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The role of FKBP5 in mood disorders: Action of FKBP5 on steroid hormone receptors leads to questions about its evolutionary importance

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Abstract

Research on the *FKBP5* gene and FKBP51 protein has more than doubled since the discovery that polymorphisms in this gene could alter treatment outcomes and depressive behavior in humans. This coincided with other data suggesting that the stress hormone axis contributes to the development of numerous mental illnesses. As a result, FKBP51 now lies at the heart of the research of many stress related psychiatric disorders, which has led to advances in the understanding of this protein and its role in humans and in animal models. Specifically, *FKBP5*–/– mice and a naturally existing overexpression of FKBP5 in 3 genera of new world monkeys have helped understand the effects of *FKBP5* *in vivo*. This review will highlight these findings as well as discuss the current evolutionary need for the *FKBP5* gene.

Keywords

FK506-binding protein 51; FKBP5 gene; Heat shock protein 90; glucocorticoid receptor; depression; post-traumatic stress disorder; suicide; polymorphisms; genome-wide association studies; stress; behavior; resilience

Introduction

Mood disorders are characterized by feelings of sadness, frustration, loss, anger, anxiety, fear, or panic that in disease become chronic and interfere with normal life. Research in the last decade has found that dysregulation of steroid hormone receptors can cause mood disorders. The hypothalamus-pituitary-adrenal (HPA) axis, for example, which produces glucocorticoids and releases them into the blood stream, has been linked to depression [1, 2].

Steroid hormones, produced in the periphery by endocrine glands [3], can cross the blood-brain-barrier and bind to steroid hormone receptor complexes that produce changes at the cellular level and global level, such as acting as transcription factors for gene expression upregulation, altering neuronal excitability, and modifying mood and behavior. Steroid hormone receptors are ubiquitously expressed in almost all human tissues including the

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brain, and are especially abundant in the parts of the brain that control mood and emotion: the hypothalamus, hippocampus, amygdala, and prefrontal cortex [1]. As a result, the brain is susceptible to mood disorders generated by aberrant function of steroid hormone receptors [4].

To this end, researchers have looked for genetic and environmental factors that increase the risk of psychiatric disease. Genome wide association studies for single nucleotide polymorphisms (SNPs) have revealed significant associations between allelic variants of the *FKBP5* gene and depression [5, 6], post-traumatic stress disorder (PTSD) [7], bipolar disorder [8], peritraumatic dissociation [9], suicide [10–13], negative personality traits [14], and aggression [15]. An environmental factor found to interact with this gene is stress [16, 17]. The current primary biological role of FKBP51 is thought to be with the protein heterocomplex of steroid hormone receptors within the HPA axis, where it helps regulate receptor sensitivity [18].

Due to the overwhelming evidence that stress and the *FKBP5* gene are involved in psychiatric diseases, studying how this gene works is imperative to understanding the mechanisms of mood disorders and finding therapies.

HPA-axis and stress

A general definition for stress is a disruption of homeostasis due to a real or perceived threat to the well-being of the organism [1, 19]. For example, upon the perception of threat, the amygdala immediately activates the autonomic nervous system and the HPA-axis.

The hypothalamic-pituitary connection provides the brain with endocrine function [20]. This system evolved to allow the brain to turn the production of hormones that are made distally in the periphery off and on. These hormones travel through the blood, cross the blood brain barrier and bind to their specific receptors in distinctive brain areas.

The brain uses multiple hormones to trigger the synthesis of cortisol, which is the most abundant stress hormone. The Hypothalamic neurons synapse at the pituitary where they release corticotropin-releasing hormone (CRH), also known as corticotropin-releasing factor (CRF) [17]. The pituitary will then respond by producing adrenocorticotrophic hormone (ACTH), and releasing it into the blood stream. ACTH will bind to its receptor in the adrenal gland, which is located above the kidneys, and trigger the adrenal cortex to synthesize glucocorticoids, including cortisol, and release them into the blood stream [17].

Glucocorticoids have two main receptors in the brain, the mineralcorticoid receptor (MR) and the glucocorticoid receptor (GR). At low concentrations, the MR is the main active receptor, while at high concentrations the GR is the main active receptor since all MRs are occupied [21, 22].

The MR and GR are cytoplasmic receptors that translocate to the nucleus upon hormone binding [23]. There, they activate as well as suppress transcription of many genes. The system is also self-regulating, such that activation of GR triggers a negative feedback loop that attenuates the axis and consequently stress-hormone production [17]. Thus the rate of

feedback inhibition can have dramatic impact on the length of time that the stress hormone system is active. GR is in virtually every tissue of the body, helping to coordinate the body's response to stress; however the feedback inhibition primarily occurs in the amygdala, hypothalamus, and the pituitary to shut down production. Some systemic functions of GR activation other than those affecting mood, decision-making or memory function, include increased metabolism and inhibition of inflammation [24].

Cellular role and biochemistry of FKBP51 with focus on steroid hormone receptors

FKBP51 (FK506 binding protein 51) is part of the immunophilin family, a superfamily of highly conserved proteins first characterized by their ability to bind to immunosuppressant drugs [25]. The superfamily is divided into two sequence families by the type of immunosuppressant to which it binds. FKBP51 is able to bind to FK506 and rapamycin, two immunosuppressants of fungal origin. In addition to their drug-binding capability, some FK506-binding immunophilins are also protein chaperones, with the related but apparently separate ability to isomerize proline residues [25].

FKBP51 (FK-506 Binding Protein 51kDa, p54, FKBP54) was originally identified as a novel FK-506 binding protein capable of peptidyl-prolyl cis-trans isomerization (PPIase) activity [26]. PPIases, like FKBP51, are able to change the conformation of proline residues, a unique amino acid with the capability of existing in cis and trans conformations [25]. Proline cis-trans transitions are important for proper protein folding [25], yet deletion of the N-terminal PPIase domain (FK1) had little effect on FKBP51's efficacy as a chaperone. Instead, the C-terminus of FKBP51, which includes three highly degenerate 34-amino-acid repeats known as tetratricopeptide repeats (TPRs), has been found to exhibit independent protein-folding activity.

Up until recently, however, FKBP51 was relatively unstudied, particularly because its function in cellular processes was not well known. In fact, it is not understood whether PPIase activity in general is necessary for cell viability. But studies have begun to elucidate its role in the biology of the cell. For example, FKBP51 was recently found to regulate the phosphorylation of the microtubule associating protein tau (MAPT, tau), a protein whose aggregates are a hallmark of Alzheimer's disease [27]. FKBP51, and other immunophilins, have also been found to interact with steroid hormone receptor heterocomplexes, an interaction mediated by the chaperone heat shock protein 90 (Hsp90) [28], [29].

Three hormone receptor complexes that interact with FKBP51 are the glucocorticoid receptor (GR), progesterone receptor (PR), and androgen receptor (AR). Each, are transcriptionally active steroid hormone receptor complexes whose activation leads to a change in the transcription rate of many genes, one of which is *FKBP5*. Paradoxically, FKBP51 also inhibits the activation of GR [30] and PR [31]. These receptors thus have a short negative feedback loop built into their activity, while AR, on the other hand, is positively regulated by FKBP51 [32]. Two questions arise from the effect of FKBP51 on GR, PR and AR. Is PPIase activity necessary? Is binding to Hsp90 necessary?

The exact mechanism of action within the steroid hormone receptor heterocomplex has been difficult to piece together, since the importance of PPIase activity of immunophilins is questionable. One study analyzing the relative importance of the PPIase and TPR domains in squirrel monkey FKBP51 rendered each of the protein domains inactive via site-directed mutagenesis and showed that while only the TPR domain was required for FKBP51 to bind to the GR and PR complex with Hsp90, both PPIase and TPR domains were required for the FKBP51 inhibitory effect on GR to be effective [32]. Other studies, however, showed that PPIase activity is not necessary for its inhibitory action on GR [33] but is necessary for its activating action on AR [34]. All three complexes do require Hsp90 for FKBP51 to have an effect, as Hsp90 was found necessary to be bound to FKBP51 for it to have its inhibitory action on GR [32], PR [31], and its activating action on AR [34]. The data indicate that, perhaps due to structural reasons, the physical presence of FKBP51 may be more important than its PPIase enzymatic activity.

SNPs and FKBP51 mechanism of action

Genome-wide association studies (GWAS) have enabled scientists to look at small changes in DNA and the effects of single base pair variations called single nucleotide polymorphisms (SNPs) on gene expression and function. SNPs in *FKBP5* have been associated with mood disorders and an increased risk for PTSD, suicide, and overt aggressive behavior. One particular SNP in the *FKBP5* gene, rs1360780, was associated with an increased number of depressive episodes [5]. A closer look at the SNP revealed three different polymorphisms possible at the site: TT homozygotes, CT heterozygotes, and CC homozygotes. Association of these SNP variations with episodes of depression and responses to antidepressant treatment showed that individuals with TT homozygosity had more frequent episodes of depression but also a faster recovery from antidepressant therapy. SNP association studies were performed with FKBP51 and other psychiatric disorders, with findings that FKBP51 SNPs are also associated with mood disorders, many of which were formed in conjunction with childhood trauma. Increased risks of developing PTSD [7], suicide [10, 12], and overt aggressive behavior were also associated with certain FKBP51 polymorphisms [15].

Mechanistically, the effect of FKBP5 polymorphisms on mood disorders is elusive. One particular area of study is the HPA axis, as FKBP51 is a known regulator of HPA-axis activity. The HPA-axis has major roles in both PTSD and depression, albeit with opposite phenotypes. Patients with Major Depressive Disorder (MDD) have a hyperactive HPA-axis, where an increased stimulation of adrenal corticotropin hormone (ACTH) and GR desensitization cause high amounts of cortisol to be released and retained in the bloodstream. PTSD patients, on the other hand, have hypersensitive GR and a hypersuppression of cortisol [16]. The SNP rs1360780 is thus of great interest here, as it is associated with increased risks of both PTSD and depression, despite these diseases having different GR sensitivities. For example, the TT genotype may provide mechanistic evidence on how FKBP51 could cause HPA-axis dysregulation, as it was shown that individuals with TT had higher basal levels of FKBP51 and thus very likely a greater inhibition effect on GR activity. However Depressed patients with TT genotypes had greater decreases of ACTH and cortisol levels in response to the DEX/CRH test than depressed patients with CC and TC genotypes. The study did not, however, compare the FKBP51 levels of healthy controls with

the TT genotype versus depressed patients with the same genotype, and so it is unclear if FKBP51 levels are higher due to depression or if all people with the genotype exhibit increased levels of FKBP51. Nevertheless healthy individuals with the TT genotype were shown to lack a normalization of cortisol levels after stress as compared to the CC and CT genotypes; TT individuals had higher cortisol levels for a longer period of time [35]. The data from the healthy controls resembled those having high FKBP51 levels, and the data of the depressed patients resembles those having low FKBP51 levels.

How do we make sense of the fact that people with the same genotype had different GR phenotypes depending on the disease state? It may be that healthy individuals only have high levels of FKBP51 in the short term, but the chronic stress state may increase FKBP51 levels in the long term, which could drive adaptive changes in GR activity. However, if FKBP51 protein levels were elevated in this genotype irrespective of disease state, it may be that another risk factor is interacting with FKBP51 to promote depression. In individuals with this genotype with probable PTSD, baseline cortisol activity was not elevated as compared to healthy controls [36], while it was in depressed patients [5]. Thus it is clear that while genotypes do not consistently affect GR in the same way, the risk for mood disorders is clearly elevated by the rs1360780 SNP. This suggests that factors other than just GR must be responsible for the differential disease phenotypes.

FKBP5 animal models

Studies of FKBP51 in animal models have proven helpful in determining endogenous and stress-response levels of FKBP51 expression in different regions of the brain. A study of *FKBP5* mRNA levels in the murine brain discovered that under basal conditions, the highest levels occurred in the hippocampus [37], especially the dentate gyrus, and the premammillary nucleus, the motor nuclei of the *nervus trigeminus* and the *nervus facialis*. Interestingly, lower levels of *FKBP5* mRNA were found in the amygdala and the hypothalamic paraventricular nucleus (PVN), the latter of which is a part of the HPA axis and a stress response mediator. Stressing the mice, however, showed a marked increase in *FKBP5* mRNA levels in these two regions. Both moderate and short-term stress and strong and long-lasting stress caused *FKBP5* mRNA levels to rise in dose-dependent fashion. Moderate stress was caused through a 4-hour restraint, and a 1-day food deprivation paradigm was used as the long-lasting stressor. Upregulation of *FKBP5* mRNA was observed in the central amygdala, the hypothalamic PVN, and the hippocampus after both conditions, with a stronger response after food deprivation in all regions. Injecting the mice with dexamethasone, a corticosteroid analog and GR agonist, also increased the levels of FKBP51 mRNA, supporting the hypothesis that the stress response and *FKBP5* mRNA levels are linked to the GR.

However, while all three regions showed increased levels of *FKBP5* mRNA, the relative increase differed based on the baseline levels already observed in the mouse brain. The hypothalamic PVN and the central amygdala, which had low endogenous *FKBP5* mRNA levels, had average *FKBP5* mRNA increases of over 600% from baseline, while the hippocampus, which has a relatively high basal level of *FKBP5* mRNA, had average increases of less than 200%. It appears that higher endogenous levels of *FKBP5* mRNA

caused the GR in those particular brain regions to become less responsive to corticosteroid stimulation. In cases of chronic stress, constant high levels of stress could result in potentially long-term elevated corticosteroid levels, and induce high levels of *FKBP5* mRNA expression, in turn causing GR activity to become resistant.

Two additional models have been studied intensively, *FKBP5*^{-/-} mice and new world monkeys. Three genera of new world monkeys have been discovered to have naturally occurring GR resistance due to excess production of FKBP51 [38]. This begs the question of whether this affects the behavior of the monkeys. An induced model of depression in monkeys exist [39], and extreme social stress causes coronary artery disease [40], presumably due to hypercortisolemia, but it is not clear whether it is FKBP5 dependent. However, it does suggest that the hypercortisolemia seen in humans with depression could be aided by a reduction in the levels of FKBP51.

The function of the HPA axis was studied in the *FKBP51*^{-/-} mice. The mice displayed a moderate GR hypersensitivity, as they produced less corticosterone (the main murine glucocorticoid) and recovered faster after dexamethasone (DEX) and stress treatment [41]. The DEX/CRH test was compared between *FKBP51*^{-/-} mice and healthy humans of the rs1360780 SNP. Healthy humans with the TT genotype displayed GR hyposensitivity to dexamethasone while the *FKBP51*^{-/-} mice displayed GR hypersensitivity, showing that reduction in levels of FKBP51 may be a successful therapy for GR insensitivity.

In terms of protein levels and protein expression, *FKBP51*^{-/-} mice exposed to chronic social defeat stress produced equal amounts of CRH mRNA as compared to wildtype before and after stress, although levels did increase after stress [42]. This demonstrated that corticosterone levels were not reduced in the *FKBP51*^{-/-} mice due to the lack of HPA activation, but rather due to the FKBP51-GR negative feedback mechanism that has been characterized so well. It was found, on the other hand, that the lack of FKBP51 alters the levels of GR. In wildtype mice, GR levels decreased during a 1 hr restraint stress experiment, yet in *FKBP51*^{-/-} mice they increased at 15 minutes then went down slightly, but remained significantly higher than wildtype. It is also possible that FKBP51 may actually be regulating the levels of GR, particularly since Hsp90 is intimately linked to proteasomal degradation [43] and Hsp90 is a part of the GR complex.

Surprisingly, general behavior was not changed in 10–16 week old (young) *FKBP51*^{-/-} mice. As a result, changes in behavior after stress were studied. Young *FKBP51*^{-/-} mice showed significantly less time immobile in the forced swim test than wildtype mice after restraint stress [41]. Moreover, FKBP51 is a protein whose expression increases with age [27], and young mice have low basal levels in the hypothalamus and amygdala. It may be that the young mice needed FKBP51 to be expressed after stress to modulate behavior, since basal FKBP51 levels were low. Twenty-two month old mice (old), however, displayed this phenotype in the forced swim test without prior stress [44]. General behavior in the old mice was also unchanged, especially in learning and memory, implying that FKBP51 may have a role limited to the biology of the stress response. But this role may be protective, as stress and its related molecules are known to cause cognitive impairment [45–51].

FKBP51 and neuropsin-mediated effects in the amygdala

Recently, FKBP51 was found to be involved in stress response in the amygdala. FKBP51 was found to be upregulated by NMDA activation and caused anxiety in mice after stress [52]. This effect was dependent on the cleavage of EphB2 by neuropsin, causing EphB2 to disassociate from the NR1 subunit of the NMDA receptor and enhancing NMDA receptor current. Neuropsin is an extracellular serine protease and EphB2 is a receptor tyrosine kinase, and both are heavily expressed in the amygdala and hippocampus, with higher basal expression in the hippocampus, similar to FKBP51. After stress, neuropsin is dramatically upregulated in the amygdala. This data was not shown in the hippocampus; it would be interesting to find out if neuropsin had a similar expression profile to FKBP51 and to see the basal and stress-induced expression of FKBP51 in neuropsin knockout mice. In amygdala neuronal cell cultures, the majority of FKBP51 expression was found to be due to the activity of neuropsin and not by corticosterone, and it may be that FKBP51 has a primary role in stress behavior in a neuropsin dependent mechanism, and that its role with GR is secondary to that. Additionally, despite FKBP51 expression upregulation by NMDA receptor activation, no effects are shown in learning and memory. It may be that a large threshold of NMDA receptor activation is needed to trigger the upregulation of FKBP51, and the large threshold would only be reached during extreme situations like stress, and thus FKBP5 would be activated to promote behavioral signatures of anxiety.

The need of the FKBP51 gene in the brain is unclear, as it seems to be extremely problematic, and its absence does not seem to have negative effects. A posited theory for the development of FKBP51 may be within the fear response. Evolutionary genetics suggest that these genes arose early in development; analysis of phylogenetic relationships among 100 FKBP domains show a clustering pattern that suggests the emergence of the FKBP genes early in eukaryotic evolution [53], and another study suggests that FKBP proteins arose even before the divergence of prokaryotes from eukaryotes [54]. As a result, FKBP51 may have played an important role in the evolution of the stress response. In the past we needed to exhibit a proper response to fear, since the reaction was critical to survival. The problem is, we no longer have the same life or death triggers.

Conclusion

It is clear that FKBP51 is a significant player in the human response to stress. It has a dramatic effect on the biology of steroid hormone receptors, and is upregulated in the amygdala as part of a stress response. SNPs within the FKBP5 gene are associated with mood disorders, but the mechanism of how this happens is not well understood. Surprisingly, the lack of FKBP51 does not appear to have deleterious side effects in mice and its presence causes steroid hormone receptor hypersensitivity. This not only makes FKBP51 an excellent drug target, but it also suggests that *FKBP5* may be genetic baggage that no longer provides a competitive advantage for natural selection. As successful adaptation allows for a species to age, genes like *FKBP5*, which at one point during the evolutionary process were necessary for their survival and propagation, may actually become deleterious to the aging process. Furthermore, societal success no longer follows Darwinian principles. As a result, it may be the role of society to combat these processes; in

the same way that bacteria adapt to antibiotic pressure, society may need to develop ways to suppress or even remove these genetic leftovers.

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
AR	adrogen receptor
CRH/CRF	Corticotropin releasing hormone/factor
FKBP5	Gene name for FKBP51 protein
FKBP51	FK506-binding protein 51
GR	Glucocorticoid receptor
GWAS	Genome-wide association studies
HPA-axis	Hypothalamic-pituitary-adrenal-axis
MDD	Major depressive disorder
MR	Mineralocorticoid receptor
NMDA	N-methyl-D-aspartate
PPIase	Peptidyl-prolyl cis-trans Isomerase activity
PR	Progesterone receptor
PTSD	Post-traumatic stress disorder
PVN	Paraventricular nucleus of the hypothalamus
TPR	Tetratricopeptide repeat

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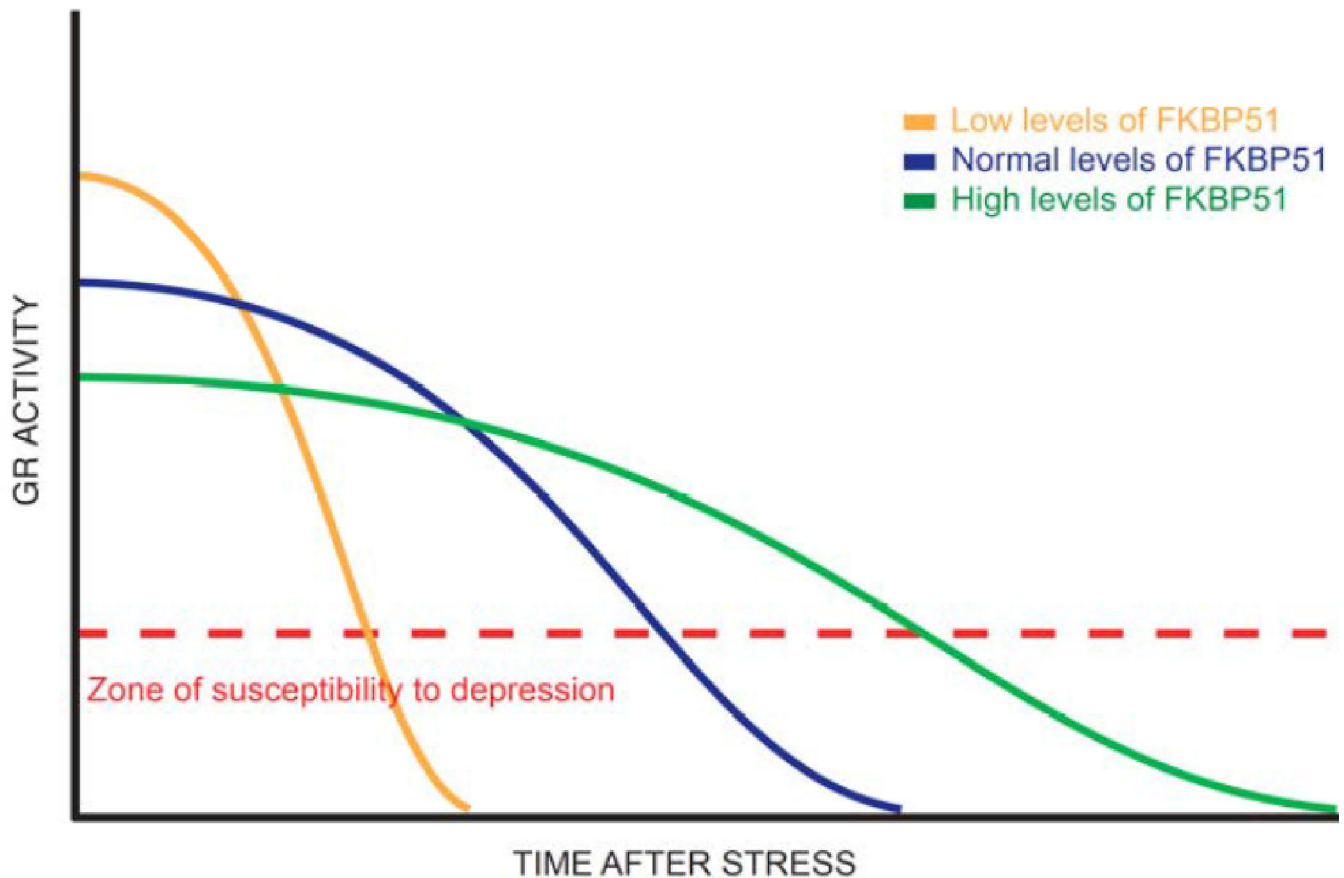


Fig. 1. FKBP5 genotype as a modulator of GR phenotype

Everyone may be vulnerable to mood disorders involving depression following stress. However, the length of time that an individual remains vulnerable can be dramatically affected by FKBP51 levels due to its ability to decrease GR activity. FKBP51 may widen the length of time after stress that a person is susceptible to stress, while individuals with low FKBP51 levels may be in this state for a shorter period of time. While the magnitude of the acute GR response to stress following an insult may be higher in individuals with low FKBP51 levels, the length of time that an individual with high levels of FKBP51 spends in a susceptible state is longer. As a result, SNP's in the FKBP5 gene may increase the likelihood of developing psychiatric disorders by altering the levels of FKBP51. This in turn changes the responsiveness of the GR, whose balance appears to be critical for normal function. Thus, in MDD, chronic stress may have a greater effect on those individuals with too much FKBP51.