jaime Hallack.

Writing-Review and Editing: Álvaro Rios, Milton Kanashiro, Mariana Mendonça, Paula Magnelli.

Statistical Analysis: Leonardo Glória, Mariana Mendonça, Paula Magnelli.

Supervision: Álvaro Rios, Milton Kanashiro.

Funding Acquisition – José Crippa, Jaime Hallack.

All authors were responsible for reviewing and approving the final manuscript.

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Declaration of competing interest

JAC and JECH are co-inventors (Mechoulam R, Crippa JA, Guimaraes FS, Zuardi A, Hallak, JE, and Breuer A) of the patent "Fluorinated CBD compounds, compositions and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023" Def. US no. Reg. 62193296; July 29, 2015; INPI on August 19, 2015 (BR11201501649 27). The University of São Paulo has licensed the patent to Phytecs Pharm (USP Resolution 15.1.130002.1.1). USP has an agreement with Prati-Donaduzzi (Toledo, Brazil) to "develop a pharmaceutical product containing synthetic CBD and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders." JAC has received travel support from and is a medical advisor of the SCBD Centre, and has a grant from the University Global Partnership Network (UGPN) – "Global priorities in cannabinoid research excellence." JAC is member of the international advisory board of the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE; funded by the National Health and Medical Research Council through the Centre of Research Excellence). The other authors report no conflicts of interest.

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References

Argentieri, M.A., Nagarajan, S., Seddighzadeh, B., Baccarelli, A.A., Shields, A.E., 2017. Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development. EBioMedicine 18, 327–350. https://doi.org/10.1016/j.ebiom.2017.03.044.

Aristizabal, M.J., Anreiter, I., Halldorsdottir, T., Odgers, C.L., McDade, T.W., Goldenberg, A., Mostafavi, S., Kobor, M.S., Binder, E.B., Sokolowski, M.B., O'Donnell, K.J., 2020. Biological embedding of experience: a primer on epigenetics. Proc. Natl. Acad. Sci. U. S. A. 117, 23261–23269. https://doi.org/10.1073/pnas.1820838116.

Arnett, M.G., Muglia, L.M., Laryea, G., Muglia, L.J., 2016. Genetic approaches to hypothalamic-pituitary-adrenal axis regulation. Neuropsychopharmacology 41, 245–260. https://doi.org/10.1038/npp.2015.215.

van Aswegen, T., Bosmans, G., Goossens, L., van Leeuwen, K., Claes, S., van den Noortgate, W., Hankin, B.L., 2021. Epigenetics in families: covariance between mother and child methylation patterns. Brain Sci. 11, 1–11. https://doi.org/10.3390/brainsci11020190.

Bakusic, J., Vrieze, E., Ghosh, M., Bekaert, B., Claes, S., Godderis, L., 2020. Increased methylation of NR3C1 and SLC6A4 is associated with blunted cortisol reactivity to stress in major depression. Neurobiol. Stress 13, 100272. https://doi.org/10.1016/j.ynstr.2020.100272.

Bianco-Miotto, T., Craig, J.M., Gasser, Y.P., van Dijk, S.J., Ozanne, S.E., 2017. Epigenetics and DOHaD: from basics to birth and beyond. J. Dev. Orig. Health Dis. 8, 513–519. https://doi.org/10.1017/S2040174417000733.

Bierer, L.M., Bader, H.N., Daskalakis, N.P., Lehrner, A., Provençal, N., Wiechmann, T., Klengel, T., Makotkine, I., Binder, E.B., Yehuda, R., 2020. Intergenerational effects of maternal holocaust exposure on FKBP5 methylation. Am. J. Psychiatr. 177, 744–753. https://doi.org/10.1176/appi.ajp.2019.19060618.

Binder, E.B., 2009. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology 34, 186–195. https://doi.org/10.1016/j.psyneuen.2009.05.021.

Borçoi, A.R., Mendes, S.O., Gasparini dos Santos, J., Mota de Oliveira, M., Moreno, I.A. A., Freitas, F.V., Pinheiro, J.A., Arpini, J.K., Cunha, E.R., Archanjo, A.B., Evangelista Monteiro de Assis, A.L., Sorroche, B.P., Rebolho Batista Arantes, L.M., Borloti, E., Álvares-da-Silva, A.M., 2020. Risk factors for depression in adults: NR3C1 DNA methylation and lifestyle association. J. Psychiatr. Res. 121, 24–30. https://doi.org/10.1016/j.jpsychires.2019.10.011.

Bowers, M.E., Yehuda, R., 2015. In: Intergenerational Transmission of Stress in Humans, 41, pp. 232–244. https://doi.org/10.1038/npp.2015.247.

Buschdorf, J.P., Meaney, M.J., 2016. Epigenetics/programming in the HPA axis. Compr. Physiol. 6, 87–110. https://doi.org/10.1002/cphy.c140027.

Bustamante, A.C., Aiello, A.E., Galea, S., Ratanatharathorn, A., Noronha, C., Wildman, D. E., Uddin, M., 2016. Glucocorticoid receptor DNA methylation, childhood maltreatment and major depression. J. Affect. Disord. 206, 181–188. https://doi.org/10.1016/j.jad.2016.07.038.

Bustamante, A.C., Aiello, A.E., Guffanti, G., Galea, S., Wildman, D.E., Uddin, M., 2018. FKBP5 DNA methylation does not mediate the association between childhood maltreatment and depression symptom severity in the Detroit neighborhood health study. J. Psychiatr. Res. 96, 39–48. https://doi.org/10.1016/j.jpsychires.2017.09.016.

Cattaneo, A., Riva, M.A., 2016. Stress-induced mechanisms in mental illness: a role for glucocorticoid signalling. J. Steroid Biochem. Mol. Biol. https://doi.org/10.1016/j.jsbmb.2015.07.021.

Cattaneo, A., Riva, M.A., 2015. Stress-induced mechanisms in mental illness: a role for glucocorticoid signalling. J. Steroid Biochem. Mol. Biol. 160, 169–174. https://doi.org/10.1016/j.jsbmb.2015.07.021.

Chen, D., Meng, L., Pei, F., Zheng, Y., Leng, J., 2017. A review of DNA methylation in depression. J. Clin. Neurosci. 43, 39–46. https://doi.org/10.1016/j.jocn.2017.05.022.

Chiarella, J., Schumann, L., Pomares, F.B., Frodl, T., Tozzi, L., Nemoda, Z., Yu, P., Szyf, M., Khalid-Khan, S., Booij, L., 2020. DNA methylation differences in stress-related genes, functional connectivity and gray matter volume in depressed and

healthy adolescents. J. Affect. Disord. 271, 160–168. https://doi.org/10.1016/j.jad.2020.03.062.
Chiarella, J., Tremblay, R.E., Szyf, M., Provencal, N., Booij, L., 2015. Impact of early environment on children's mental health: lessons from DNA methylation studies with monozygotic twins. Twin Res. Hum. Genet. 18, 1–12. https://doi.org/10.1093/aje/kwv204.
Conradt, E., Lester, B.M., Appleton, A.A., Armstrong, D.A., Marsit, C.J., 2013. The roles of DNA methylation of NR3C1 and 11β-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. Epigenetics 8, 1321–1329. https://doi.org/10.4161/epi.26634.
Crespi, B.J., 2020. Evolutionary and genetic insights for clinical psychology. Clin. Psychol. Rev. 78, 101857 https://doi.org/10.1016/j.cpr.2020.101857.
Criado-Marrero, M., Rein, T., Binder, E.B., Porter, J.T., Koren, J., Blair, L.J., 2018. Hsp90 and FKBP51: complex regulators of psychiatric diseases. Philos.Trans.R.Soc.B: Biol. Sci. 373, 1–9. https://doi.org/10.1098/rstb.2016.0532.
Daskalakis, N.P., Yehuda, R., 2014. Site-specific methylation changes in the glucocorticoid receptor exon 1F promoter in relation to life adversity: systematic review of contributing factors. Front. Neurosci. 8, 1–8. https://doi.org/10.3389/fnins.2014.00369.
Del-Ben, C.M., Vilela, J.A.A., Crippa, J.A.de S., Hallak, J.E.C., Labate, C.M., Zuardi, A.W., 2001. Confiabilidade da "Entrevista Clínica Estruturada para o DSM-IV - Versão Clínica" traduzida para o português. Rev. Bras. Psiquiatr. 23, 156–159. https://doi.org/10.1590/S1516-44462001000300008.
di Sante, J., Ismaylova, E., Nemoda, Z., Gouin, J.P., Yu, W.J., Caldwell, W., Vitaro, F., Szyf, M., Tremblay, R.E., Booij, L., 2018. Peripheral DNA methylation of HPA axis-related genes in humans: cross-tissue convergence, two-year stability and behavioural and neural correlates. Psychoneuroendocrinology 97, 196–205. https://doi.org/10.1016/j.psyneuen.2018.07.019.
Duis, J., Cox, O.H., Ji, Y., Seifuddin, F., Lee, R.S., Wang, X., 2018. Effect of genotype and maternal affective disorder on intronic methylation of FK506 binding protein 5 in cord blood DNA. Front. Genet. 9, 1–12. https://doi.org/10.3389/fgene.2018.00648.
Efstathopoulos, P., Andersson, F., Melas, P.A., Yang, L.L., Villaescusa, J.C., Ruegg, J., Ekström, T.J., Forsell, Y., Galanti, M.R., Lavebratt, C., 2018. NR3C1 hypermethylation in depressed and bullied adolescents. Transl. Psychiatry 8. https://doi.org/10.1038/s41398-018-0169-8.
Erickson, N., Julian, M., Muzik, M., 2019. Perinatal depression, PTSD, and trauma: impact on mother–infant attachment and interventions to mitigate the transmission of risk. Int.Rev.Psychiatry 31, 245–263. https://doi.org/10.1080/09540261.2018.1563529.
Evans, J.a, 2007. Diaphragmatic defects and limb deficiencies - taking sides. Am. J. Med. Genet. A 143A, 2106–2112. https://doi.org/10.1002/ajmg.a.31889.
Farrell, C., Doolin, K., Leary, N.O., Jairaj, C., Roddy, D., Tozzi, L., Morris, D., Harkin, A., Frodl, T., Nemoda, Z., Szyf, M., Booij, L., O'Keane, V., 2018. DNA methylation differences at the glucocorticoid receptor gene in depression are related to functional alterations in hypothalamic-pituitary-adrenal axis activity and to early life emotional abuse. Psych. Res. 265, 341–348. https://doi.org/10.1016/j.psychres.2018.04.064.
First, M.B., Pincus, H.A., 2002. The DSM-IV text revision: rationale and potential impact on clinical practice. Psychiatr. Serv. 53, 288–292. https://doi.org/10.1176/appi.ps.53.3.288.
Fleitlich-Bilyk, B., Goodman, R., 2004. Prevalence of child and adolescent psychiatric disorders in Southeast Brazil. J. Am. Acad. Child Adolesc. Psychiatry 43, 727–734. https://doi.org/10.1097/01.chi.0000120021.14101.ca.
Flint, J., Kendler, K.S., 2014. The genetics of major depression. Cell Press Neuron Rev. 81, 484–503. https://doi.org/10.1016/j.neuron.2014.01.027.
Galbally, M., Watson, S.J., van IJzendoorn, M., Saffery, R., Ryan, J., de Kloet, E.R., Oberlander, T.F., Lappas, M., Lewis, A.J., 2020. The role of glucocorticoid and mineralocorticoid receptor DNA methylation in antenatal depression and infant stress regulation. Psychoneuroendocrinology 115. https://doi.org/10.1016/j.psyneuen.2020.104611.
Gilbert, R., Widom, C.S., Browne, K., Fergusson, D., Webb, E., Janson, S., 2009. Burden and consequences of child maltreatment in high-income countries. Lancet 373, 68–81. https://doi.org/10.1016/S0140-6736(08)61706-7.
Gomes, M.v, Gomes, C.C., Jr, W.P., Ramos, E.S., 2007. In: Methylation Pattern at the KvDMR in a Child With Beckwith – Wiedemann Syndrome Conceived by ICSI, 629, pp. 625–629. https://doi.org/10.1002/ajmg.a.
Goodman, R., Ford, T., Richards, H., Gatward, R., Meltzer, H., 2000. The development and well-being assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J. Child Psychol. Psychiatry 41, 645–655. https://doi.org/10.1111/j.1469-7610.2000.tb02345.x.
Goodman, S.H., Rouse, M.H., Connell, A.M., Broth, M.R., Hall, C.M., Heyward, D., 2011. Maternal depression and child psychopathology: a meta-analytic review. Clin. Child. Fam. Psychol. Rev. https://doi.org/10.1007/s10567-010-0080-1.
Grasso, D.J., Drury, S., Briggs-Gowan, M., Johnson, A., Ford, J., Lapidus, G., Scranton, V., Abreu, C., Covault, J., 2020. Adverse childhood experiences, posttraumatic stress, and FKBP5 methylation patterns in postpartum women and their newborn infants. Psychoneuroendocrinology 114, 104604. https://doi.org/10.1016/j.psyneuen.2020.104604.
Han, K.M., Won, E., Sim, Y., Kang, J., Han, C., Kim, Y.K., Kim, S.H., Joe, S.H., Lee, M.S., Tae, W.S., Ham, B.J., 2017. Influence of FKBP5 polymorphism and DNA methylation on structural changes of the brain in major depressive disorder. Sci. Rep. 7, 1–12. https://doi.org/10.1038/srep42621.
Hoehe, M.R., Morris-Rosendahl, D.J., 2018. The role of genetics and genomics in clinical psychiatry. Clin. Neurosci. 20, 169–178. https://doi.org/10.31887/DCNS.2018.20.3/mhoehe.
Höhne, N., Poidinger, M., Merz, F., Pfister, H., Brückl, T., Zimmermann, P., Uhr, M., Holsboer, F., Ising, M., 2014. FKBP5 genotype-dependent DNA methylation and mRNA regulation after psychosocial stress in remitted depression and healthy controls. Int. J. Neuropsychopharmacol. 18, 1–9. https://doi.org/10.1093/ijnp/pyu087.
Jiang, S., Postovit, L., Cattaneo, A., Binder, E.B., Aitchison, K.J., 2019. Epigenetic modifications in stress response genes associated with childhood trauma. Front. Psychiatry 10, 1–19. https://doi.org/10.3389/fpsyt.2019.00808.
Juruena, M.F., Bocharova, M., Agustini, B., Young, A.H., 2018. Atypical depression and non-atypical depression: is HPA axis function a biomarker? A systematic review. J. Affect. Disord. 233, 45–67. https://doi.org/10.1016/j.jad.2017.09.052.
Kang, C., Shi, J.X., Gong, Y., Wei, J., Zhang, M., Ding, H., Wang, K., Yu, Y., Wang, S., Han, J., 2020. Interaction between FKBP5 polymorphisms and childhood trauma on depressive symptoms in Chinese adolescents: the moderating role of resilience. J. Affect. Disord. 266, 143–150. https://doi.org/10.1016/j.jad.2020.01.051.
Kang, J.I., Kim, T.Y., Choi, J.H., So, H.S., Kim, S.J., 2019. Allele-specific DNA methylation level of FKBP5 is associated with post-traumatic stress disorder. Psychoneuroendocrinology 103, 1–7. https://doi.org/10.1016/j.psyneuen.2018.12.226.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of. Arch. Gen. Psychiatry 62, 593–602. https://doi.org/10.1001/archpsyc.62.6.593.
King, L., Robins, S., Chen, G., Yerko, V., Zhou, Y., Nagy, C., Feeley, N., Gold, I., Hayton, B., Turecki, G., Zelkowitz, P., 2017. Perinatal depression and DNA methylation of oxytocin-related genes: a study of mothers and their children. Horm. Behav. 96, 84–94. https://doi.org/10.1016/j.yhbeh.2017.09.006.
Klengel, T., Binder, E.B., 2013. Allele-specific epigenetic modification: a molecular mechanism for gene-environment interactions in stress-related psychiatric disorders? Epigenomics 5, 109–112. https://doi.org/10.2217/epi.13.11.
Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., Pace, T.W.W., Mercer, K.B., Mayberg, H.S., Bradley, B., Nemeroff, C.B., Holsboer, F., Heim, C.M., Ressler, K.J., Rein, T., Binder, E.B., 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 16, 33–41. https://doi.org/10.1038/nn.3275.
Klinger-König, J., Hertel, J., van der Auwera, S., Frenzel, S., Pfeiffer, L., Waldenberger, M., Golchert, J., Teumer, A., Nauck, M., Homuth, G., Völzke, H., Grabe, H.J., 2019. Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. Neuropsychopharmacology 44, 930–938. https://doi.org/10.1038/s41386-019-0319-6.
Kundakovic, M., Jaric, I., 2017. The epigenetic link between prenatal adverse environments and neurodevelopmental disorders. Genes (Basel) 8. https://doi.org/10.3390/genes8030104.
Kwong, A.S.F., López-López, J.A., Hammerton, G., Manley, D., Timpson, N.J., Leckie, G., Pearson, R.M., 2019. Genetic and environmental risk factors associated with trajectories of depression symptoms from adolescence to young adulthood. JAMA Netw. Open 2, 1–14. https://doi.org/10.1001/jamanetworkopen.2019.6587.
Labonte, B., Yerko, V., Gross, J., Mechawar, N., Meaney, M.J., Szyf, M., Turecki, G., 2012. Differential glucocorticoid receptor exon 1 B, 1 C, and 1 H expression and methylation in suicide completers with a history of childhood abuse. Biol. Psychiatry 72, 41–48. https://doi.org/10.1016/j.biopsych.2012.01.034.
Lane, W.G., Dubowitz, H., 2021. Social determinants of health, personalized medicine, and child maltreatment. Pediatr. Res. 89, 368–376. https://doi.org/10.1038/s41390-020-01290-9.
Lee, K.Y., Jeong, S.H., Kim, S.H., Ahn, Y.M., Kim, Y.S., Jung, H.Y., Bang, Y.W., Joo, E.J., 2014. Genetic role of BDNF Val66Met and 5-HTTLPR polymorphisms on depressive disorder. Psychiatry Investig. 11, 192–199. https://doi.org/10.4306/pi.2014.11.2.192.
LeMoult, J., Humphreys, K.L., Tracy, A., Hoffmeister, J.A., Ip, E., Gotlib, I.H., 2020. Meta-analysis: exposure to early life stress and risk for depression in childhood and adolescence. J. Am. Acad. Child Adolesc. Psychiatry 59, 842–855. https://doi.org/10.1016/j.jaac.2019.10.011.
Liu, P.Z., Nusslock, R., 2017. How stress gets under the skin: early life adversity and glucocorticoid receptor epigenetic regulation. Curr. Genomics 19, 653–664. https://doi.org/10.2174/1389202919666171228164350.
Lowe, R., Gemma, C., Beyan, H., Hawa, M.I., Bazeos, A., David Leslie, R., Montpetit, A., Rakyan, V.K., Ramagopalan, S.v., 2013. Buccals are likely to be a more informative surrogate tissue than blood for epigenome-wide association studies. Epigenetics 8, 445–454. https://doi.org/10.4161/epi.24362.
Matosin, N., Arloth, J., Martinelli, S., Czamara, D., Maitra, M., Halldorsdottir, T., Cruceanu, C., Kaul, D., Gassen, N.C., Hafner, K., Müller, N.S., Worf, K., Rehawi, G., Nagy, C., Scarr, E., Tao, R., Jaffe, A.E., Arzberger, T., Falkai, P., Kleinmann, J.E., Weinberger, D.R., Mechawar, N., Schmitt, A., Dean, B., Turecki, G., Hyde, T.M., Binder, E.B., 2021. Brain Expressed FKBP5 Delineates a Therapeutic Subtype of Severe Mental Illness. https://doi.org/10.1101/2021.01.27.428487 bioRxiv 1, 2021.01.27.428487.
McGowan, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonté, B., Szyf, M., Turecki, G., Meaney, M.J., 2009. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat. Neurosci. 12, 342–348. https://doi.org/10.1038/nn.2270.
McKenna, B.G., Hammen, C., Brennan, P.A., 2021. HPA-axis multilocus genetic profile score moderates the association between maternal prenatal perceived stress and offspring depression in early adulthood. Dev. Psychopathol. 33, 122–134. https://doi.org/10.1017/S0954579419001639.
Mendonça, M.S., Mangiavacchi, P.M., Sousa, P.F.de, Crippa, J.A.S., Mendes, A.v, 2019. Epigenetic variation at the SLC6A4 gene promoter in mother – child pairs with major depressive disorder. J. Affect. Disord. 245, 716–723. https://doi.org/10.1016/j.jad.2018.10.369.

Menke, A., 2019. Is the HPA axis as target for depression outdated, or is there a new hope? Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00101.
Murgatroyd, C., Quinn, J.P., Sharp, H.M., Pickles, A., Hill, J., 2015. Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene. Transl. Psychiatry 5, e560–e565. https://doi.org/10.1038/tp.2014.140.
Na, K.S., Chang, H.S., Won, E., Han, K.M., Choi, S., Tae, W.S., Yoon, H.K., Kim, Y.K., Joe, S.H., Jung, I.K., Lee, M.S., Ham, B.J., 2014. Association between glucocorticoid receptor methylation and hippocampal subfields in major depressive disorder. PLoS One 9, 1–9. https://doi.org/10.1371/journal.pone.0085425.
Nantharat, M., Wanitchanon, T., Amesbutr, M., Tammachote, R., Praphanphoj, V., 2015. Glucocorticoid receptor gene (NR3C1) promoter is hypermethylated in Thai females with major depressive disorder. Genet. Mol. Res. 14, 19071–19079. https://doi.org/10.4238/2015.December.29.15.
Nemoda, Z., Szyf, M., 2017. Epigenetic alterations and prenatal maternal depression. Birth Defects Res. 109, 888–897. https://doi.org/10.1002/bdr2.1081.
Oberlander, T., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., Devlin, A.M., 2008. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 3, 97–106.
Olerup, O., Zetterquist, H., 1992. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens 39, 225–235. https://doi.org/10.1111/j.1399-0039.1992.tb01940.x.
Otte, C., Gold, S.M., Penninx, B.W., Pariante, C.M., Etkin, A., Fava, M., Mohr, D.C., Schatzberg, A.F., 2016. Major depressive disorder. Nat. Rev. Dis. Primers 2, 1–21. https://doi.org/10.1038/nrdp.2016.65.
Palma-Gudiel, H., Córdova-Palomera, A., Leza, J.C., Fañanás, L., 2015. Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: a critical review. Neurosci. Biobehav. Rev. 55, 520–535. https://doi.org/10.1016/j.neubiorev.2015.05.016.
Rachdaoui, N., Sarkar, D.K., 2014. Transgenerational epigenetics and brain disorders. In: International Review of Neurobiology. Academic Press Inc., pp. 51–73. https://doi.org/10.1016/B978-0-12-801311-3.00002-0
Radtke, K.M., Schauer, M., Gunter, H.M., Ruf-Leuschner, M., Sill, J., Meyer, A., Elbert, T., 2015. Epigenetic modifications of the glucocorticoid receptor gene are associated with the vulnerability to psychopathology in childhood maltreatment. Transl. Psychiatry 5, 1–7. https://doi.org/10.1038/tp.2015.63.
Ramo-Fernández, L., Boeck, C., Koenig, A.M., Schury, K., Binder, E.B., Gündel, H., Fegert, J.M., Karabatsiakis, A., Kolassa, I.T., 2019. The effects of childhood maltreatment on epigenetic regulation of stress-response associated genes: an intergenerational approach. Sci. Rep. 9, 1–12. https://doi.org/10.1038/s41598-018-36689-2.
Roy, B., Shleton, R.C., Dwivedi, Y., 2017. DNA methylation and expression of stress related genes in PBMC of MDD patients with and without serious suicidal ideation. Physiol. Behav. 89, 115–124. https://doi.org/10.1016/j.jpsychires.2017.02.005.DNA.
Saito, T., Shinozaki, G., Koga, M., Tanichi, M., Takeshita, S., Nakagawa, R., Nagamine, M., Cho, H.R., Morimoto, Y., Kobayashi, Y., Yoshino, A., Toda, H., 2020. Effect of interaction between a specific subtype of child abuse and the FKBP5 rs1360780 SNP on DNA methylation among patients with bipolar disorder. J. Affect. Disord. 272, 417–422. https://doi.org/10.1016/j.jad.2020.03.120.
Sawyer, K.M., Zunszain, P.A., Dazzan, P., Pariante, C.M., 2019. Intergenerational transmission of depression: clinical observations and molecular mechanisms. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0265-4.
Serpeloni, F., Radtke, K.M., Hecker, T., Sill, J., Vukojevic, V., de Assis, S.G., Schauer, M., Elbert, T., Nätt, D., 2019. Does prenatal stress shape postnatal resilience? – an epigenome-wide study on violence and mental health in humans. Front. Genet. 10 https://doi.org/10.3389/fgene.2019.00269.
Silva, R.C., Maffioletti, E., Gennarelli, M., Baune, B.T., Minelli, A., 2021. Biological correlates of early life stressful events in major depressive disorder. Psychoneuroendocrinology 125, 105103. https://doi.org/10.1016/j.psyneuen.2020.105103.
Smith, A.K., Kilaru, V., Klengel, T., Merce, K.B., Bradley, B., Conneely, K.N., Ressler, K.J., Binder, E.B., 2015. DNA extracted from saliva for methylation studies of psychiatric traits: evidence tissue specificity and relatedness to brain. Am. J. Med. Genet. B Neuropsychiatr. Genet. 13, 36–44. https://doi.org/10.1158/1541-7786.MCR-15-0224.Loss.
Spitzer, R.L., Kroenke, K., Williams, J.B.W., 1999. Validation and utility of a self-report version of PRIME-MD. J. Am. Med. Assoc. 282, 1737–1744. https://doi.org/10.1001/jama.282.18.1737.
Sullivan, P.F., Geschwind, D.H., 2019. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. HHS Public Access 177, 162–183. https://doi.org/10.1016/j.cell.2019.01.015.Defining.
Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatr. https://doi.org/10.1176/appi.ajp.157.10.1552.
Thapar, A., Riglin, L., 2020. The importance of a developmental perspective in psychiatry: what do recent genetic-epidemiological findings show? Mol. Psychiatry 25, 1631–1639. https://doi.org/10.1038/s41380-020-0648-1.
Tian, H., He, Y., Xue, Y., Gao, Y.Q., 2022. Expression regulation of genes is linked to their CpG density distributions around transcription start sites. Life Sci. Alliance 5. https://doi.org/10.26508/lsa.202101302.
Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., Pomares, F.B., Chiarella, J., O'Keane, V., Frodl, T., 2018a. Epigenetic changes of FKBP5 as a link connecting genetic and environmental risk factors with structural and functional brain changes in major depression. Neuropsychopharmacology 43, 1138–1145. https://doi.org/10.1038/npp.2017.290.
Tozzi, L., Farrell, C., Booij, L., Doolin, K., Nemoda, Z., Szyf, M., Pomares, F.B., Chiarella, J., O'Keane, V., Frodl, T., 2018b. Epigenetic changes of FKBP5 as a link connecting genetic and environmental risk factors with structural and functional brain changes in major depression. Neuropsychopharmacology 43, 1138–1145. https://doi.org/10.1038/npp.2017.290.
Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., el Hage, W., Surget, A., Belzung, C., Camus, V., 2021. Neuroinflammation and depression: a review. Eur. J. Neurosci. 53, 151–171. https://doi.org/10.1111/ejn.14720.
Tyrka, A.R., Parade, S.H., Welch, E.S., Ridout, K.K., Price, L.H., Marsit, C., Philip, N.S., Carpenter, L.L., 2016. Methylation of the leukocyte glucocorticoid receptor gene promoter in adults: associations with early adversity and depressive, anxiety and substance-use disorders. Transl. Psychiatry 6. https://doi.org/10.1038/tp.2016.112.
Tyrka, A.R., Ridout, K.K., Parade, S.H., Paquette, A., Marsit, C.J., Seifer, R., 2015. Childhood maltreatment and methylation of FK506 binding protein 5 gene (FKBP5). Dev. Psychopathol. 27, 1637–1645. https://doi.org/10.1017/S0954579415000991.
Vukojevic, V., Kolassa, I.T., Fastenrath, M., Gschwind, L., Spalek, K., Milnik, A., Heck, A., Vogler, C., Wilker, S., Demougin, P., Peter, F., Atucha, E., Stetak, A., Roozendaal, B., Elbert, T., Papassotiropoulos, A., de Quervain, J.F.D., 2014. Epigenetic modification of the glucocorticoid receptor gene is linked to traumatic memory and post-traumatic stress disorder risk in genocide survivors. J. Neurosci. 34, 10274–10284. https://doi.org/10.1523/JNEUROSCI.1526-14.2014.
Weaver, I.C.G., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854. https://doi.org/10.1038/nn1276.
Weaver, I.C.G., Meaney, M.J., Szyf, M., 2006. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proc. Natl. Acad. Sci. U. S. A. 103, 3480–3485. https://doi.org/10.1073/pnas.0507526103.
Williams, J.B.W., Gibbon, M., First, M.B., Spitzer, R.L., Davies, M., Borus, J., Kane, J., Howes, M.J., Pope, H.J., Rounsaville, B., Wittchen, H.-U., 1992. The structured clinical interview for DSM-III-R (SCID) reliability description of sites. Arch. Gen. Psychiatry 49, 630–636. https://doi.org/10.1001/archpsyc.1992.01820080038006.
World Health Organization, 2016. In: Media Centre: Depression. Depression Fact Sheet, pp. 4–7.
Yehuda, R., Daskalakis, N.P., Lehrner, A., et al., 2014. Influences of maternal and paternal PTSD on epigenetic gene in holocaust survivor offspring. Am. J. Psychiatr. 171, 872–880. https://doi.org/10.1176/appi.ajp.2014.13121571.Influences.
Yehuda, R., Flory, J.D., Bierer, L.M., Henn-Haase, C., Lehrner, A., Desarnaud, F., Makotkine, I., Daskalakis, N.P., Marmar, C.R., Meaney, M.J., 2015. Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans with posttraumatic stress disorder. Biol. Psychiatry 77, 356–364. https://doi.org/10.1016/j.biopsych.2014.02.006.
Zannas, A.S., Wiechmann, T., Gassen, N.C., Binder, E.B., 2016. Gene-stress-epigenetic regulation of FKBP5: clinical and translational implications. Neuropsychopharmacology 41, 261–274. https://doi.org/10.1038/npp.2015.235.
Zhang, T.Y., Labonté, B., Wen, X.L., Turecki, G., Meaney, M.J., 2013. Epigenetic mechanisms for the early environmental regulation of hippocampal glucocorticoid receptor gene expression in rodents and humans. Neuropsychopharmacology 38, 111–123. https://doi.org/10.1038/npp.2012.149.
Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Binder, E.B., Uhr, M., Lieb, R., Moffitt, T.E., Caspi, A., Holsboer, F., Ising, M., 2011. Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. Am. J. Psychiatr. 168, 1107–1116. https://doi.org/10.1176/appi.ajp.2011.10111577.