SOLISCH, Sven, BOCZAR, Agata, DRYJA, Patryk, SOLISCH, Bianka and JARMOŁOWICZ, Jakub. FKBP5 gene - current knowledge, new approach and possible biomarker function: a narrative review. Journal of Education, Health and Sport. 2024;75:56217. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.75.56217
https://apcz.umk.pl/JEHS/article/view/56217

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.11.2024. Revised: 20.11.2024. Accepted: 05.12.2024. Published: 05.12.2024.

FKBP5 gene - current knowledge, new approach and possible biomarker function: a narrative review

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Abstract

Introduction

Over the past few decades, the level of interest in the use of complex molecular pathways in the course of various diseases has increased significantly. Despite the rapid development of medicine, the potential and role of FKBP5 as a biomarker has not yet been fully characterized, although current studies are promising.

Material and methods of research: The literature included in the PubMed databases is searched through the words such as *FKBP5* gene, stress-related disorders, biomarkers.

Aim of the study

The aim of this paper is to provide a comprehensive review of the current state of knowledge regarding the characteristics, current use in diagnosis or treatment of various diseases and to determine the possible function of the biomarker for the *FKBP5* gene.

Description of the state of knowledge

FKBP5 participates in the regulation of the HPA axis and thus in the stress response. This translates into the course of many diseases, but the exact mechanism of action has not been unequivocally confirmed in previous studies on all conditions involving FKBP5.

Conclusions

In general, FKBP5 has a huge diagnostic and therapeutic potential in many disease entities. FKBP5 may act as a biomarker. However, further studies are needed to clarify the current observations and to search for further implications in the pathogenesis or diagnostic and therapeutic procedures in the course of various diseases.

Key words: *FKBP5* gene, stress-related disorders, biomarkers, HPA axis, long-term stress

1. Introduction

The *FKBP5* gene encodes the FK506 binding protein (FKBP5), which is involved in the regulation of the HPA axis and the chronic stress response. The associations of increased or decreased *FKBP5* expression in the course of numerous disease manifestations in our body have been demonstrated. A deeper understanding of the mechanisms responsible for the

molecular activity of FKBP5 in the course of various metabolic pathways and not only has allowed the discovery of many diagnostic and therapeutic possibilities involving it. Over the past few decades, the perception of the use of FKBP5 only in the course of neuropsychiatric or endocrine diseases has changed. Associations have also been noted with oncological or cardiological disease entities. In this review, we will focus on the characteristics and possibilities of diagnostic and therapeutic use of FKBP5 in diseases associated with it that have been known for years, as well as in the course of newly detected diseases. In addition, we will present the effect of some drugs on the functioning of molecular pathways involving FKBP5. We also provide insight into the possible use of FKBP5 as a biomarker of various pathological processes occurring in our body.

2. Materials and methods

A comprehensive literature search was conducted using PubMed electronic databases. The search strategy utilized a combination of keywords related to *FKBP5* gene, stress-related disorders and biomarkers. The search was limited to articles published in English from inception to 2024. Additional studies were identified through manual searches of reference lists of relevant articles.

3. Description of the state of knowledge

Activation of the HPA axis leads to the production of cortisol in response to stress stimuli. One of the mediators involved in this metabolic pathway is FKBP5, the increased level of which results in the disruption of the HPA axis regulation. It is well known that a chronic stress reaction is associated with the pathogenesis of many diseases, especially neuropsychiatric disorders. The resources of medical databases indicate that the potential for using FKBP5 is significant. Its role in the pathogenesis of diseases from various fields of medicine has been successfully identified and its potential function as a biomarker has been indicated.

4. Characterization of the basic properties and use of the *FKBP5* gene

Intracellular FK506 binding protein (FKBP5) is encoded by the *FKBP5* gene (consisting of 13 exons and 12 introns), which is located in the human genome on chromosome 6p21 (1-4). The function of this protein is to regulate the sensitivity of the glucocorticoid receptor (GR) to cortisol and to cooperate with heat shock protein 90 (hsp90) as a chaperone (1, 5). Due to its properties, FKBP5 is classified as immunophiline, which indicates the ability to bind to immunosuppressive drugs (6). From a biochemical point of view, three main domains can be

distinguished within the 457-amino acid FKBP5: a peptidyl-prolyl cis-trans isomerase (PPIase) FKBP-Type 1 domain, a PPIase FKBP-like domain, and a tetratricopeptide repeat (TPR) domain (7). Due to its properties, FKBP5 in cooperation with hsp90 is involved in many molecular processes, including the regulation of stress responses via adrenal hormones (8). Namely, after binding to the glucocorticoid receptor, a complex is formed that is characterized by reduced affinity for cortisol and, consequently, weakened nuclear translocation (9, 10). This in turn causes a decrease in the sensitivity of the glucocorticoid receptor to cortisol and prolongs the body's response to stress in the mechanism of ineffective negative feedback loop of the HPA (hypothalamus–pituitary–adrenal) axis (5).

Although the main role of FKBP5 is believed to be in the regulation of steroid hormone receptors described above, in recent years there has been growing interest in the potential influence of FKBP5 in the pathogenesis or diagnosis, or even as a target for drugs in conditions such as post-traumatic stress disorder (PTSD), depression, Alzheimer's disease (AD), trigeminal neuralgia, alcoholic liver disease, type 2 diabetes mellitus, thyroid cancer and female genital cancer (11-23).

5. The influence of FKBP5 on neuropsychiatric diseases

Neuropsychiatric disorders are an important element of modern medicine. In the 21st century, due to significant environmental and behavioral changes as well as the extension of life expectancy, the number of cases of depression, PTSD and AD is increasing year by year (24). Alzheimer's disease (AD) is the most common neurodegenerative disease entity classified as senile dementia, because the initial symptoms usually manifest after the age of 65 and are related to age and gender, as women are much more often affected (25). Gender differences in incidence are probably due to the longer lifespan of women, the concentration of certain sex hormones and the level and time of *FKBP5* expression (26). Namely, with age and progression of Alzheimer's disease, the level of *FKBP5* expression increases significantly and has an inhibitory effect on tau protein clearance (27). According to the latest studies, FKBP5 increases earlier in men than in women - respectively in middle age in men and in old age in women (14). This discovery introduces new possibilities for the proper understanding and diagnosis of Alzheimer's disease according to the patient's gender (28). The above observations allow us to consider FKBP5 as a biomarker of AD in the near future (14).

Another disease entity associated with FKBP5 is post-traumatic stress disorder (PTSD). This is a mental disorder that is a kind of response of the body to an extremely stressful event that exceeds the person's ability to cope with it and adapt (15). As mentioned above, FKBP5 directly

affects the regulation of the HPA axis and the duration of the stress response in the body. Hence, the connections between excessive expression of *FKBP5* and the development of PTSD seem to be natural (29). Unfortunately, research results remain ambiguous - initially, no connection was found between the level of *FKBP5* expression and the predisposition to PTSD (30). However, the development of advanced molecular techniques in recent years has allowed for a more detailed examination of the possible correlation. Other researchers have found interesting connections between FKBP5 and PTSD (15). First, evidence was found for an epigenetic mechanism through the process of DNA demethylation of specific regions, in which long-term exposure to cortisol resulting from an impaired negative feedback loop of the HPA axis in the course of increased *FKBP5* expression may increase genetic predisposition to stronger glucocorticoid receptor transcription (31). The above observation therefore implies a potential role of FKBP5 in the development of a pathological response to stressful situations, including the occurrence of PTSD (15). Moreover, it was possible to prove that there is a link between specific FKBP5 variants and the occurrence of stress in early life resulting in the development of PTSD or depression later on (32).

In turn, depression is a mental illness from the group of affective disorders characterized by generally low mood (18). It can already be described as a global problem and forecasts for the coming decades indicate that depression will be the most common disease in the world (33, 34). Among the pathomechanisms responsible for the occurrence of the disease and clinical manifestations, there are many factors, including genetic, biological, psychosocial and environmental dimensions (35-38). One of the most important seems to be the fact that about 60% of people suffering from depression show abnormal functioning of the HPA axis (39, 40). Moreover, a significant role of dysregulation of the HPA axis in the pathogenesis as well as the response to the applied treatment of depression has been proven (41). As is known, the changes described above are caused by improper functioning of FKBP5, which has been associated with depression in many studies (42-45). Moreover, the *FKBP5* polymorphism not only affects the manifestation of the disease itself, but also allows for prediction of the response of a given organism to the applied antidepressant treatment (46, 47). According to the latest reports from the world of science, it is the demethylation of *FKBP5* described above, in combination with trauma experienced in childhood, that leads to dysregulation of the HPA axis and is associated with the manifestation of severe depression in adulthood (48). All the above examples are an important element in the best possible knowledge and understanding of the mechanisms leading to the occurrence and treatment of specific neuropsychiatric disorders.

6. Drugs used in neuropsychiatric disorders in relation to FKBP5

An inseparable element of stress reactions related to the HPA axis is FKBP5 and its impact on the glucocorticosteride receptor (49, 50). We already know that the DNA methylation process increases the response to the treatment of neuropsychiatric diseases (51). In addition, the results of the latest research confirm the influence of many drugs and substances on the level of FKBP5 by methylation of the appropriate gene (52, 53). Thanks to these observations, the role of FKBP5 as a potential therapeutic goal in the course of neuropsychiatric diseases associated with significant stress dependent on the HPA axis seems to be obvious (54). Below are the main groups of drugs that can inhibit FKBP5 with the best effect.

6.1. Ligands to FKBP5

Drugs that can act as a ligand for FKBP5, i.e. tacrolimus and rapamycin are the first to come. Due to the immunosuppressive properties of these drugs and the ability to act as a ligand, FKBP5 belongs to the immunophilin family. These drugs inhibit mTOR activity and thus reduce cell proliferation. It was found that chronic use of rapamycin did not affect the level of FKBP5 while acute administration to its mice experiencing mental disorders increased the level of FKBP5 (55, 56). Therefore, it is necessary to study the potential use of them in humans.

6.2. Serotonin reuptake inhibitors (SSRIs)

Serotonin reuptake inhibitors (SSRIs) are one of the main antidepressants used among people. Their impact has been demonstrated on reduction in the activity of CRH releasing neurons, and thus limiting the stress reaction depending on the HPA axis (57). In the research on the mice, the beneficial effect of fluoxetine was shown to reduce *FKBP5* expression in certain regions of the brain, in addition, pharmacogenetic connections between fluoxetine and FKBP5 were proved (58, 59). Other studies focused on citalopram as another SSRIs - depending on the type of polymorphism of *FKBP5*, various results were obtained, which is why its role seems to be smaller than the aforementioned fluoxetine and requires more accurate considerations (60, 61). Unfortunately, the results of those studies are not clear, so there is a need for further actions to clearly confirm the correlation between SSRIs and the beneficial effect on the HPA axis.

6.3. Serotnin and noradrenaline reuptake inhibitors (SNRIs)

Duloxetine belongs to the group of serotnin and noradrenaline reuptake inhibitors (SNRIs), which is another group of antidepressant drugs (62). Its action, however, remains ambiguous because it caused an increase in the level of *FKBP5* mRNA among healthy rats while reducing the level of *FKBP5* mRNA in rats showing mental disorders. These discoveries probably prove a key issue, namely that animals subjected to chronic stress show the ability to change the regulation of the activity of the FKBP5-GR complex (63).

6.4. Antipsychotics

Another group of drugs used in psychiatry, which may affect FKBP5, are antipsychotics (e.g. chlorpromazine or clozapine) used to treat schizophrenia. Many studies have shown that patients experiencing psychosis or schizophrenia can show a flattened HPA axis response to stress (64). Studies conducted with these drugs showed a relationship with methylation levels and thus also *FKBP5* expression (65).

6.5. Glucocorticosterides

Unobvious drugs that have a positive way to adjust the HPA axis in conjunction with FKBP5 are dexamethason and prednisolone. As glucocorticosteride analogues, the above substances lead to an increase in FKBP5 with a subsequent decrease in the expression of the GR. Thanks to this, they potentially affect mood disorders and act antipsychotically (66-68). However, these considerations require further research (17).

7. The influence of FKBP5 on other than neuropsychiatric diseases

Considering the properties and potential therapeutic possibilities of FKBP5 only in relation to neuropsychiatric diseases would be a grave mistake (23). After all, dysregulation of the HPA axis, and consequently, abnormal stress response, is also observed in other fields of medicine, such as endocrinology or oncology (19, 20, 22).

Endocrinology is a branch of medicine that deals with the influence of hormones on the functioning of the body in health and disease. One of these hormones is cortisol, produced mainly in the adrenal cortex. Cortisol is the final link in the stress response initiated in the central nervous system. When its excess occurs, we are dealing with a disease entity called Cushing's syndrome (69). First, it must be determined whether Cushing's syndrome is endogenous (too high concentration of our own cortisol) or exogenous (external supply of cortisol or its analogues, usually in the course of glucocorticosteroid treatment). Excessive cortisol production can come from two sources. If it occurs in response to excessively high levels of adrenocorticotropic hormone (ACTH), we are dealing with ACTH-dependent Cushing's syndrome and it is usually associated with the presence of a functioning pituitary adenoma (then we talk about Cushing's disease). However, if the increase in cortisol level is not accompanied by a simultaneous increase in ACTH, ACTH-independent Cushing's syndrome is diagnosed, which is usually caused by hyperplastic disease of the adrenal glands (70). Unfortunately, excess cortisol and its derivatives are not only an aesthetic problem (widened, reddened face, characteristic silhouette or stretch marks), but above all cardiovascular complications and deterioration of the quality of life or even a significant

increase in mortality (71-73). All this indicates that Cushing's syndrome is a significant problem that we have to deal with. Therefore, many researchers are trying to find possibilities of earlier diagnosis or individual predispositions to Cushing's syndrome (19). It was established that FKBP5, due to its mechanism of action through blocking the proper functioning of GR, is a promising research target directly correlating with the manifestation of Cushing's syndrome (9, 74). It has been shown that the level of *FKBP5* expression increases in response to long-term elevated levels of glucocorticosteroid hormones (75). Therefore, FKBP5 has been recognized as a non-hormonal biomarker of Cushing's syndrome (19).

A disease on the border of endocrinology and oncology is papillary thyroid cancer (PTC). According to the latest studies, significant expression of *FKBP5* in the cells of this tumor has been demonstrated (20). Furthermore, further analysis showed that increased expression of *FKBP5* was associated with a worse clinical prognosis due to the fact of inhibiting apoptosis and stimulating the proliferation of PTC cells. Interestingly, studies on mice confirmed the correlation between the slowing down of PTC growth and the reduced level of *FKBP5* expression (76). The above observations give hope that FKBP5 may be a useful tool used in the diagnosis and prognosis of PTC. Moreover, numerous studies have pointed to the participation of FKBP5 in the pathogenesis of other cancers, including prostate cancer, gastric cancer, and clear cell renal cancer (77-79). Similar conclusions can also be drawn from studies on gynecological cancers - recently, the participation of FKBP5 in the development of cervical cancer has also been confirmed, where FKBP5 may potentially act as a biomarker (22). This is related to the immunophilin nature of FKBP5 and its participation in many signaling pathways, including the evasion of the immune response by tumor cells (80, 81).

Cancer is one of the main problems that modern medicine has to deal with, but we cannot forget about other problems, such as type 2 diabetes mellitus (T2DM). It is one of the most common diseases in modern societies and consists of excessively high blood glucose levels in response to insulin resistance in the tissues, which leads to a relative insulin deficiency (82). Moreover, the clinical implications of this biochemical condition include complications such as cardiovascular events, stroke, polyneuropathy, limb amputations or even premature death (83). The role of FKBP5 and related abnormalities in the dysregulation of the HPA axis and DNA methylation in the development of T2DM is increasingly emphasized (84-86). Two potential regulatory mechanisms are suspected in which FKBP5 is associated with T2DM - this is via AKt and peroxisome proliferator-activated receptor γ (PPARγ) (23). It has been found that high levels of FKBP5 affect the reduction of AKt phosphorylation, which directly translates into reduced insulin efficacy (87, 88). In turn, the action via PPARγ has not yet been thoroughly

studied. It has been noted that FKBP5 increases PPARγ activity, which stimulates adipocyte proliferation and differentiation and the associated increase in lipogenic gene expression (89, 90). Moreover, it has been shown that it is the reduction of FKBP5 levels that is mainly responsible for increased glucose tolerance (91). The above considerations demonstrate the enormous potential of using FKBP5 as a bridge to understand pathogenesis through the regulation of specific signaling pathways for diseases of civilization significance, such as T2DM or the aforementioned cancers (92).

8. FKBP5 as a biomarker

The development of molecular technologies in biology and immunohistochemistry forces modern medicine to constantly search for new diagnostic and therapeutic possibilities. One of the most important challenges seems to be linking specific substances with the prediction or prognosis of specific diseases, i.e. finding biomarkers. As mentioned above, in diseases such as AD, Cushing's syndrome or cervical cancer, a possible biomarker function is attributed to FKBP5 (14, 19, 22). However, the potential of this protein is much greater, as indicated by numerous studies. Although it was not possible to clearly link increased *FKBP5* expression with Cushing's disease, a significant increase in the course of pituitary adenomas in general has been demonstrated (93). This discovery, combined with the establishment of FKBP5 as a biomarker of increased cortisol levels, leaves much room for further research (94). Further assumptions about the usefulness of FKBP5 in predicting the course of the disease have been made in relation to breast cancer. Researchers have found a correlation between high levels of *FKBP5* expression and a high risk of breast cancer metastasis, which is associated with a poorer prognosis (95). Furthermore, recent reports indicate that for a specific type of breast cancer, the luminal B subtype of breast cancer (LBBC), the level of *FKBP5* expression affecting the properties of CD8+ cytotoxic lymphocytes is a promising prognostic indicator (96). As it turns out, this topic is of interest not only to oncologists or endocrinologists, but even to cardiologists dealing with heart failure (97). Recently, the results of studies suggesting the role of FKBP5 as a biomarker in patients with dilated cardiomyopathy (DCM) treated with left ventricular assist device support (LVAD) have been very promising. It is believed that this will lead to more effective therapeutic management in this group of patients (98). As mentioned at the beginning of this work, FKBP5 is directly involved in the regulation of the HPA axis and thus in stress reactions, so it seems natural to look for correlations between the level of expression of this protein and the occurrence of neuropsychiatric disorders (99). Further studies bring us closer to the practical use of FKBP5 as a biomarker not only in AD, but also in other diseases particularly

associated with long-term stress, such as PTSD or depression (27, 100, 101). The researchers indicate that the use of miRNA associated with FKBP5 as a biomarker allows for the prediction of the development of PTSD in people who have recently experienced a trauma. They also point to the need to conduct further studies in this matter in order to expand possible diagnostic and therapeutic possibilities (102). In turn, in the course of chronic depression, it was possible to prove the relationship between the reduced level of *FKBP5* expression and the increased level of GR expression, which can also serve as a biomarker of this disease (103).

9. Summary

The article briefly discusses the most important issues concerning FKBP5 - current knowledge on the possibilities of its use in diagnostics and treatment of various diseases and the possible function as a biomarker. Due to the direct influence on the HPA axis and the related participation in stress reactions, the correlation between FKBP5 and the pathogenesis of diseases associated with long-term stress such as PTSD or depression is presented (27). Additionally, the correlation of FKBP5 level with hypercortisolemia is described and the potential role as a biomarker in the course of Cushing's syndrome is determined (19). It was found that many drugs can interact at the molecular level with FKBP5, the role of SSRIs is particularly emphasized and the need for further observations in relation to other drugs used in the treatment of neuropsychiatric diseases is indicated (57). The aim of the latest studies is to perceive FKBP5 as a biomarker in various disease entities - especially endocrine, oncological and neuropsychoatric, as well as cardiological.

10. Author's contributions

The authors confirm contribution to the paper as follows:

Conceptualization: Sven Solisch

Methodology: Sven Solisch, Agata Boczar and Jakub Jarmołowicz

Software: Jakub Jarmołowicz

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Formal analysis: Patryk Dryja, Agata Boczar and Jakub Jarmołowicz

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All authors have read and agreed with the published version of the manuscript.

11. Founding Statement

This research received no external funding.

12. Institutional Review Board Statement

Not applicable.

13. Informed consent statement

Not applicable.

14. Data Availability Statement

Not applicable.

15. Conflicts of Interest

The authors declare no conflict of interest.

References

1. Hähle A, Merz S, Meyners C, Hausch F. The Many Faces of FKBP51. *Biomolecules*. 2019;9(1):35. Published 2019 Jan 21. doi:10.3390/biom9010035

2. Gebru NT, Hill SE, Blair LJ. Genetically engineered mouse models of FK506-binding protein 5. *J Cell Biochem*. Published online February 13, 2023. doi:10.1002/jcb.30374

3. Zannas AS, Wiechmann T, Gassen NC, Binder EB. Gene-Stress-Epigenetic Regulation of FKBP5: Clinical and Translational Implications. *Neuropsychopharmacology*. 2016;41(1):261-274. doi:10.1038/npp.2015.235

4. Matosin N, Halldorsdottir T, Binder EB. Understanding the Molecular Mechanisms Underpinning Gene by Environment Interactions in Psychiatric Disorders: The FKBP5 Model. *Biol Psychiatry*. 2018;83(10):821-830. doi:10.1016/j.biopsych.2018.01.021

5. Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*. 2009;34 Suppl 1:S186-S195. doi:10.1016/j.psyneuen.2009.05.021

6. Wiederrecht G, Hung S, Chan HK, et al. Characterization of high molecular weight FK-506 binding activities reveals a novel FK-506-binding protein as well as a protein complex. *J Biol Chem*. 1992;267(30):21753-21760.

7. Schiene-Fischer C, Yu C. Receptor accessory folding helper enzymes: the functional role of peptidyl prolyl cis/trans isomerases. *FEBS Lett*. 2001;495(1-2):1-6. doi:10.1016/s0014-5793(01)02326-2

8. Pratt WB. The role of heat shock proteins in regulating the function, folding, and trafficking of the glucocorticoid receptor. *J Biol Chem*. 1993;268(29):21455-21458.

9. Wochnik GM, Rüegg J, Abel GA, Schmidt U, Holsboer F, Rein T. FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *J Biol Chem*. 2005;280(6):4609-4616. doi:10.1074/jbc.M407498200

10. Scammell JG, Denny WB, Valentine DL, Smith DF. Overexpression of the FK506-binding immunophilin FKBP51 is the common cause of glucocorticoid resistance in three New World primates. *Gen Comp Endocrinol*. 2001;124(2):152-165. doi:10.1006/gcen.2001.7696

11. Sinars CR, Cheung-Flynn J, Rimerman RA, Scammell JG, Smith DF, Clardy J. Structure of the large FK506-binding protein FKBP51, an Hsp90-binding protein and a component of steroid receptor complexes. *Proc Natl Acad Sci U S A*. 2003;100(3):868-873. doi:10.1073/pnas.0231020100

12. Häusl AS, Balsevich G, Gassen NC, Schmidt MV. Focus on FKBP51: A molecular link between stress and metabolic disorders. *Mol Metab*. 2019;29:170-181. doi:10.1016/j.molmet.2019.09.003

13. Weiwad M, Edlich F, Kilka S, et al. Comparative analysis of calcineurin inhibition by complexes of immunosuppressive drugs with human FK506 binding proteins. *Biochemistry*. 2006;45(51):15776-15784. doi:10.1021/bi061616p

14. Wen H, He Y, Tang Y, et al. Altered immune response is associated with sex difference in vulnerability to Alzheimer's disease in human prefrontal cortex. *Brain Pathol*. Published online November 4, 2024. doi:10.1111/bpa.13318

15. Hawn SE, Sheerin CM, Lind MJ, et al. GxE effects of FKBP5 and traumatic life events on PTSD: A meta-analysis. *J Affect Disord*. 2019;243:455-462. doi:10.1016/j.jad.2018.09.058

16. Fan B, Ma J, Zhang H, et al. Association of FKBP5 gene variants with depression susceptibility: A comprehensive meta-analysis. *Asia Pac Psychiatry*. 2021;13(2):e12464. doi:10.1111/appy.12464

17. Malekpour M, Shekouh D, Safavinia ME, et al. Role of FKBP5 and its genetic mutations in stress-induced psychiatric disorders: an opportunity for drug discovery. *Front Psychiatry*. 2023;14:1182345. Published 2023 Jun 16. doi:10.3389/fpsyt.2023.1182345

18. Zhang Y, Yue W, Li J. The association of FKBP5 gene polymorphism with genetic susceptibility to depression and response to antidepressant treatment- a systematic review. *BMC Psychiatry*. 2024;24(1):274. Published 2024 Apr 12. doi:10.1186/s12888-024-05717-z

19. Birtolo MF, Armignacco R, Benanteur N, et al. Whole blood transcriptomic signature of Cushing's syndrome. *Eur J Endocrinol*. 2024;191(1):55-63. doi:10.1093/ejendo/lvae083

20. Zhang Y, Deng Y, Zhou M, Wu B, Zhou J. Intraglandular dissemination: a special pathological feature. *Front Oncol*. 2024;14:1428274. Published 2024 Jul 29. doi:10.3389/fonc.2024.1428274

21. Ma J, Yang Z, Gao H, Huda N, Jiang Y, Liangpunsakul S. FK-binding protein 5: Possible relevance to the pathogenesis of metabolic dysfunction and alcohol-associated liver disease. *J Investig Med*. 2024;72(1):128-138. doi:10.1177/10815589231207793

22. Ndiaye M, Diop G, Derbois C, et al. Gene expression profiling of peripheral blood mononuclear cells from women with cervical lesions reveals new markers of cancer. *Oncol Rep*. 2023;49(6):118. doi:10.3892/or.2023.8555

23. Agam G, Atawna B, Damri O, Azab AN. The Role of FKBPs in Complex Disorders: Neuropsychiatric Diseases, Cancer, and Type 2 Diabetes Mellitus. *Cells*. 2024;13(10):801. Published 2024 May 8. doi:10.3390/cells13100801

24. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4

25. Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol*. 2018;14(8):457-469. doi:10.1038/s41582-018-0032-9

26. Lopez-Lee C, Torres ERS, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron*. 2024;112(8):1208-1221. doi:10.1016/j.neuron.2024.01.024

27. Blair LJ, Nordhues BA, Hill SE, et al. Accelerated neurodegeneration through chaperone-mediated oligomerization of tau. *J Clin Invest*. 2013;123(10):4158-4169. doi:10.1172/JCI69003

28. Zannas AS. Molecular integrators of stress and aging: the example of FKBP5. *Acta Neuropathol*. 2023;145(6):713-715. doi:10.1007/s00401-023-02572-2

29. Castro-Vale I, van Rossum EF, Machado JC, Mota-Cardoso R, Carvalho D. Genetics of glucocorticoid regulation and posttraumatic stress disorder--What do we know?. *Neurosci Biobehav Rev*. 2016;63:143-157. doi:10.1016/j.neubiorev.2016.02.005

30. Kohrt BA, Worthman CM, Ressler KJ, et al. Cross-cultural gene- environment interactions in depression, post-traumatic stress disorder, and the cortisol awakening response: FKBP5 polymorphisms and childhood trauma in South Asia. *Int Rev Psychiatry*. 2015;27(3):180-196. doi:10.3109/09540261.2015.1020052

31. Klengel T, Mehta D, Anacker C, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci*. 2013;16(1):33-41. doi:10.1038/nn.3275

32. Wang Q, Shelton RC, Dwivedi Y. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: A systematic review and meta-analysis. *J Affect Disord*. 2018;225:422-428. doi:10.1016/j.jad.2017.08.066

33. Clark SL, Hattab MW, Chan RF, et al. A methylation study of long-term depression risk. *Mol Psychiatry*. 2020;25(6):1334-1343. doi:10.1038/s41380-019-0516-z

34. Zhdanava M, Pilon D, Ghelerter I, et al. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *J Clin Psychiatry*. 2021;82(2):20m13699. Published 2021 Mar 16. doi:10.4088/JCP.20m13699

35. Gharraee B, Zahedi Tajrishi K, Sheybani F, et al. Prevalence of major depressive disorder in the general population of Iran: A systematic review and meta-analysis. *Med J Islam Repub Iran*. 2019;33:151. Published 2019 Dec 25. doi:10.34171/mjiri.33.151

36. Kraus C, Kadriu B, Lanzenberger R, Zarate CA Jr, Kasper S. Prognosis and improved outcomes in major depression: a review. *Transl Psychiatry*. 2019;9(1):127. Published 2019 Apr 3. doi:10.1038/s41398-019-0460-3

37. Bialek K, Czarny P, Strycharz J, Sliwinski T. Major depressive disorders accompanying autoimmune diseases - Response to treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;95:109678. doi:10.1016/j.pnpbp.2019.109678

38. Lozupone M, Panza F. Social determinants of late-life depression epigenetics. *Epigenomics*. 2020;12(7):559-562. doi:10.2217/epi-2019-0392

39. Watanuki T, Funato H, Uchida S, et al. Increased expression of splicing factor SRp20 mRNA in bipolar disorder patients. *J Affect Disord*. 2008;110(1-2):62-69. doi:10.1016/j.jad.2008.01.003

40. Cherian K, Schatzberg AF, Keller J. HPA axis in psychotic major depression and schizophrenia spectrum disorders: Cortisol, clinical symptomatology, and cognition. *Schizophr Res*. 2019;213:72-79. doi:10.1016/j.schres.2019.07.003

41. Farrell C, Doolin K, O' Leary N, et al. 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. *Psychiatry Res*. 2018;265:341-348. doi:10.1016/j.psychres.2018.04.064

42. Szczepankiewicz A, Leszczyńska-Rodziewicz A, Pawlak J, et al. FKBP5 polymorphism is associated with major depression but not with bipolar disorder. *J Affect Disord*. 2014;164:33-37. doi:10.1016/j.jad.2014.04.002

43. Fabbri C, Corponi F, Albani D, et al. Pleiotropic genes in psychiatry: Calcium channels and the stress-related FKBP5 gene in antidepressant resistance. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;81:203-210. doi:10.1016/j.pnpbp.2017.10.005

44. Lekman M, Laje G, Charney D, et al. The FKBP5-gene in depression and treatment response--an association study in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Cohort. *Biol Psychiatry*. 2008;63(12):1103-1110. doi:10.1016/j.biopsych.2007.10.026

45. Kirchheiner J, Lorch R, Lebedeva E, et al. Genetic variants in FKBP5 affecting response to antidepressant drug treatment. *Pharmacogenomics*. 2008;9(7):841-846. doi:10.2217/14622416.9.7.841

46. Singh AB, Bousman CA. Antidepressant Pharmacogenetics. *Am J Psychiatry*. 2017;174(5):417-418. doi:10.1176/appi.ajp.2017.17020173

47. Lett TA, Walter H, Brandl EJ. Pharmacogenetics and Imaging-Pharmacogenetics of Antidepressant Response: Towards Translational Strategies. *CNS Drugs*. 2016;30(12):1169-1189. doi:10.1007/s40263-016-0385-9

48. Kwon A, Kim S, Jeon H, Lee HS, Lee SH. Influence of *FKBP5* Variants and Childhood Trauma on Brain Volume in Non-clinical Individuals. *Front Behav Neurosci*. 2021;15:663052. Published 2021 Jun 3. doi:10.3389/fnbeh.2021.663052

49. Pérez-Ortiz JM, García-Gutiérrez MS, Navarrete F, Giner S, Manzanares J. Gene and protein alterations of FKBP5 and glucocorticoid receptor in the amygdala of suicide victims. *Psychoneuroendocrinology*. 2013;38(8):1251-1258. doi:10.1016/j.psyneuen.2012.11.008

50. Bremner JD, Vythilingam M, Vermetten E, et al. Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse. *Psychoneuroendocrinology*. 2003;28(6):733-750. doi:10.1016/s0306-4530(02)00067-7

51. Roberts S, Keers R, Breen G, et al. DNA methylation of FKBP5 and response to exposure-based psychological therapy. *Am J Med Genet B Neuropsychiatr Genet*. 2019;180(2):150-158. doi:10.1002/ajmg.b.32650

52. Bailus BJ, Scheeler SM, Simons J, et al. Modulating FKBP5/FKBP51 and autophagy lowers HTT (huntingtin) levels. *Autophagy*. 2021;17(12):4119-4140. doi:10.1080/15548627.2021.1904489

53. Schreiber KH, Ortiz D, Academia EC, Anies AC, Liao CY, Kennedy BK. Rapamycin-mediated mTORC2 inhibition is determined by the relative expression of FK506-binding proteins. *Aging Cell*. 2015;14(2):265-273. doi:10.1111/acel.12313

54. Bauder M, Meyners C, Purder PL, et al. Structure-Based Design of High-Affinity Macrocyclic FKBP51 Inhibitors. *J Med Chem*. 2021;64(6):3320-3349. doi:10.1021/acs.jmedchem.0c02195

55. Hadamitzky M, Herring A, Kirchhof J, et al. Repeated Systemic Treatment with Rapamycin Affects Behavior and Amygdala Protein Expression in Rats. *Int J Neuropsychopharmacol*. 2018;21(6):592-602. doi:10.1093/ijnp/pyy017

56. Hadamitzky M, Herring A, Keyvani K, et al. Acute systemic rapamycin induces neurobehavioral alterations in rats. *Behav Brain Res*. 2014;273:16-22. doi:10.1016/j.bbr.2014.06.056

57. Bevilacqua L, Carli V, Sarchiapone M, et al. Interaction between FKBP5 and childhood trauma and risk of aggressive behavior. *Arch Gen Psychiatry*. 2012;69(1):62-70. doi:10.1001/archgenpsychiatry.2011.152

58. Wei K, Xu Y, Zhao Z, et al. Icariin alters the expression of glucocorticoid receptor, FKBP5 and SGK1 in rat brains following exposure to chronic mild stress. *Int J Mol Med*. 2016;38(1):337-344. doi:10.3892/ijmm.2016.2591

59. Maruf AA, Greenslade A, Arnold PD, Bousman C. Antidepressant pharmacogenetics in children and young adults: A systematic review. *J Affect Disord*. 2019;254:98-108. doi:10.1016/j.jad.2019.05.025

60. Zobel A, Schuhmacher A, Jessen F, et al. DNA sequence variants of the FKBP5 gene are associated with unipolar depression. *Int J Neuropsychopharmacol*. 2010;13(5):649-660. doi:10.1017/S1461145709991155

61. Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. *Psychiatr Serv*. 2009;60(11):1446-1457. doi:10.1176/appi.ps.60.11.1446

62. Frampton JE, Plosker GL. Duloxetine: a review of its use in the treatment of major depressive disorder. *CNS Drugs*. 2007;21(7):581-609. doi:10.2165/00023210-200721070-00004

63. Skogh E, Reis M, Dahl ML, Lundmark J, Bengtsson F. Therapeutic drug monitoring data on olanzapine and its N-demethyl metabolite in the naturalistic clinical setting. *Ther Drug Monit*. 2002;24(4):518-526. doi:10.1097/00007691-200208000-00010

64. Berger M, Kraeuter AK, Romanik D, Malouf P, Amminger GP, Sarnyai Z. Cortisol awakening response in patients with psychosis: Systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2016;68:157-166. doi:10.1016/j.neubiorev.2016.05.027

65. Mitjans M, Catalán R, Vázquez M, et al. Hypothalamic-pituitary-adrenal system, neurotrophic factors and clozapine response: association with FKBP5 and NTRK2 genes. *Pharmacogenet Genomics*. 2015;25(5):274-277. doi:10.1097/FPC.0000000000000132

66. Pariante CM. Risk factors for development of depression and psychosis. Glucocorticoid receptors and pituitary implications for treatment with antidepressant and glucocorticoids. *Ann N Y Acad Sci*. 2009;1179:144-152. doi:10.1111/j.1749-6632.2009.04978.x

67. Xu J, Wang R, Liu Y, et al. Short- and long-term alterations of FKBP5-GR and specific microRNAs in the prefrontal cortex and hippocampus of male rats induced by adolescent stress contribute to depression susceptibility. *Psychoneuroendocrinology*. 2019;101:204-215. doi:10.1016/j.psyneuen.2018.11.008

68. van Alem CMA, Schmidbauer M, Rong S, et al. Liposomal Delivery Improves the Efficacy of Prednisolone to Attenuate Renal Inflammation in a Mouse Model of Acute Renal Allograft Rejection. *Transplantation*. 2020;104(4):744-753. doi:10.1097/TP.0000000000003060

69. Juszczak A, Morris D, Grossman A. Cushing’s Syndrome. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; September 5, 2024.

70. Hakami OA, Ahmed S, Karavitaki N. Epidemiology and mortality of Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab*. 2021;35(1):101521. doi:10.1016/j.beem.2021.101521

71. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. *Lancet*. 2015;386(9996):913-927. doi:10.1016/S0140-6736(14)61375-1

72. Braun LT, Vogel F, Reincke M. Long-term morbidity and mortality in patients with Cushing's syndrome. *J Neuroendocrinol*. 2022;34(8):e13113. doi:10.1111/jne.13113

73. Bride MM, Crespo I, Webb SM, Valassi E. Quality of life in Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab*. 2021;35(1):101505. doi:10.1016/j.beem.2021.101505

74. Bali U, Phillips T, Hunt H, Unitt J. FKBP5 mRNA Expression Is a Biomarker for GR Antagonism. *J Clin Endocrinol Metab*. 2016;101(11):4305-4312. doi:10.1210/jc.2016-1624

75. Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG. Squirrel monkey immunophilin FKBP51 is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology*. 2000;141(11):4107-4113. doi:10.1210/endo.141.11.7785

76. Gao Z, Yu F, Jia H, Ye Z, Yao S. FK506-binding protein 5 promotes the progression of papillary thyroid carcinoma. *J Int Med Res*. 2021;49(4):3000605211008325. doi:10.1177/03000605211008325

77. Mao S, Zhang D, Chen L, et al. FKBP51 promotes invasion and migration by increasing the autophagic degradation of TIMP3 in clear cell renal cell carcinoma. *Cell Death Dis*. 2021;12(10):899. Published 2021 Oct 1. doi:10.1038/s41419-021-04192-8

78. Periyasamy S, Hinds T Jr, Shemshedini L, Shou W, Sanchez ER. FKBP51 and Cyp40 are positive regulators of androgen-dependent prostate cancer cell growth and the targets of FK506 and cyclosporin A. *Oncogene*. 2010;29(11):1691-1701. doi:10.1038/onc.2009.458

79. Wang RG, Zhang D, Zhao CH, Wang QL, Qu H, He QS. FKBP10 functioned as a cancer-promoting factor mediates cell proliferation, invasion, and migration via regulating PI3K signaling pathway in stomach adenocarcinoma. *Kaohsiung J Med Sci*. 2020;36(5):311-317. doi:10.1002/kjm2.12174

80. Dornan J, Taylor P, Walkinshaw MD. Structures of immunophilins and their ligand complexes. *Curr Top Med Chem*. 2003;3(12):1392-1409. doi:10.2174/1568026033451899

81. Marrone L, D'Agostino M, Giordano C, et al. Scaffold proteins of cancer signaling networks: The paradigm of FK506 binding protein 51 (FKBP51) supporting tumor intrinsic properties and immune escape. *Oncol Res*. 2023;31(4):423-436. Published 2023 Jun 27. doi:10.32604/or.2023.028392

82. Baeuerle PA, Baltimore D. I kappa B: a specific inhibitor of the NF-kappa B transcription factor. *Science*. 1988;242(4878):540-546. doi:10.1126/science.3140380

83. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664. doi:10.2337/dc12-1801

84. Panagiotou C, Lambadiari V, Maratou E, et al. Insufficient glucocorticoid receptor signaling and flattened salivary cortisol profile are associated with metabolic and inflammatory indices in type 2 diabetes. *J Endocrinol Invest*. 2021;44(1):37-48. doi:10.1007/s40618-020-01260-2

85. de Wilde J, Smit E, Mohren R, et al. An 8-week high-fat diet induces obesity and insulin resistance with small changes in the muscle transcriptome of C57BL/6J mice. *J Nutrigenet Nutrigenomics*. 2009;2(6):280-291. doi:10.1159/000308466

86. Willmer T, Goedecke JH, Dias S, Louw J, Pheiffer C. DNA methylation of FKBP5 in South African women: associations with obesity and insulin resistance. *Clin Epigenetics*. 2020;12(1):141. Published 2020 Sep 21. doi:10.1186/s13148-020-00932-3

87. Vitale I, Pietrocola F, Guilbaud E, et al. Apoptotic cell death in disease-Current understanding of the NCCD 2023. *Cell Death Differ*. 2023;30(5):1097-1154. doi:10.1038/s41418-023-01153-w

88. Cho H, Mu J, Kim JK, et al. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). *Science*. 2001;292(5522):1728-1731. doi:10.1126/science.292.5522.1728

89. Stechschulte LA, Qiu B, Warrier M, et al. FKBP51 Null Mice Are Resistant to Diet-Induced Obesity and the PPARγ Agonist Rosiglitazone. *Endocrinology*. 2016;157(10):3888-3900. doi:10.1210/en.2015-1996

90. Smedlund KB, Sanchez ER, Hinds TD Jr. FKBP51 and the molecular chaperoning of metabolism. *Trends Endocrinol Metab*. 2021;32(11):862-874. doi:10.1016/j.tem.2021.08.003

91. Balsevich G, Häusl AS, Meyer CW, et al. Stress-responsive FKBP51 regulates AKT2-AS160 signaling and metabolic function. *Nat Commun*. 2017;8(1):1725. Published 2017 Nov 23. doi:10.1038/s41467-017-01783-y

92. Jubb AW, Boyle S, Hume DA, Bickmore WA. Glucocorticoid Receptor Binding Induces Rapid and Prolonged Large-Scale Chromatin Decompaction at Multiple Target Loci. *Cell Rep*. 2017;21(11):3022-3031. doi:10.1016/j.celrep.2017.11.053

93. Yang Y, Babayan L, Mirzakhanian A, et al. Circulating FK506 binding protein 51 mRNA expression in patients with pituitary adenomas. *Heliyon*. 2023;9(1):e12678. Published 2023 Jan 4. doi:10.1016/j.heliyon.2022.e12678

94. Bancos I, Hatipoglu BA, Yuen KCJ, Chandramohan L, Chaudhari S, Moraitis AG. Evaluation of FKBP5 as a cortisol activity biomarker in patients with ACTH-dependent Cushing syndrome. *J Clin Transl Endocrinol*. 2021;24:100256. Published 2021 Jun 6. doi:10.1016/j.jcte.2021.100256

95. Fiaz T, Nadeem MS, Afzal O, et al. Peripheral mRNA Expression and Prognostic Significance of Emotional Stress Biomarkers in Metastatic Breast Cancer Patients. *Int J Mol Sci*. 2022;23(22):14097. Published 2022 Nov 15. doi:10.3390/ijms232214097

96. Tong F, Lu G, Zang J, et al. FKBP5 associated CD8 T cell infiltration is a novel prognostic biomarker in luminal B breast cancer. *J Int Med Res*. 2023;51(11):3000605231211771. doi:10.1177/03000605231211771

97. Kolur V, Vastrad B, Vastrad C, Kottureshetti S, Tengli A. Identification of candidate biomarkers and therapeutic agents for heart failure by bioinformatics analysis. *BMC Cardiovasc Disord*. 2021;21(1):329. Published 2021 Jul 4. doi:10.1186/s12872-021-02146-8

98. Wei Y, Cao H, Peng YY, Zhang B. Alterated gene expression in dilated cardiomyopathy after left ventricular assist device support by bioinformatics analysis. *Front Cardiovasc Med*. 2023;10:1013057. Published 2023 Mar 17. doi:10.3389/fcvm.2023.1013057

99. Lafta MS, Sokolov AV, Landtblom AM, Ericson H, Schiöth HB, Abu Hamdeh S. Exploring biomarkers in trigeminal neuralgia patients operated with microvascular decompression: A comparison with multiple sclerosis patients and non-neurological controls. *Eur J Pain*. 2024;28(6):929-942. doi:10.1002/ejp.2231

100. Binder EB, Salyakina D, Lichtner P, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet*. 2004;36(12):1319-1325. doi:10.1038/ng1479

101. Yeo S, Enoch MA, Gorodetsky E, et al. The influence of FKBP5 genotype on expression of FKBP5 and other glucocorticoid-regulated genes, dependent on trauma exposure. *Genes Brain Behav*. 2017;16(2):223-232. doi:10.1111/gbb.12342

102. Kang HJ, Yoon S, Lee S, et al. FKBP5-associated miRNA signature as a putative biomarker for PTSD in recently traumatized individuals. *Sci Rep*. 2020;10(1):3353. Published 2020 Feb 25. doi:10.1038/s41598-020-60334-6

103. Hori H, Yoshida F, Ishida I, et al. Blood mRNA expression levels of glucocorticoid receptors and FKBP5 are associated with depressive disorder and altered HPA axis. *J Affect Disord*. 2024;349:244-253. doi:10.1016/j.jad.2024.01.080