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Involvement of the FKBP5 gene in the pathogenesis of stress-related disorders and antidepressant response: An update

Review

The FKBP5 gene has been shown to modulate stress responses by regulating glucocorticoid receptor sensitivity. Because stressful events are increasingly recognized as important environmental risk factors of psychiatric disorders, FKBP5 has recently become a candidate gene in research on stress-related conditions. This review aims to provide a concise overview of current knowledge about the FKBP5 gene and its clinical implications and suggest directions for future research. Firstly, the functional role of the gene will be described. Associations with affective and post-traumatic stress disorders will then be discussed in the context of gene-by-environment interactions. Finally, the usefulness of FKBP5 genotype as predictor of antidepressant drug response will be outlined.
Keywords: FKBP5, stress, affective disorders, PTSD, antidepressant response

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INTRODUCTION

Psychiatric disorders are the result of an interplay between genetic and environmental influences. Identifying those genetic factors could improve knowledge of pathophysiological mechanisms, as well as development of new treatment approaches. FK506 binding protein 51 (FKBP5) has been proposed as a candidate gene for stress-related conditions due to its role in the regulation of neurobiological stress responses. Initial evidence of pathophysiological implications of the FKBP5 gene dates back to the early 2000's (Binder, Salyakina, & Lichtner, 2004; Fallin et al., 2005; Koenen et al., 2005), but it was not until the publication of a seminal

review paper (Binder, 2009) that interest in this gene has started to grow. Since then, several lines of research have provided new evidence on the involvement of the FKBP5 gene in stress-related conditions and drug response, shifting the focus from direct genetic effects to gene-by-environment (G x E) interactions. To understand the scope and the implications of this change of paradigms, an updated overview of the latest research on the FKBP5 gene is required.

This paper integrates recent findings on the FKBP5 gene with the aim of updating the existing knowledge about its involvement in stress-related disorders. Firstly, an overview on the functional role of FKBP5 in glucocorticoid-signaling will be provided. Secondly, focus will be placed on associations between the FKBP5 gene and affective disorders, suicidal behavior and post-traumatic stress disorder (PTSD). Even though such stress-related conditions share underlying pathophysiology, genetic influences will be discussed individually for the sake of comprehension. Finally, reports of the FKBP5 gene as a biomarker of antidepressant treatment response will be reviewed.

METHODS

Scientific databases (PubMed, PsycInfo) were searched for published reports on the FKBP5 gene (August 2013). Search terms included: FKBP5, FK506 binding protein 5. Only human studies were included in the review. Table 1 provides an overview of the key studies investigating the link between the FKBP5 gene and stress-related conditions. Table 2 includes reports examining the associations between FKBP5 polymorphisms and response to antidepressant drug treatment.

Table 1. Studies examining associations between FKBP5 polymorphisms and stress-related disorders.

Study	n	Ethnic background	G x E	SNP	Risk allele	Main finding
Depression						
Appel et al. (2011)	2157	Caucasian	Yes	rs1360780	T	TT genotype interacted with childhood physical, sexual and abuse to increase adult depression.
Dackis, Rogosch, Oshri and Cicchetti (2012)	236	African-American (53.8) Caucasian (33.9) Hispanic (8.5) Other (3.8)	Yes	rs3800373 rs9296158 rs1360870 rs9470080	C A T T	A haplotype formed by the risk alleles interacted with child maltreatment to increase limbic irritability. This interaction moderated the indirect effect of maltreatment on depression and dissociative experiences via limbic irritability.
Fani et al.(2013)	103	African-American	No	rs1360780	T	T-allele was associated with higher attention bias for threat, increased hippocampal activation to threat and differences in hippocampal morphology.
Kang et al. (2012)	130	Korean	Yes	rs1360780 rs9296158 rs9470080	T A T	Minor alleles predicted higher anxiety and depression after prolonged stress exposure in cancer patients.
Lavebratt, Aberg, Sjöholm and Forsell (2010)	2743	Caucasian	Yes	rs1360780	T	T-allele and TT genotype were overrepresented in men with depression. No interaction was found between FKBP5 genotype and childhood problems or negative life events.
Lewis, Collishaw, Harold, Rice and Thapar (2012)	436	Caucasian	Yes	rs1260780 rs4713916 rs2800373	-- -- --	Recurrent maternal depression did not interact with FKBP5 genotype to predict child and adolescent depression symptoms.
Shinozaki et al. (2011)	131	Non-Hispanic Caucasian	Yes	rs1360780 rs3800373 rs9296258 rs9470080	T -- A T	Minor alleles were associated with higher depression scores in kidney transplant recipients.
Tatro et al. (2010)	57	???	No	rs3800373 rs1360780	G T	Change in severity of depressive mood correlated with FKBP5 gene expression in carriers of risk alleles homozygous.
Velders et al. (2011)	2928	???	No	rs9470080 rs9394309 rs7748266 rs1360780	G -- -- --	G-allele was associated with higher rate of depressive symptoms.

Table 1. *Continued*

Study	n	Ethnic background	G x E	SNP	Risk allele	Main finding
White et al. (2012)	139	Caucasian	Yes	rs7748266	T	Risk alleles and haplotypes interacted with childhood emotional neglect to predict increased threat-related amygdala reactivity.
				rs1360780	T	
				rs9296158	A	
				rs3800373	G	
				rs9470080	T	
				rs9394309	G	
Zimmermann et al. (2011)	884	Caucasian	Yes	rs3800373	C	Homozygozity for the minor alleles interacted with prior trauma exposure to increase the risk of development of major depressive episodes.
				rs1360780	T	
				rs4713916	A	
				rs9296158	A	
				rs9470080	T	
Bipolar disorder						
Ceulemans et al. (2011)	673	Caucasian	No	rs9296157	--	None of the FKBP5 SNPs studied were associated with bipolar disorder.
				rs3800374	--	
				rs7757037	--	
				rs755658	--	
				rs2294807	--	
				rs992105	--	
				rs3798346	--	
				rs9366890	--	
				rs9296158	--	
				rs4713899	--	
				rs737054	--	
				rs3777747	--	
				rs9380524	--	
				rs1360780	--	
				rs2143404	--	
				rs4713902	--	
				rs17542466	--	
				rs1334894	--	
				rs6912833	--	

Table 1. *Continued*

Study	n	Ethnic background	G x E	SNP	Risk allele	Main finding
				rs9470080	--	
				rs13192954	--	
				rs17614642	--	
Roy, Hodgkinson, Deluca, Goldman and Enoch (2012)	474	African-American	Yes	rs3800373	A	AA-genotype interacted with childhood abuse to increase risk for suicidal behavior.
Supriyanto et al. (2011)	447	Japanese	No	rs2800373	T	None of the FKBP5 polymorphisms were associated with completed suicide, but a haplotype formed by the minor alleles of rs2800373 and rs1360780 was overrepresented in suicide victims.
				rs1360780	C	
				rs2395635	--	
PTSD						
Binder et al. (2008)	762	African-American (95.2)	Yes	rs3800373	C	Four polymorphisms interacted with childhood abuse to predict increased adult PTSD symptoms.
				rs992105	--	
		Caucasian (2.2)		rs9296158	A	
		Hispanic (0.6)		rs737054	--	
		Asian (0.1)		rs2360780	T	
		Mixed (0.9)		rs1334894	--	
		Other (0.1)		rs9470080	T	
				rs4713916	--	
Koenen et al. (2005)	46	African-American (52.0)	No	rs3800373	C	Minor alleles were associated with increased risk of peritraumatic dissociation in children with medical injury.
				rs1360780	T	
		Caucasian (48.0)				
Klengel et al. (2013)	1963	African-American	Yes	rs1360780	T	T-allele interacted with early trauma to predict recurrent and lifetime PTSD.
Xie et al. (2010)	2427	Caucasian (47.2)	Yes	rs3800373	--	TT genotype (rs9470080) interacted with childhood abuse to increase the risk of PTSD only in African-Americans.
		African-American (52.9)		rs9296158	--	
				rs1360780	--	
				rs9470080	T	
Psychosis						
Collip et al. (2013)	401	Caucasian	Yes	rs9296158	A	Risk alleles interacted with childhood trauma to increase psychotic symptoms.
				rs1043805	A	
				rs1360780	T	
				rs4713916	A	

Only alleles that showed significant associations ($p \leq 0.05$) are included in the table. Dashes (--) indicate polymorphisms that did not show any significant association. Question marks (???) indicate that information about the sample's ethnic backround was not reported in the respective studies. SNP: Single-nucleotide polymorphism.

Table 2. Studies examining associations between FKBP5 polymorphisms and response to antidepressant drug treatment.

Study	n	Ethnic background	Patient group	Antidepressant drug	Outcome measure	Predictive FKBP5 SNPs	Main finding
Binder et al. (2004)	633	Caucasian	MDD (86.6) Bipolar disorder (12.0) Dysthymic disorders (1.4)	Doctor´s choice. Concomitant treatment: Mood stabilizers (21.6) Antipsychotics (7.7) Benzodiazepines (48.7)	HAM-D	rs1360780 rs1334894 rs755658 rs4713916 rs3800373	Minor alleles predicted response to antidepressant drug treatment. TT genotype (r1360780) was associated with more lifetime depressive episodes.
Ellsworth et al. (2013)	529	White non-Hispanic	MDD	Citalopram Escitalopram	QIDS HAM-D	None	None of the 127 FKBP5 SNPs examined predicted response to antidepressant drug treatment.
Horstmann et al. (2010)	387	Caucasians	MDD (90.7) Bipolar disorder (9.3) Psychotic depression (14.3)	Doctor´s choice. Concomitant treatment: Mood stabilizers (18.0) Antipsychotics (21.0) Benzodiazepines (35.0)	HAM-D	rs1360780	TT genotype was associated with response to antidepressant drug treatment (4.3% of the variance). Gene-by-gene interactions between FKBP5 rs1360780 and GRIK4 and HTR2A SNPs predicted 13.1% of the variance for remission.
Lekman et al. (2008)	2562	White non-Hispanic (83.6) African-American (16.4)	MDD	Citalopram	QIDS	rs1360780 rs4713916	T-allele (rs1360780) was overrepresented in non-Hispanic White patients with depression. Rs4713916 genotype predicted remission of depressive symptoms after antidepressant drug treatment.
Sarginson, Lazzeroni, Ryan, Schatzberg and Murphy (2010)	246	Caucasian (91.9) Other (8.1)	MDD	Paroxetine (50.4) Mirtazapine (49.6)	HAM-D	None	None of the FKBP5 SNPs examined (rs1360780, rs3800373) predicted response to antidepressant drug treatment.
Tsai, Hong, Chen and Yu (2007)	125	Chinese	MDD (95.2) Dysthymic disorders (4.8)	Fluoxetine	HAM-D	None	FKBP5 rs1360780 did not predict response to antidepressant drug treatment.
Zobel et al. (2010)	552	Caucasian	MDD	Citalopram	HAM-D Dex/CRH test Hippocampal volume	rs3800373 rs4713916	Major homozygous genotypes were associated with higher risk of developing depression, and predicted hippocampal volume and HPA response to antidepressant drug treatment.

Only polymorphisms that significantly predicted response to antidepressant treatment ($p \leq 0.05$) are included in the table. Dex/CRH test: dexamethasone/corticotrophin-releasin hormone test; HAM-D: Hamilton Depression Rating Scale; MDD: Major depressive disorder; QIDS: Quick Inventory of Depressive Symptomatology; SNP: Single nucleoid polymorphism.

GLUCOCORTICOID-SIGNALING AND FKBP5 FUNCTION

A combined effect of (epi-)genetic predispositions and environmental factors determines an individual's susceptibility to psychiatric disorders (Mehta & Binder, 2012). The physiological stress response plays a central role in coping with negative life events. Individual differences in neuroendocrine response systems, such as the hypothalamic-pituitary-adrenal (HPA) axis, are therefore of particular interest in the detection of risk factors for stress-related conditions (Spijker & van Rossum, 2012).

Stress induces the release of corticotropin releasing hormone from the paraventricular nucleus in the hypothalamus, which stimulates pituitary adrenocorticotrophine hormone synthesis, in turn increasing the release of glucocorticoids from the adrenal cortex (Mehta & Binder, 2012). Glucocorticoids participate in the termination of stress response via the activation of glucocorticoid receptors (GR), a ligand-activated transcription factor that promotes negative feedback inhibition of the HPA-axis. Upon cortisol-binding, GR translocates from the cytosol to the cell nucleus, where it exhibits its transcription and translation actions. GR function is modulated by a molecular hetero-complex that comprises hsp90/hsp70 chaperones and a number of co-chaperones, including FKBP5. When FKBP5 is bound to the GR complex, the receptor has lower affinity for cortisol, leading to a reduction of the amount of activated GR translocation and cellular glucocorticoid resistance (i.e. reduced glucocorticoid sensitivity) (Hartmann et al., 2012). Glucocorticoids induce FKBP5 expression as a part of an intracellular ultra-short negative feedback loop for GR activity (Binder, 2009; Hartmann et al., 2012).

Proper termination of physiological stress responses after stressor exposure is necessary for a healthy regulation, and prolonged or excessive activation of the HPA-axis has been implicated in the pathogenesis of stress-related disorders (Binder, 2009; Mehta & Binder, 2012). For example, impaired GR signaling results in an attenuation of the negative feedback inhibition. This can lead to glucocorticoid resistance and HPA-axis hyperactivity, two alterations commonly observed in mood disorders (Binder, 2009; Menke et al., 2012; Spijker & van Rossum, 2012). On the other hand, an increase in GR sensitivity due to enhanced negative feedback is observed in anxiety disorders such as PTSD (Mehta et al., 2011; Sarapas et al., 2011; van Zuiden et al., 2012; Yehuda et al., 2009).

FKBP5 POLYMORPHISMS AND THEIR FUNCTIONAL ROLE IN GR SIGNALING

Individual differences in HPA-axis regulation are due to genetic factors and/or the combined effect with environmental exposures (e.g., early stressful life events, trauma exposure) that alter the baseline response to this system (Mehta & Binder, 2012). Indeed, GR-related genes have been shown to shape the physiological stress responsiveness (Mahon, Zandi, Potash, Nestadt, & Wand, 2013; Menke et al., 2012). In humans, several polymorphisms in the gene that codes for FKBP5, located on

the chromosome 6p21, seem to define distinct GR functioning (Binder, 2009). For example, common single-nucleotide polymorphisms (SNPs) of the FKBP5 gene have been associated with higher FKBP5 protein/mRNA expression and increased GR resistance, leading to impaired negative feedback inhibition of the HPA-axis after exposure to psychosocial stressors (Binder, Bradley, & Liu, 2008; Ising et al., 2008; Lekman et al., 2008; Mahon et al., 2013; Touma et al., 2011).

Importantly, this genetic association with GR function appears to be state-dependent, in other words specific alleles might lead to different GR function depending on the disease-status of the individual. For example, the minor allele of polymorphisms initially associated with high FKBP5 induction in healthy individuals (e.g., rs1360780) have been linked to lower FKBP5 gene expression and GR hypersensitivity in patients with depression (Menke et al., 2013) or PTSD (Mehta et al., 2011; Sarapas et al., 2011). Mehta et al. (2011) hypothesized that this state-dependence could be mediated by changes in the expression of other GR chaperones and systems influencing the HPA-axis. In a recent study, the same group also identified a long-term epigenetic mechanism (i.e. alterations in gene activity not caused by changes in the DNA sequence) that mediates the combined effects of early life stress exposure and FKBP5 SNPs on the risk of developing stress-related psychiatric disorders (Klengel et al., 2013). Allele-specific changes in FKBP5 DNA methylation in response to childhood abuse were shown to alter the responsiveness of FKBP5 to GR activation, leading to long-term dysregulation of the stress hormone system and a global effect on the immune system and brain regions associated with stress regulation.

Sex-specific effects have been reported in the association between the FKBP5 gene and GR function. In a study by Mahon et al. (2013) only male participants showed a positive genetic association with high cortisol levels in response to acute psychosocial stress. This male-specific effect could be related to the influence of sex hormones on FKBP5 and other GR-related genes (Binder, 2009). Nevertheless, sex-specific effects of the FKBP5 gene were not observed in other similar studies (Binder et al., 2008; Ising et al., 2008; Luijk et al., 2010).

FKBP5 AND RISK FOR STRESS-RELATED PSYCHIATRIC CONDITIONS

Mood disorders

Consistent with abnormalities in the HPA-axis feedback regulation and GR signaling in affective disorders, GR-related genes, including FKBP5, have been implicated in their pathogenesis (Binder, 2009; Spijker & van Rossum, 2012). In fact, FKBP5 genotype-dependent differences in GR sensitivity have been detected in patients with major depression, suggesting that the FKBP5 gene might delineate neuroendocrinologically distinct subtypes of depression (Menke et al., 2013).

High risk of developing depressive symptoms has been associated with FKBP5 polymorphisms (Lavebratt, Aberg, Sjöholm, & Forsell, 2010; Lekman et al., 2008; Velders et al., 2011; Zobel et al., 2010). However, there are some inconsistencies regarding the concrete genotypes that increase the vulnerability to depression. While some studies support a model in which carriers of the minor alleles are at higher

risk of depression (Lavebratt et al., 2010; Velders et al., 2011), others identified an over-representation of major alleles in patients with depression (Zobel et al., 2010). In the same direction, a correlation between change in the severity of depressive symptoms and FKBP5 gene expression was observed in HIV-infected individuals, but only in those homozygous for the major allele (i.e. carriers of two copies of the major allele) of the FKBP5 SNP examined (Tatro et al., 2010).

Results of these early reports in which direct genetic effects on disease status were detected have not been replicated in several other studies (Appel et al., 2011; Binder et al., 2004; Kang et al., 2012; Lewis, Collishaw, Harold, Rice, & Thapar, 2012; Shinozaki et al., 2011; Zimmermann et al., 2011). For example, Binder et al. (2004) found an association between FKBP5 genotype and lifetime depressive episodes, but failed to detect differences in SNPs frequencies between patients with depression and controls. Furthermore, a comprehensive meta-analysis that evaluated the relationship between FKBP5 polymorphisms and mood disorders yielded only one positive association (Feng et al., 2011). As an explanation of lack of consistent replication, the importance of FKBP5 gene-by-environment interactions in depression has been highlighted (Appel et al., 2011; Kang et al., 2012; Shinozaki et al., 2011; Zimmermann et al., 2011).

Early stressful events have been shown to increase the susceptibility to mood disorders in adulthood (Zimmermann et al., 2011), and FKBP5 gene seems to moderate this relationship. Appel et al. (2011) found a significant interaction between childhood abuse and FKBP5 genotype on the severity of adult depressive symptoms and lifetime major depression. More specifically, childhood abuse increased the vulnerability to depression only in homozygous for the minor allele of the SNP examined. This interaction effect, however, was not observed with childhood neglect, suggesting that FKBP5 moderates particularly the effect of abuse-related stress (Appel et al., 2011).

An interaction between adverse life events and FKBP5 polymorphisms was also observed in a prospective longitudinal community study (Zimmermann et al., 2011). Homozygosity for the minor allele of five FKBP5 SNPs increased the risk of developing a major depressive episode in individuals with prior trauma exposure. Interestingly, this relationship was dose-dependent, with stronger interaction effect with increasing trauma severity. These results were replicated in one of the two additional independent samples analyzed in this study.

The moderating role of FKBP5 gene in the risk effect of long-lasting stress is further supported by studies that examine the influence of FKBP5 polymorphisms on the development of depression after relatively uniform stressful experiences, such as diagnosis and treatment of severe medical conditions. Shinozaki et al. (2011) and Kang et al. (2012) found that FKBP5 polymorphisms predicted the development of depressive symptoms after kidney transplant or two cycles of chemotherapy. Nonetheless, results reported in the study by Shinozaki et al. (2011) should be interpreted carefully since no correction for multiple comparisons was applied and there were no data about the pre-transplant depression status.

While most evidence points to significant G x E interactions, some studies have failed to provide support to this relationship. A common FKBP5 polymorphism did not modulate the risk for depression in individuals exposed to childhood problems

or negative life events during the previous year (Lavebratt et al., 2010). Similarly, FKBP5 genotype did not interact with recurrent maternal depression to increase the vulnerability to child and adolescent depression (Lewis et al., 2012). Besides the possibility that significant G x E interactions were not detected due to low statistical power, or that they might not be applicable to the FKBP5 SNPs studied, it is likely that FKBP5 is only sensitive to certain types of severe psychosocial stressors (Appel et al., 2011) and during sensitive periods in early development (Klengel et al., 2013). Given the cumulative evidence of a combined effect of FKBP5 and childhood trauma on depression, the main genetic effects detected in some of the previously discussed reports might be due to the presence of high rates of trauma in the study samples, as most of those studies were based on clinical samples (e.g., Lavebratt et al., 2010; Lekman et al., 2008; Tatro et al., 2010; Zobel et al., 2010) in which early stressful events tend to be high (Appel et al., 2011; Zimmermann et al., 2011).

Evidence for an association between the FKBP5 gene and bipolar disorder is less conclusive. While Willour et al. (2009) reported an over-transmission of several FKBP5 alleles in families with bipolar disorder, these findings were not replicated in three other independent studies in which none of the SNPs tested yielded significant associations (Ceulemans et al., 2011; Fallin et al., 2005; Gawlik et al., 2006).

Suicidal behavior

FKBP5 seems to be also involved in the pathophysiology of suicidal behavior. Haplotypes of the FKBP5 gene have been associated with completed suicide in a Japanese sample (Supriyanto et al., 2011), although due to the lack of the psychiatric history of the victims it cannot be excluded that the identified relationship is mediated by the effects of the FKBP5 gene on mood disorders or other psychiatric pathologies associated with suicide. To disentangle this issue, Pérez-Ortiz, García-Gutiérrez, Navarrete, Giner, & Manzanarez (2013) examined FKBP5 expression in the amygdala of suicide victims without any underlying psychiatric disorder and found significant reductions of both FKBP5 gene and protein expression compared to controls, thus implicating FKBP5 in the neurobiological mechanisms of suicidal behavior.

G x E studies suggest a moderating role of FKBP5 genotype in the association between childhood trauma and suicide (Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010; Roy, Hodgkinson, Deluca, Goldman, & Enoch, 2012). In other words, childhood trauma exposure increased the risk of attempting suicide only in carriers of certain FKBP5 allelic-variants or haplotypes.

Post-traumatic stress disorder

Both stressful life events (e.g., childhood trauma) and GR-related genes have been shown to affect HPA-axis activity, and as described above, alterations in stress regulation are present in PTSD (Mehta & Binder, 2012). In addition, PTSD is the only psychiatric disorder in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) that requires the exposure to a traumatic event. It is therefore not surprising that G x E interactions contribute significantly to shaping the individual differences in the susceptibility to PTSD (for a review on

G x E vulnerability factors for PTSD, see Mehta & Binder, 2012).

To date only a handful of studies have examined the effect of FKBP5 polymorphisms on the risk to develop PTSD after early trauma exposure. Binder et al. (2008) detected four FKBP5 SNPs that interacted with child abuse to predict PTSD symptomatology in adulthood in a population of mostly African-Americans. In this sample, the non-risk alleles exerted a protective action against the development of adult PTSD after severe child abuse in a gene dose-dependent manner, that is, carriers of two non-risk alleles reported lower PTSD symptoms than carriers of only one non-risk allele. The moderating effect of FKBP5 on the relationship between childhood trauma and PTSD has been replicated in African Americans (Mehta et al., 2011; Xie et al., 2010) but not in European Americans (Xie et al., 2010). The lack of associations observed in the European American cohort might be due to ethnic-specific genetic linkage disequilibrium (i.e. shared inheritance of two or more allelic variants), or to differences in the severity of trauma exposure between the two samples (Mehta & Binder, 2012; Xie et al., 2010). As already observed in several studies on depression, genetic main effects on PTSD symptoms were non-significant in these studies (Binder et al., 2008; Xie et al., 2010), thus further highlighting the importance of G x E interactions in stress-related conditions.

FKBP5 polymorphisms have also been associated with peritraumatic dissociation (i.e. dissociative experiences such as depersonalization and derealization at the time of a traumatic event), a risk factor for PTSD, in children that suffered an acute medical injury (Koenen et al., 2005). Moreover, FKBP5 variants might define biologically distinct subtypes of PTSD, since different GR sensitivity, baseline cortisol levels and whole-blood gene expression pattern were associated with FKBP5 genotype in a sample of patients with PTSD (Mehta et al., 2011).

Reduced FKBP5 gene expression has been proposed as a state marker of PTSD (Sarapas et al., 2011; Yehuda et al., 2009) and it predicted high levels of PTSD symptoms in response to military deployment in a prospective study (van Zuiden et al., 2012). Interestingly, clinical response to cognitive behavioral therapy has been associated with normalization of the FKBP5 gene expression levels in patients with PTSD (Levy-Gigi, Szabó, Kelemen, & Kéri, 2013).

ANTIDEPRESSANT DRUG RESPONSE

Since the first report in 2004 in which common FKBP5 polymorphisms predicted the response to antidepressant drug treatment (Binder et al., 2004), several replication pharmacogenetic studies have found both positive and negative associations between FKBP5 markers and antidepressant response across independent samples (Ellsworth et al., 2013; Horstmann et al., 2010; Lekman et al., 2008; Niitsu, Fabbri, Bentini, & Serretti, 2013; Sarginson, Lazzeroni, Ryan, Schatzberg, & Murphy, 2010; Tsai, Hong, Chen, & Yu, 2007; Zobel et al., 2010). Associations between FKBP5 SNPs and remission of depressive symptoms and response to treatment with selective serotonin reuptake inhibitors (SSRIs) have been found in both the STAR*D cohort and the Mayo study (Horstmann et al., 2010; Lekman et al., 2008). Positive FKBP5

genetic associations with antidepressants response were also reported in a recent comprehensive meta-analysis on pharmacogenetics in major depression (Niitsu et al., 2013). Furthermore, FKBP5 allelic-variants predicted smaller hippocampal volume and lack of reduction of HPA-axis hyperactivity after SSRI treatment (Zobel et al., 2010), two indicators of clinical non-response. However, none of the FKBP5 SNPs tested in this study predicted change in the severity of depression (Zobel et al., 2010).

Data challenging the strong genetic associations initially reported comes from studies by Tsai et al., (2007) and Sarginson et al. (2010), in which no FKBP5 gene effect on antidepressant efficacy was detected. Moreover, the FKBP5 polymorphisms most commonly found to be associated with clinical improvements after antidepressant treatment (i.e. rs1360780, rs3800373 and rs4713916) were not predictive of SSRI response in a recent report (Ellsworth et al., 2013).

Several factors might explain the discrepancies between the described findings. First, study samples might differ in terms of age distribution and severity or subtypes of patients. For instance, Binder et al. (2004) included inpatients with major depression, bipolar and dysthymic disorders in the sample, whereas the study group in Sarginson et al. (2010) consisted of elderly outpatients diagnosed with major depression. The ethnic origin of the study sample is another factor that might account for the divergent results, since certain genetic associations have been found in Caucasians and White non-Hispanics but not in African-American population nor in other ethnic subgroups (e.g., Lekman et al., 2008; Niitsu et al., 2013; Tsai et al., 2007). Finally, some of the studies have followed a naturalistic approach in which patients were treated according to doctors' choice (e.g., Binder et al., 2004; Horstmann et al., 2010), while in others a standardized routine treatment with a defined antidepressant was applied (e.g., Ellsworth et al., 2013; Lekman et al., 2008; Sarginson et al., 2010; Tsai et al., 2007; Zobel et al., 2010), which could result in significant differences in the response rates among studies (Tsai et al., 2007).

Perhaps genes x gene (G x G) interactions, rather than direct genetic effects, have a more important role in the pharmacogenetics of antidepressant drugs. For example, Horstmann et al. (2010) reported a significant interaction between FKBP5 and another GR-related gene (i.e. GRIK4) genotypes on the prediction of the antidepressant treatment. Furthermore, when different multi-marker models were tested, those that included G x G effects accounted for a higher percentage of the variance of treatment response than models considering only genetic main effects. Finally, antidepressant drugs have been shown to reduce the abnormally high FKBP5 gene expression levels in patients with depression that successfully responded to the treatment, although there was no association between baseline FKBP5 mRNA levels and treatment response (Cattaneo et al., 2013).

CONCLUSIONS AND FUTURE DIRECTIONS

In the last years, several lines of research have implicated the FKBP5 gene in the etiology of stress-related phenomena. Consistent evidence supports associations between the FKBP5 polymorphisms and depression, suicidal behavior and PTSD. However, additional replication studies are warranted to provide conclusive data on the role of this gene in bipolar disorder and other conditions. For example, a recent report suggests that FKBP5 polymorphisms might also confer risk for psychotic experiences (Collip et al., 2013). The use of endophenotype-based approaches in addition to the classic genetic association studies will aid attempts to further link the FKBP5 gene to psychiatric disorders. In fact, some studies have already implicated the FKBP5 gene in endophenotypes associated with stress-related psychopathology, such as increased amygdala reactivity (White et al., 2012) and limbic system irritability after childhood trauma (Dackis, Rogosch, Oshri, & Cicchetti, 2012), as well as attention bias for threat and hippocampal alterations (Fani et al., 2013).

Increasing evidence highlights the importance of G x E studies for the detection of risk factors of stress-related psychopathology. Indeed, interaction between FKBP5 polymorphisms and early life stress exposure, rather than direct genetic effects, seems to better predict the development of PTSD, adult depression and suicide behavior. Importantly, the modulatory role of FKBP5 gene might not apply to all types of early stressors, as it seems to be specific for the effects of severe trauma-related stress. Upcoming epigenetic studies will contribute to elucidating mechanisms by which the interaction of FKBP5 gene and childhood trauma increases the susceptibility to mood disorders and PTSD.

Inconsistent findings with regard to the concrete FKBP5 polymorphisms and allelic-variants that increase the vulnerability to stress-related disorders are commonly reported. It is possible that, due to the high linkage disequilibrium in the FKBP5 gene and variations in allele frequencies by ethnicity (Binder, 2009), some of the SNPs tested might reflect the action of other functional variants in linkage disequilibrium, thus limiting the detection of significant associations. In addition, little is known about the functional impact of the FKBP5 polymorphisms on GR signaling. Future studies should therefore address these issues to better identify genetic and environmental conditions that render individuals from different ethnic backgrounds vulnerable to stress-related disorders. Moreover, detailed knowledge about the functional properties of FKBP5 polymorphisms might facilitate the identification of biologically distinct subtypes of depression and PTSD, which could lead to advances in the diagnosis and treatment of these disorders.

Finally, FKBP5 polymorphisms have also been demonstrated to play a promising role in pharmacogenetics of antidepressant drugs. For instance, FKBP5 genotype could potentially be harnessed as biomarker of SSRI response. However, more research is needed to fully resolve the involvement of the FKBP5 gene in the response to antidepressant treatment, with special focus on G x G interactions.

To sum up, gaining further knowledge of the FKBP5 gene could improve understanding and treatment of stress-related disorders that might be useful for future interventions. To this end, it might be advantageous not just to consider the FKBP5 gene alone, but in concert with the environment and other genes.

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