Gene–Stress–Epigenetic Regulation of *FKBP5*: Clinical and Translational Implications

Anthony S Zannas^{1,2}, Tobias Wiechmann¹, Nils C Gassen¹ and Elisabeth B Binder^{*,1,3}

¹Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany; ²Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; ³Department of Psychiatry and Behavioral Sciences, Emory University Medical School, Atlanta, GA, USA

Stress responses and related outcomes vary markedly across individuals. Elucidating the molecular underpinnings of this variability is of great relevance for developing individualized prevention strategies and treatments for stress-related disorders. An important modulator of stress responses is the FK506-binding protein 51 (FKBP5/FKBP51). FKBP5 acts as a co-chaperone that modulates not only glucocorticoid receptor activity in response to stressors but also a multitude of other cellular processes in both the brain and periphery. Notably, the *FKBP5* gene is regulated via complex interactions among environmental stressors, *FKBP5* genetic variants, and epigenetic modifications of glucocorticoid-responsive genomic sites. These interactions can result in *FKBP5* disinhibition that has been shown to contribute to a number of aberrant phenotypes in both rodents and humans. Consequently, FKBP5 blockade may hold promise as treatment intervention for stress-related disorders, and recently developed selective FKBP5 blockers show encouraging results *in vitro* and in rodent models. Although risk for stress-related disorders is conferred by multiple environmental and genetic factors, the findings related to *FKBP5* illustrate how a deeper understanding of the molecular and systemic mechanisms underlying specific gene–environment interactions may provide insights into the pathogenesis of stress-related disorders.

Neuropsychopharmacology Reviews (2016) **41**, 261–274; doi:10.1038/npp.2015.235; published online 2 September 2015

INTRODUCTION

Psychological stress is a well-established risk factor for a multitude of disease phenotypes. Stressor exposure, including psychological stress, has been linked with a host of psychiatric disorders, including posttraumatic stress disorder (PTSD), major depression (MDD) (Kendler *et al*, 1999), cognitive impairment (Tsolaki *et al*, 2009), psychotic disorders (van Winkel *et al*, 2008), and addictions (Sinha, 2007). Furthermore, psychological stress has been shown to impact risk for medical conditions, such as cardiovascular disease, cancer, and immune disorders (Cohen *et al*, 2007; Kaltsas *et al*, 2012). Given that stress-related medical and psychiatric conditions are among the leading causes of morbidity and mortality, improved understanding of how stress contributes to their pathogenesis could have tremendous implications for reducing disease burden on individuals and societies.

Outcomes following stressor exposure vary markedly across individuals. For example, despite the ubiquity of traumatic events in human societies, only a proportion of individuals develops PTSD following trauma exposure (Galea *et al*, 2005), and several individuals may even show positive psychological changes, known as posttraumatic growth (PTG) (Jin *et al*, 2014). In line with these findings in humans, distinct rodent strains show variable rates of negative behavioral outcomes following similar stressors (Russo *et al*, 2012; Uchida *et al*, 2011). Substantial heterogeneity exists even for negative outcomes that follow stressor exposure. For example, exposure of different individuals to similar traumatic experiences may lead to the development of PTSD, MDD, or a combination of the two phenotypes (Belleville *et al*, 2012; Nillni *et al*, 2013). These pleiotropic effects of stressor exposure likely result from complex interactions among stressful experiences over the lifetime, other environmental factors, and multiple genetic and epigenetic factors that modulate stress responses and can shape stress-related phenotypes (Zannas and West, 2014b).

An important modulator of stress responses and the focus of this review is FK506-binding protein 51 (FKBP5/FKBP51),

*Correspondence: Dr E Binder, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, Munich 80804, Germany, Tel: +49 89 30622301, Fax: +49 89 30622610, E-mail: binder@psych.mpg.de

Received 1 May 2015; revised 6 July 2015; accepted 7 July 2015; accepted article preview online 13 August 2015

which, among other functions, acts as a co-chaperone that modulates glucocorticoid receptor (GR) activity. In the first section, we will introduce the molecular mechanisms through which FKBP5 is not only induced by stressors and interacts with the GR but also with other molecular partners to impact a number of cellular processes. Subsequently, we will focus on gene–environment–epigenetic interactions that regulate FKBP5 levels, and we will highlight the pleiotropic consequences of FKBP5 disinhibition. Finally, we will discuss the clinical and translational implications of these molecular mechanisms and future directions for this line of research.

ROLE OF FKBP5 IN GR SIGNALING AND STRESS RESPONSES

Several studies have shown that FKBP5 exerts an inhibitory role on GR signaling with intracellular as well as systemic effects. FKBP51/FKBP5 is a 51-kDa immunophilin that belongs to the family of FK506-binding proteins, originally named after their ability to bind the immunosuppressant FK506 (Wiederrecht *et al*, 1992). Functional characterization of FKBP5 revealed that it has peptidyl-prolyl *cis*–*trans* isomerase activity and contains a tetratricopeptide repeat protein domain (Schiene-Fischer and Yu, 2001; Schmidt *et al*, 2012), which enables the protein to act as a co-chaperone that changes folding and activity of other proteins. Among the multiple molecular interactions of FKBP5 and particularly important for stress regulation is its binding to heat-shock protein 90 (Hsp90), P23 protein, and other co-chaperones of the steroid receptor complex (Schiene-Fischer and Yu, 2001). By interacting with this complex, FKBP5 can modulate sensitivity of the GR. In particular, *in vitro* experiments have shown that FKBP5 reduces interaction of the GR complex with the transport protein dynein, delays nuclear translocation of the GR, and decreases GR-dependent transcriptional activity (Wochnik *et al*, 2005). Upon glucocorticoid binding, however, FKBP5 is exchanged for FK506-binding protein 52 (FKBP52/FKBP4), a co-chaperone that recruits dynein to the GR complex and promotes nuclear translocation and transcriptional regulation (Davies *et al*, 2002; Wochnik *et al*, 2005). The role of FKBP5 in GR signaling is summarized in Figure 1.

To understand how the above-described effects of intracellular regulation of GR-sensitivity affect stress responsivity at the organismal level, it is important to briefly review the function of the primary effector of the stress response, the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is initiated via input of cortical and limbic brain regions at the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) and angiotensin vasopressin that act on the anterior pituitary to stimulate the secretion of ACTH into the peripheral blood stream. This peptide hormone then promotes the adrenal secretion of glucocorticoids (Chrousos and Gold, 1992). Circulating glucocorticoids exert actions in essentially every body organ via activation of two receptors, the high affinity

mineralocorticoid receptor (MR) and the lower affinity GR. Both are intracellular receptors, which after nuclear translocation can activate or repress a large number of glucocorticoid-responsive genes (Nicolaidis *et al*, 2014). In this review, we will focus on the GR, as MR–FKBP5 interactions are less well studied. The GR affects gene transcription not only by binding of its homodimer to glucocorticoid response element (GRE) sequences in regulatory regions of target genes (Bamberger *et al*, 1996) but also via GRE-independent interactions of the GR monomer with other transcription factors (Scheinman *et al*, 1995) (Figure 1). The pattern of GR-mediated transcriptional regulation is tissue specific and depends on the GR isoform expressed and the accessibility of genomic binding sites (Lu and Cidlowski, 2005; Nicolaidis *et al*, 2014). In addition to regulating adaptive stress responses, including metabolism, immune activation, and cell proliferation and differentiation, GR activation mediates multiple negative feedback loops that restrain HPA axis activity. In the brain, GR activation leads to rapid inhibition of genes that encode mediators of the HPA axis, such as CRH and ACTH (Russell *et al*, 2010; Watts, 2005). Negative feedback regulation is also promoted by GR occupancy in the hippocampus (Sapolsky *et al*, 1990), a brain region that has been shown to suppress HPA basal activity and reactivity to stress (Jacobson and Sapolsky, 1991). Lastly, GR activation in multiple tissues results in rapid induction of FKBP5 transcription and translation (Jaaskelainen *et al*, 2011). Given the inhibitory effect of FKBP5 on GR activity, the intracellular GR-mediated FKBP5 induction creates an ultra-short, negative feedback loop that regulates GR activity (Denny *et al*, 2000; Zannas and Binder, 2014a; Figure 1).

By modulating GR signaling, FKBP5 has the potential to modulate the actions of glucocorticoids, hormones with pleiotropic effects that can affect essentially every body tissue (Chrousos and Gold, 1992; Nicolaidis *et al*, 2014). In fact, the function of FKBP5 was initially discovered in New World monkeys, which have very high circulating glucocorticoid levels but usually do not present with any symptoms associated with this dysregulation. This has been attributed to inherently high FKBP5 levels that confer GR resistance (Scammell *et al*, 2001). As we discuss below, FKBP5 dysregulation, and in particular FKBP5 disinhibition, has been linked with a number of stress-related disorders.

ROLE OF FKBP5 IN OTHER MOLECULAR PROCESSES

Although in psychiatry and neuroscience FKBP5 is most commonly discussed as a modulator of glucocorticoid signaling, it is important to highlight that it also interacts with a host of other molecular partners, affecting several cellular processes. Detailed description of these processes is beyond the scope of this review, but the most important interactions of FKBP5 are summarized here and in more detail in Figure 2. As co-chaperone of the Hsp90 complex,

Figure 1. Schematic representation of the molecular events involved in glucocorticoid-mediated FKBP5 induction, the resulting intracellular negative feedback loop, and effects on other biological processes. Glucocorticoids enter the cytoplasm (a) and activate the glucocorticoid receptor (GR) complex. FKBP5 binding to the complex reduces affinity of glucocorticoids to the GR and delays translocation of the GR to the nucleus. However, exchange of FKBP5 for FKBP4 (b) results in GR translocation to the nucleus (c). The GR can either interact as a monomer with other transcription factors (d) or form a homodimer that binds to DNA at glucocorticoid response elements. Overall, GR functions result in transactivation or transrepression of a large number of genes. The *FKBP5* gene is highly responsive to GR, but responsiveness depends on *FKBP5* polymorphisms and methylation status (e). The synthesized *FKBP5* mRNA translocates to the cytoplasm (f) where it is translated into FKBP5 protein. FKBP5 then inhibits GR activity not only forming an ultra-short, intracellular negative feedback loop of GR signaling but also modulating several other biological pathways (g).

FKBP5 interacts with steroid receptors other than the GR, including the MR, progesterone (PR), estrogen (ER), and androgen (AR) receptors. Similar to its effects on GR, FKBP5 inhibits MR and PR activity (Barent *et al*, 1998; Gallo *et al*, 2007; Hubler *et al*, 2003), whereas it promotes ER and AR activity (Shrestha *et al*, 2015; Stechschulte and Sanchez, 2011), a function that may have important implications in the pathogenesis of prostate cancer (Stechschulte and Sanchez, 2011). Furthermore, FKBP5 has been shown to interact with molecular pathways involved in immune regulation and relevant for oncogenesis. In particular, FKBP5 interacts with and inhibits calcineurin (Baughman *et al*, 1995; Li *et al*, 2002; Weiwad *et al*, 2006) and interacts with the inhibitor of nuclear factor kappa-B (NF- κ B) kinase subunit alpha (IKK- α), promoting NF- κ B signaling (Bouwmeester *et al*, 2004; Romano *et al*, 2004). This latter effect has been implicated in the pathogenesis of melanoma, where FKBP5 has been suggested as a marker of malignant potential and FKBP5 blockade as possible treatment for this malignancy (Romano *et al*, 2010). FKBP5 has also been

shown to negatively regulate protein kinase B (Akt) signaling, an interaction with important implications for cancer response to chemotherapy and cerebral ischemia/reperfusion injury (Pei *et al*, 2009; Wei *et al*, 2014). This interaction could also exert effects on the mammalian target of rapamycin pathway, a pathway that is activated by Akt and has been implicated in the antidepressant activity of ketamine (Li *et al*, 2010; Markman *et al*, 2010). More recently, FKBP5 was shown to have effects on autophagy and on the glycogen synthase kinase 3 beta and these may contribute to antidepressant drug actions (Gassen *et al*, 2014; Gassen *et al*, 2015). Lastly, FKBP5 has been shown to synergize with Hsp90 to block degradation of tau, contributing to accumulation of pathogenic tau species in the brain and to Alzheimer-type pathology (Blair *et al*, 2013).

The constant interplay of these processes gives rise to a complex network of FKBP5-modulated intracellular events. The specific pattern of this intracellular crosstalk may vary across tissues and may contribute to the pleiotropic consequences of FKBP5 dysregulation.

Figure 2. Selected interactions of FKBP51/FKBP5 and their impact on molecular processes. As discussed in the text, FKBP51 exerts an inhibitory effect on GR function, thus having a crucial role in stress physiology. FKBP51 further interacts with PHLPP, Akt, and Beclin1 and affects Akt/Beclin1-driven autophagy. As PHLPP dephosphorylates Akt at serine 473, inactive Akt is recruited to Beclin1, resulting in lower inhibitory phosphorylation of Beclin1 and thus the induction of autophagic pathways. Impact on autophagy might be a link of FKBP51 with diseases characterized by defective autophagy, including neurodegeneration, inflammatory diseases, and aging. FKBP51 further interacts with CDK5 and PP2A resulting in inhibition of GSK3 β and activation of promoters targeted by the transcription factors TCF/LEF. FKBP51 shows high affinity to calcineurin (PP2b), and high levels of FKBP51 result in inhibition of PP2b-directed NFAT-signaling, thus affecting T-cell proliferation and function. Green color represents activation and red color represents inhibition by FKBP51.

GENE–STRESS–EPIGENETIC REGULATION OF FKBP5

FKBP5 Gene Regulation

The *FKBP5* gene is located on the short arm of chromosome 6 (6p21.31), spans around 155 kb, and consists of 13 exons (Figure 3). *FKBP5* transcription is induced not only by GR but also by AR and PR activation (Hubler *et al*, 2003; Hubler and Scammell, 2004; Magee *et al*, 2006; U *et al*, 2004). GR-induced transcription is mediated by binding of the GR to GREs, which are located in a region spanning over 100 kb and range from upstream of *FKBP5* promoter to introns 2, 5, and 7 of the gene (Paakinaho *et al*, 2010). These enhancer elements promote transcription via the formation of three-dimensional (3D) chromatin loops and by coming into direct contact with the transcription start site and RNA polymerase II (Jaaskelainen *et al*, 2011; Klengel *et al*, 2013b). Active epigenetic marks, such as histone H3 lysine 4 methylation, lysine 27 acetylation, and lysine 36 trimethylation, indicate that at least in some tissues the locus conformation is already open before induction by steroids (Jaaskelainen *et al*, 2011).

FKBP5 is expressed at baseline and shows robust induction by GR across several tissues and species, but expression patterns show substantial variability. At baseline, in both

humans and mice, *FKBP5* expression levels differ across tissues, being markedly elevated in metabolically active tissues, such as adipocytes, and higher in T cells as compared with other peripheral blood cell types (<http://biogps.org/>). In humans, an over eightfold increase in *FKBP5* mRNA has been observed in peripheral blood cells 3 h after oral administration of 1.5 mg of the GR agonist dexamethasone, and *FKBP5* is in fact the most robustly induced transcript followed by *IL1R2*, *ZBTB16*, *ECHDC3*, and *DDIT4* (Menke *et al*, 2012). Similar robust induction by GR activation has been noted in omental and subcutaneous adipose tissues (Pereira *et al*, 2014). However, *FKBP5* induction can vary across individuals and has been proposed as a marker of GR sensitivity (Kelly *et al*, 2012; Menke *et al*, 2012; Vermeer *et al*, 2003). In the rodent brain, *FKBP5* has the highest expression levels in the hippocampus, with much lower expression in other brain regions (Scharf *et al*, 2011). Substantial variability of *FKBP5* expression is similarly observed in the human brain, with high levels noted, for example, in the hippocampus but low levels in the hypothalamus (<http://human.brain-map.org/>). Following stimulation with dexamethasone or stress exposure, *FKBP5* expression is dramatically increased in a number of brain regions (Scharf *et al*, 2011), with the largest changes observed in the amygdala and the

Figure 3. Schematic overview of key features of the *FKBP5* locus. Shown tracks are from the UCSC genome browser (<https://genome.ucsc.edu>). *FKBP5* splicing variants are derived from the RefSeq Genes Track. Bisulfite sequencing loci are shown as a custom track and are based on Klengel *et al* (2013b) and Yehuda *et al* (2013). As shown, these CpG sites are distinct from CpGs covered by the Illumina 450K array (shown for two blood cell lines and one neuroblastoma cell line based on ENCODE/HAIB; warm colors, high methylation; cold colors, low methylation levels). Glucocorticoid response elements (GREs) are displayed for A549 and ECC-1 cells and are derived from transcription factor (glucocorticoid receptor) ChIP-sequencing data of the ENCODE project. Conserved GREs are highlighted with red asterisk and are derived from the HMR Conserved Transcription Factor Binding Sites track (z-score cutoff: 1.64). GxE SNPs represent SNPs identified in gene–environment interaction studies and are mapped based on the Common SNPs(142) track (see also Table 1). The H3K27Ac Mark and H3K4Me3 tracks show data from two different blood cells lines derived from the ENCODE project.

PVN, whereas the hippocampus shows a much less pronounced *FKBP5* induction. This likely reflects the high baseline levels of *FKBP5* in this brain region that may confer relative GR resistance. *FKBP5* expression can also be influenced by other factors. For example, *FKBP5* expression increases with age in many regions of the mouse brain, including the hippocampus and cortical and subcortical structures (Jinwal *et al*, 2010). In humans, increases in the hippocampus, postcentral gyrus, superior frontal gyrus, and entorhinal cortex have been documented (Blair *et al*, 2013; Jinwal *et al*, 2010). Changes in *FKBP5* mRNA levels have also been reported in peripheral blood cells across the menstrual cycle, with lower levels observed during the follicular phase of the cycle (Kinouchi *et al*, 2008).

The tissue- and context-specific *FKBP5* expression should be taken into account when examining the consequences of *FKBP5* dysregulation and when considering *FKBP5* as candidate therapeutic target. Tissues with high baseline *FKBP5* expression may be particularly amenable and susceptible to such interventions. On the other hand, tissues showing low baseline expression levels might be more relevant for dynamic regulation within the stress response. As we will discuss below, dynamic *FKBP5* responses appear to be particularly relevant for gene–stress interactions and related outcomes.

FKBP5 Genetic Variation

With the use of tagging experiments and, more recently, next-generation sequencing, *FKBP5* variants have been

described in detail (Ellsworth *et al*, 2013a; Ellsworth *et al*, 2013b; Pelleymounter *et al*, 2011) (Figure 2). The best-characterized polymorphisms comprise a haplotype that spans the whole gene, contains up to 18 single-nucleotide polymorphisms (SNPs) in strong linkage disequilibrium in Caucasians ($r^2 > 0.8$, distance > 500 kb, 1000 genomes next-generation sequencing project), and is commonly tagged by rs3800373, rs9296158, or rs1360780. This haplotype has been associated with heightened induction of *FKBP5* mRNA in response to GR activation (Binder *et al*, 2004).

This functionality was shown to be likely conferred by rs1360780, a SNP located in an enhancer region, 488 bp away from a functional GRE in intron 2 of the gene, with the rarer T allele facilitating GR-mediated induction of *FKBP5* mRNA (Klengel *et al*, 2013b). As shown by chromatin conformation capture experiments in lymphoblastoid cell lines, T allele is associated with a chromatin 3D conformation that promotes direct contact of the intron 2 GRE with the transcription start site. This change in conformation is likely supported by the ability of the sequence containing the T allele to bind TATA-box binding protein, a protein shown to bring long range enhancer elements in contact with the transcriptional machinery (Bertolino and Singh, 2002), with significantly higher affinity than the alternate C allele (Klengel *et al*, 2013b). Consequently, T allele is associated with alteration of the ultra-short *FKBP5*-mediated feedback inhibition of the GR, especially during the stress recovery period (Zannas and Binder, 2014a). However, other polymorphisms within or outside of this *FKBP5* haplotype may also have functional

effects, either at baseline or following transcriptional induction (Ellsworth *et al*, 2013a).

Overall, the rs1360780 T allele, and related haplotypes, is associated with an increase in GR-induced *FKBP5* upregulation. This then leads to a more dynamic *FKBP5*-mediated intracellular inhibition of GR that interferes with GR-dependent feedback of the HPA axis on the systemic level and can contribute to HPA axis dysregulation and stress-related phenotypes. This has been supported by studies showing prolonged cortisol responses and self-reported anxiety symptoms in T allele carrying healthy adults and adolescents after exposure to psychosocial stressors (Buchmann *et al*, 2014; Hohne *et al*, 2014; Ising *et al*, 2008) and increased cortisol levels in infants carrying the T allele following exposure to a female stranger coupled with brief parental separation (Luijk *et al*, 2010). In line with these findings, T allele has been associated with non-suppression of the HPA axis in healthy adults, as measured with the dexamethasone suppression (DST) and the dexamethasone–corticotropin releasing hormone (Dex-CRH) tests (Binder *et al*, 2008; Touma *et al*, 2011). Similar non-suppression of the HPA axis has been shown in MDD patients with the T allele, who show less suppression of the HPA axis in the DST paradigm and less *FKBP5* mRNA induction in peripheral blood (Menke *et al*, 2013). However, the effects of *FKBP5* genotype on the HPA axis have been shown to vary across age groups, with aged, but not young, T-allele carriers showing suppressed cortisol responses following the Dex-CRH test in one study (Fujii *et al*, 2014a). Opposite effects of the T-allele in a low-dose dexamethasone suppression test have been observed with PTSD (Mehta, 2011). Here, the T allele was associated with GR super-suppression in PTSD, while hypocortisolism was seen in PTSD patients carrying the other genotype. Although the mechanisms of this opposite effect on GR sensitivity in PTSD vs MDD are not clear, one could consider that hypocortisolism has been described as an adaptive response to heightened levels of stress (Fries *et al*, 2005). *FKBP5* risk allele could thus be associated with maladaptive HPA axis responses, but the direction of these may vary depending on stress and disease context. Different endocrine profiles in PTSD depending on *FKBP5* genotype status may also contribute to some controversial reports on increased GR sensitivity and hypocortisolism in this disorder (Sriram *et al*, 2012; Yehuda *et al*, 1990).

The T allele has also been associated with increased attention bias toward threat, threat- and fear-induced hippocampal activation, as well as alterations in hippocampal shape and amygdala volume (Fani *et al*, 2013; Holz *et al*, 2014; Pagliaccio *et al*, 2015). These findings suggest that the ‘risk’ haplotype contributes to neuroendocrine dysregulation and perturbations in brain circuitry that may predispose to the development of stress-related psychiatric disorders. Indeed, studies have linked this haplotype with increased risk for relapse and recurrent course of MDD and PTSD (Binder *et al*, 2004; Wilker *et al*, 2014), maladaptive personality traits and attitudes (Minelli *et al*, 2013; Shibuya

et al, 2010; Suzuki *et al*, 2014), worse cognitive performance (Fujii *et al*, 2014b), and higher risk for bipolar disorder (Willour *et al*, 2009), but lower risk for substance dependence and less severe withdrawal syndromes (Huang *et al*, 2014; Jensen *et al*, 2014; Levran *et al*, 2014). However, the main effects of *FKBP5* genotypes are generally not consistently replicated and none of the GWAS meta-analyses show strong signals for this genetic locus yet. More consistent are reports of *FKBP5* × specific environmental stress interactions altering the risk for psychiatric disorders.

Gene–Stress Interactions Involving *FKBP5*

An increasing number of studies have linked interactions between *FKBP5* genotypes and stressors with diverse phenotypes (Table 1). Phenotypes examined to date include MDD or depressive symptoms (Appel *et al*, 2011; Dackis *et al*, 2012; Kohrt *et al*, 2015; VanZomeran-Dohm *et al*, 2015; Zimmermann *et al*, 2011), PTSD and related phenotypes (Binder *et al*, 2008; Boscarino *et al*, 2012; Klengel and Binder, 2013a; Koenen *et al*, 2005; Xie *et al*, 2010), suicidality (Roy *et al*, 2010; Roy *et al*, 2012), aggression and violent behaviors (Bevilacqua *et al*, 2012), psychosis (Collip *et al*, 2013), cognitive performance (Hernaes *et al*, 2014), and general physical illness (Lessard and Holman, 2014). In 14 of these 18 study samples, equalling a total of 12 000 subjects, the alleles associated with higher *FKBP5* induction and prolonged cortisol responses are also the alleles associated with higher risk for the disorders. Interestingly, the effect is observed in different ethnic groups, including African American, Nepalese, European American, and European, suggestive of a similar functional relevance of the tested polymorphisms across ethnicities (Table 1).

These positive findings, however, have to be viewed in the context of the absence of a formal meta-analysis, which may be more difficult to conduct owing to the diverse outcomes and differences in study design and environmental measures employed by published studies. It is also important to note that gene–environment interaction studies are fraught with a number of limitations, including the complex nature of potential confounders involved in such studies, their generally low power and specific statistical issues as well as publication bias (Almli *et al*, 2014; Dick *et al*, 2015; Keller, 2014; Kraft and Aschard, 2015; Munafò *et al*, 2014), that could lead to spurious findings. Despite these limitations and the relative uncertainty of statistical interactions, the findings from studies examining *FKBP5*–stress interactions could inform issues common to gene–environment interactions ($G \times E$) studies in psychiatry as they extend the reported statistical interactions with experimental evidence for potential molecular and systemic mechanisms.

First, these studies suggest that the same ‘risk’ genotypes may lead to diverse phenotypes following exposure to similar stressors. As discussed above, stressors have been linked with a multitude of phenotypes, ranging from PTSD, MDD, and cognitive disorders to cardiovascular disease, cancer, and immune disorders (Cohen *et al*, 2007; Kaltsas *et al*, 2012;

TABLE 1 Human Studies Examining Interactions Between Stress and *FKBP5* Genotype on Psychiatric and Other Phenotypes and Related Endophenotypes

Reference	Sample size	Ethnicity (%)	Outcome (instrument)	Stress measure/paradigm	SNP examined	Risk allele	p-Value	Primary study findings
<i>Major depression and depressive symptoms</i>								
Appel et al (2011)	2144	Caucasian	Depression (BDI-II)	CTQ	rs1360780	T	p = 0.006	The T allele interacted with childhood abuse to increase MDD risk
Zimmermann et al (2011)	884 (discovery sample), 1037 (Dunedin study replication sample), and 1116 (E-Risk study replication sample)	All subjects Caucasian in the discovery sample and > 90% Caucasian in the replication samples	Depressive episodes (M-CIDI)	M-CIDI	rs3800373 rs9296158 rs1360780 rs9470080 rs4713916	C A T T A	p < 0.05	In the discovery sample, risk alleles interacted with lifetime trauma to predict the higher risk for MDD. Similar interaction was observed with childhood trauma for rs1360780 in the E-Risk but not the Dunedin sample
Dackis et al (2012)	236	African American (53.8) Caucasian (33.9) Hispanic (8.5) Other (3.8)	Depression (BDI-II) Dissociation (DES) Limbic irritability (LSCL-33)	CTQ	rs3800373 rs9296158 rs1360780 rs9470080	C A T T	p < 0.05	The risk haplotype interacts with childhood trauma having direct effects on limbic irritability and indirect effects on depression and dissociation
VanZomeren-Dohm et al (2015)	489	—	Depressive symptoms (MacArthur Health and Behavior Questionnaire)	MacArthur Health and Behavior Questionnaire	rs1360780	—	p < 0.05	<i>FKBP5</i> genotype interacts with peer victimization and child sex to shape risk for depressive symptoms
Kohrt et al (2015)	682	Brahman (16.1) Chhetri (63.2) Dalit/Nepali (17.4) Janajati (3.2)	Depressive symptoms (BDI) PTSD (PCL-C)	CTQ TEI SLERS	rs9296158 rs1360780 rs3800373 rs9470080	A — — —	p = 0.022	The risk genotype interacts with childhood maltreatment to predict depressive symptoms but not PTSD
<i>Posttraumatic stress disorder, posttraumatic growth, and related phenotypes</i>								
Koenen et al (2005)	46	African American (52.2) Caucasian (47.8)	PDEQ PTSD-RI	Medical injury severity scores	rs3800373 rs1360780	C T	p < 0.05	Risk alleles increase risk for peritraumatic dissociation in medically injured children
Binder et al (2008)	762	African American (95.2) Caucasian (2.2) Hispanic (0.6) Asian (0.1) Mixed (0.9) Other (1.0)	PTSD diagnosis (CAPS) and severity (mPSS), Depression (BDI)	CTQTEI	rs3800373 rs992105 rs9296158 rs737054 rs1360780 rs1334894 rs9470080 rs4713916	C — A — T — T —	p < 0.002 — p < 0.001 — p < 0.002 — p < 0.002 —	Risk alleles interacted with childhood but not adulthood trauma to predict greater PTSD symptomatology
Xie et al (2010)	2427	African American (52.9) Caucasian (47.1)	PTSD diagnosis (SSADDA)	SSADDA	rs3800373 rs9296158 rs1360780 rs9470080	— — — T	— — — p = 0.004	rs9470080 T-allele African American homozygotes had higher risk for PTSD if exposed to early trauma but lower risk if not exposed
Boscarino et al (2012)	410	Caucasian	Lifetime and early-onset PTSD	ACES	rs9470080	T	p = 0.026 (lifetime PTSD) p = 0.016 (early-onset PTSD)	The T allele confers risk that interacts with other genes and early trauma to predict PTSD risk
Klengel et al (2013)	1963	African American	PTSD (PSS, CAPS)	CTQ TEI	rs1360780	T	p = 0.012 (current PTSD symptoms) p < 0.001 (lifetime PTSD)	The T allele interacted with childhood maltreatment to predict increased current PTSD symptomatology and higher risk for lifetime PTSD
Dunn et al (2014)	204	Non-Hispanic African American	PTSD PTG	Severity of exposure to the hurricane Katrina	rs1360780 rs9296158 rs9470080	C — —	p = 0.011 but non-significant after correction for multiple testing	<i>FKBP5</i> rs1360780 T-allele carriers experienced greater PTG following exposure to the hurricane Katrina
<i>Suicide attempts</i>								
Roy et al (2010)	427	African American	Suicide attempt	CTQ	rs3800373 rs9296158 rs1360780 rs9470080 rs4713902 rs3777747	A G C — — —	p = 0.011 p = 0.028 p = 0.02 — — —	Risk genotypes interacted with childhood trauma to confer risk for suicide attempts
Roy et al (2012)	474	African American	Suicide attempts	CTQ	rs3800373	C	p = 0.0087	The risk allele had an additive effect with <i>CRHBP</i> genotype on risk for suicide attempts in individuals exposed to high early trauma
<i>Aggression and violent behaviors</i>								
Bevilacqua et al (2012)	411	Caucasian	Aggression (BGHA) Hostility (BDHI) Impulsiveness (BIS) Violence (prison records)	CTQ	rs3800373 rs9296158 rs1360780 rs9470080	C A T T	p = 0.017 p = 0.08 p = 0.015 p = 0.043	Risk genotypes interacted with early trauma to increase risk for aggression scores and reported violence
<i>Psychosis</i>								
Collip et al (2013)	401	Caucasian	CAPE	CTQ	rs9296158 rs1360780 rs1043805 rs4713916	A T A A	p < 0.01 p < 0.01 p < 0.001 p = 0.08	Risk alleles interacted with childhood trauma to predispose to psychotic symptoms

TABLE 1 (Continued)

Reference	Sample size	Ethnicity (%)	Outcome (instrument)	Stress measure/ paradigm	SNP examined	Risk allele	p-Value	Primary study findings
<i>Physical health</i>								
Lessard and Holman (2014)	527	Caucasian	Physical health (health survey)	DIST	rs1360780	T	$p < 0.001$ for childhood trauma $p = 0.006$ for adulthood stressors	Only in T-allele carriers, childhood trauma and adulthood stress to predict worse physical health
<i>Neuroimaging and neuroendocrine endophenotypes</i>								
Luijk <i>et al</i> (2010)	589 infants	—	Attachment behavior Salivary cortisol before and after stress exposure	Strange Situation Procedure	rs1360780	T	$p = 0.01$	T-allele carriers show stronger cortisol reactivity in response to the stress paradigm
White <i>et al</i> (2012)	139	Caucasian	Amygdala reactivity measured by fMRI	CTQ	rs3800373 rs9296158 rs1360780 rs9470080 rs7748266 rs9394309	G A T T T G	$p = 0.003$ $p = 0.002$ $p = 0.002$ $p = 0.011$ $p = 0.011$ $p = 0.097$	Risk alleles interacted with childhood emotional neglect to predict greater dorsal amygdala reactivity
Hemaus <i>et al</i> (2014)	184	Caucasian	Cognitive performance Hippocampal volume	CTQ	rs9296158 rs4713916 rs992105 rs3800373	— — — —	— — — —	Childhood trauma did not interact with <i>FKBP5</i> and <i>BDNF</i> to predict cognitive performance or hippocampal volumes
Hohne <i>et al</i> (2014)	116	Caucasian	Childhood adverse events (M-CID) Acute depression symptoms (BDI-II) Change in plasma cortisol	Change in plasma cortisol after TSST	rs1360780	T	$p < 0.05$	After exposure to psychosocial stressors, adult and adolescent healthy T-allele carriers showed more robust and prolonged cortisol responses and smaller changes in <i>FKBP5</i> mRNA
Pagliaccio <i>et al</i> (2014)	120	White (57.5) African American (30.0) Other or mixed race (12.5)	PAPA CAPA Amygdala activity, connectivity, volume (fMRI)	PAPA CAPA Behavioral tasks	rs1360780 as part of a polygenic score	T	$p = 0.04$	Higher polygenic scores were associated with smaller left but not right amygdala and hippocampus volumes in the context of low levels of stressor exposure
Holz <i>et al</i> (2014)	153	Caucasian	Amygdala activity, connectivity, volume (fMRI) SCID-I Substance use inventory BDI	CFA CTQ	rs1360780	T	$p = 0.049$	Childhood emotional neglect interacted with the T allele to predict increased threat-related activity in the right amygdala
Buchmann <i>et al</i> (2014)	195	—	Plasma cortisol	CTQ TSST Family adversity index measured by parent interview	rs1360780	T	$p < 0.05$	T-allele carriers show more pronounced cortisol responses to TSST. Childhood maltreatment is associated with lower cortisol levels and faster cortisol recovery but only in CC homozygotes.
Pagliaccio <i>et al</i> (2015)	107	African American (37.4) White (62.6)	Amygdala and hippocampal activity (fMRI) PAPA CAPA Tanner Pubertal Staging Questionnaire	PAPA CAPA Facial emotion processing task	rs1360780 as part of a polygenic score comprised of 10 SNPs within <i>CRHR1</i> , <i>NR3C2</i> , <i>NR3C1</i> , and <i>FKBP5</i>	T	$p = 0.037$ but non-significant after correction for multiple testing	Life events interacted with polygenic score to predict left hippocampal activity during the facial emotion processing task

Abbreviations: ACES, adverse childhood experiences study scale; BDHI, Buss-Durkee hostility inventory; BDI, Beck depression inventory; BGHA, Brown-Goodwin lifetime history of aggression questionnaire; BIS, Barratt impulsiveness scale; BDNF, brain-derived neurotrophic factor; CAPA, child and adolescent psychiatric assessment; CAPE, community assessment of psychic experiences; CAPS, clinician administered PTSD scale; CFA, childhood family adversity; CRHBP, corticotropin releasing hormone binding protein; CTQ, child trauma questionnaire; DES, dissociative experiences scale; DIST, diagnostic interview schedule trauma section; fMRI, functional magnetic resonance imaging; LSCL-33, Limbic system checklist-33; PAPA, preschool age psychiatric assessment; PCL-C, PTSD checklist-civilian version; PDEQ, peritraumatic dissociative experiences questionnaire; PSS, PTSD symptom scale; PTG, posttraumatic growth; PTSD, posttraumatic stress disorder; PTSD-RI, PTSD reaction index; SLERS, stressful life events rating scale for cross cultural study (SLERS); SNP, single nucleotide polymorphism; SSADDA, semi-structured assessment for drug dependence and alcoholism; TEI, traumatic events inventory; TSST, Trier social stress test.

Kendler *et al*, 1999; Sinha, 2007; Tsolaki *et al*, 2009; van Winkel *et al*, 2008). Phenotypes are generally thought to emerge through complex interactions among genetic, developmental, and environmental factors, and their development has been hypothesized to be mediated by underlying risk endophenotypes that lie in closer etiopathogenic proximity to risk genotypes such as altered endocrine regulation (Gottesman and Gould, 2003; Zannas and West, 2014b). Such an endophenotype, characterized by stress vulnerability, could be conferred by 'risk' *FKBP5* polymorphisms. This shared vulnerability may then contribute to the development of diverse phenotypes, depending on other genetic,

developmental, and environmental factors. In the case of *FKBP5*, this differential vulnerability could be driven by brain region-specific effects. An important brain region associated with *FKBP5*-related risk is the amygdala. In this brain region, the knockdown of *Fkbp5* in mice was shown to prevent stressor-induced increases in fear (Attwood *et al*, 2011), and two studies in humans have shown that *FKBP5* variants interact with childhood adversity to predict threat-induced activity in this region (Holz *et al*, 2014; White *et al*, 2012). *FKBP5* genotype was further shown to moderate, as part of a polygenic risk score comprised of selected HPA axis SNPs, stress-related structural and functional changes

not only in the amygdala but also in the hippocampus in humans. Specifically, higher polygenic scores were associated with smaller left, but not right, amygdala and hippocampus volumes in the context of low levels of stressor exposure (Pagliaccio *et al*, 2014). The authors suggested that this atypical finding might be explained by an overriding effect of high levels of stress exposure on genetic influences. Brain region-specific effects of environmental stressors on FKBP5 pathways have also been observed in transgenic mice. For example, mice lacking the *Fkbp5* gene show stress-induced decline in synapsin expression in the prefrontal cortex but not in the hippocampus (Schmidt *et al*, 2015). Understanding the brain region- but also cell type-specific effects of FKBP5 may offer valuable insights into the pathogenesis of stress-related conditions. In addition to such cell- and tissue-specific effects, differential sensitivity to effects of molecular partners of FKBP5 could also contribute to diverse symptom presentations. For example, the effects of FKBP5 dysregulation on NF- κ B signaling in the periphery could contribute to proinflammatory conditions and cancer (Romano *et al*, 2004; Romano *et al*, 2010). Similarly, tumorigenic effects could be mediated by the consequences of FKBP5 dysregulation on Akt signaling (Pei *et al*, 2009).

Second, outcomes have been shown to depend on the timing of the trauma exposure. Several studies have consistently shown that early trauma exposure in carriers of the haplotype associated with higher FKBP5 mRNA induction increases the risk for psychiatric disorders in adulthood (Appel *et al*, 2011; Binder *et al*, 2008; Dackis *et al*, 2012; Lessard and Holman, 2014; Roy *et al*, 2010; Roy *et al*, 2012; Xie *et al*, 2010; Zimmermann *et al*, 2011). Although similar interactions have been observed in some studies with traumatic events occurring beyond childhood, in adolescence and early adulthood (Lessard and Holman, 2014; Zimmermann *et al*, 2011), other studies found that FKBP5–stress interactions are triggered only by childhood trauma (Binder *et al*, 2008; Klengel *et al*, 2013b) (Table 1). In a recent study in adolescents, FKBP5 genotype moderated the effects of current peer victimization but not early institutionalization before the age of 2 years (VanZomeren-Dohm *et al*, 2015). These time-dependent findings are in accordance with studies highlighting the role of stressor timing on neuroplasticity and risk for psychopathology (Gee and Casey, 2015). The exact role of stressor timing, type, and duration and the potential synergistic effect of multiple stressor exposures will need to be further delineated in longitudinal gene–environment interaction studies.

Finally, so-called FKBP5 risk alleles do not confer risk under all circumstances. The same alleles have also been associated with PTG, for example, following exposure to the Hurricane Katrina (Dunn *et al*, 2014), as well as less depression in the context of early institutionalization but low current stress (VanZomeren-Dohm *et al*, 2015) and less lifetime PTSD in the absence of child abuse in a highly traumatized cohort (Klengel *et al*, 2013b). Furthermore, in some, but not all studies, the FKBP5 allele associated with stronger mRNA induction has also been associated with a

favorable response to antidepressant drug treatment (Binder *et al*, 2004; Zou *et al*, 2010), while a worse response to psychotherapy was reported for PTSD patients carrying the risk allele (Wilker *et al*, 2014). As previously discussed, these heterogeneous outcomes raise the possibility that what such alleles may confer is increased plasticity, with opposite outcomes being then possible depending on the presence of positive or negative environmental influences (Belsky and Hartman, 2014; Belsky *et al*, 2009; Belsky and Pluess, 2013). Yet the exact role of timing, type and duration of these genotype-dependent environmental challenges and the molecular and cellular mechanisms underlying such differential outcomes remain to be elucidated by future studies.

Epigenetic Regulation of FKBP5 and a Potential Role in Mediating Gene–Stress Interactions

An important mechanism that mediates lasting environmental effects on gene function occurs at the level of epigenetic regulation of gene transcription (Feil and Fraga, 2011; Telese *et al*, 2013). Epigenetic changes consist of a number of biochemical processes, including DNA methylation and hydroxymethylation, posttranslational histone modifications, and non-coding RNAs. Among these, DNA methylation is the most established lasting epigenetic modification induced by early life stressor exposure (Franklin *et al*, 2010; Weaver *et al*, 2004; Zannas and West, 2014b). Importantly, DNA methylation changes have been shown to occur in an allele-specific manner (Meaburn *et al*, 2010), suggesting that epigenetic changes induced by stressors may also depend on genetic context.

In light of these facts, a plausible question is whether allele-specific DNA methylation changes may mediate the interaction between childhood abuse and FKBP5. In fact, in rs1360780 T allele carriers, but not individuals with the alternate genotype, exposure to childhood abuse was shown to be associated with lower methylation of CpG sites located near the functional FKBP5 intron 7 GRE in DNA from peripheral blood cells (Klengel and Binder, 2013a; Klengel and Binder, 2015). Reporter gene assays showed that decreased methylation in this region is associated with disinhibited GR-induced transcription of FKBP5 and GR resistance as revealed in *ex vivo* assays of GR sensitivity (Klengel *et al*, 2013b). This reduced methylation was observed specifically with exposure to childhood but not adult trauma and did not correlate with current plasma cortisol levels. Previous studies have shown that GR binding to GREs can induce CpG demethylation, and this demethylation can lead to de-repressed transcriptional responses to subsequent glucocorticoid exposure (Thomassin *et al*, 2001); thus we hypothesize that early trauma in FKBP5 risk allele carriers leads to enhanced GR activation and demethylation of FKBP5 GREs, and to further disinhibition of FKBP5 transcriptional regulation and GR resistance, selectively in T allele carriers (Figure 1). To test this hypothesis, human hippocampal precursors (Anacker *et al*, 2011) were treated with dexamethasone, a selective GR agonist, at several

differentiation stages. Dexamethasone exposure during proliferation and early differentiation induced demethylation of the same CpGs in intron 7 of the *FKBP5* gene that shows reduced methylation with early trauma. In fact, these three CpGs are located within or between the three predicted consensus GRE sites in this locus, while the ones not affected are located upstream. This further suggests a direct causal effect of GR activation in this demethylation. This demethylation was stable to a 20-day washout when the cells were treated during differentiation but not in cells treated after differentiation. Taken together, these data support a developmentally restricted effect of early trauma and glucocorticoid exposure on selective *FKBP5* methylation sites that appears to occur across peripheral and neuronal tissues and to depend on susceptible *FKBP5* variants. The molecular mechanisms associated with the differential epigenetic effects depending on developmental stage have not yet been elucidated, but strong developmental regulation has been reported for several epigenetic readers and writers (Lv *et al*, 2013).

Notably, *FKBP5* methylation changes have been observed but may also vary across species and in different environmental contexts. In mice, *Fkbp5* demethylation is induced by systemic glucocorticoid exposure in the hippocampus, hypothalamus, and peripheral blood (Lee *et al*, 2010). However, the mouse glucocorticoid-susceptible CpGs are located not in intron 7, as in humans, but in intron 1 of the gene. On the other hand, CpG sites located within intron 5 of *Fkbp5* have been shown to be demethylated with aging in mice (Sabbagh *et al*, 2014). Aging has also been shown to accelerate *FKBP5* demethylation in several regions in the human brain, but this effect was observed in intron 7 and promoter region of the gene (Blair *et al*, 2013). These species-specific differences in the epigenetic regulation of *FKBP5* across species are supported by data showing that only GREs located within the introns 1 and 5 of the gene are conserved across mice, rats, and humans (Figure 2). It will be important to further elucidate the species- and context-specific pattern of epigenetic modifications in *FKBP5* to promote translatability and potential utility of these modifications as biomarkers of distinct stress phenotypes.

The mechanisms underlying these changes in DNA methylation levels remain poorly understood. Active DNA demethylation through receptor-mediated processes is a plausible mechanism (Kress *et al*, 2006; Nelson *et al*, 2008), but the potential involvement of active demethylation and hydroxymethylation as intermediate step and how this may be targeted to selective CpGs has not been examined. An additional contributing mechanism may be the downregulation of DNA methyltransferase 1 (Yang *et al*, 2012). Uncovering the molecular events that underlie stressor-induced epigenetic modifications of *FKBP5* could offer the opportunity to understand mechanisms that may allow reversal of these molecular processes and the consequent phenotypes.

FKBP5 DISINHIBITION: CLINICAL AND TRANSLATIONAL IMPLICATIONS

Several lines of evidence suggest that *FKBP5* disinhibition may, in many cases, predispose an individual to the development of pathological phenotypes. This was initially supported by gene–environment interaction studies showing that the haplotype associated with higher *FKBP5* mRNA induction confers vulnerability to the development of stress-related psychiatric disorders following traumatic exposure (Table 1). More recently, postmortem studies have found *FKBP5* overexpression in several brain regions in association with Alzheimer's disease and schizophrenia (Blair *et al*, 2013; Sinclair *et al*, 2013). Although postmortem investigations offer the advantage of examining *FKBP5* levels in brain tissue, they also have the caveat of not accounting for confounding factors, such as stressor exposure or cortisol levels, which may drive and thus confound the putative differences in *FKBP5* levels between cases and controls. Beyond psychiatric phenotypes, *FKBP5* disinhibition has also been implicated in a multitude of other medical conditions, including poor glucocorticoid responses in asthma (Stechschulte and Sanchez, 2011; Woodruff *et al*, 2007), insulin resistance in metabolically active tissues (Pereira *et al*, 2014), and immune dysregulation that may contribute to the pathogenesis of melanoma and other cancer types (Kim *et al*, 2012; Romano *et al*, 2004; Romano *et al*, 2010). Taken together, these lines of evidence support a model where *FKBP5* disinhibition may represent a stress-sensitive endophenotype for a number of disease phenotypes.

These human studies have been corroborated by studies in animal models. Given the current lack of humanized *Fkbp5* transgenic mice, animal studies to date have either examined conventional *Fkbp5* knockouts (KO) or conditional *Fkbp5* knockdown. Compared with wild-type mice, *Fkbp5* KOs generally exhibit a more resilient phenotype, characterized by lower corticosterone levels and improved sleep architecture and behavioral responses following restraint, forced swim, and social defeat stress, as well as enhanced cognitive flexibility in the radial arm water maze (Albu *et al*, 2014; Hartmann *et al*, 2012; O'Leary *et al*, 2011; Sabbagh *et al*, 2014; Touma *et al*, 2011). However, to mechanistically dissect the role of *Fkbp5* disinhibition in stress-related phenotypes, it will be important to examine its possibly distinct role in different brain regions. For example, selective *Fkbp5* silencing in the amygdala was shown to confer resilience to restraint stress exposure (Attwood *et al*, 2011). Higher levels of hypothalamic *Fkbp5* expression were related to increased body weight gain in mice on high-fat diet (Balsevich *et al*, 2014), suggesting additional brain region-specific links to peripheral metabolic phenotypes beyond downstream activation of immune pathways.

These observations spurred efforts to develop drugs that block *FKBP5* activity. Until recently, such efforts had been hindered by their non-selective binding to other FKBP5s,

most importantly FKBP4 (Gaali *et al*, 2011), which, as we discussed above, has opposite effects on GR signaling (Figure 1). To overcome this issue, highly selective FKBP5 ligands (SAFit) were recently developed, based on an induced-fit mechanism. These compounds were shown to stimulate neurite outgrowth in primary hippocampal neurons and to promote homeostasis of the HPA axis and stress-coping behaviors in mice (Gaali *et al*, 2015). Although these findings are encouraging, the precise cellular and molecular mechanisms that underlie SAFit activity remain unknown. In particular, it will be critical to elucidate which molecular interactions of FKBP5 and, consequently, which cellular processes are differentially affected by SAFit in different cell types, regions, and organisms. For example, FKBP5 inhibitors block the interaction with the GR but not the Akt pathway (Fabian *et al*, 2013). A more detailed assessment of differential effects of downstream partners will need to be performed to assess the optimal combination of blocked downstream target for specific disease phenotypes. Finally, in certain cases and selective tissues, FKBP5 upregulation may represent an adaptive and desirable response to heightened levels of stress, and in such cases FKBP5 blockade could lead to adverse consequences. This is suggested, for example, by studies showing that high-induction FKBP5 alleles may be associated with favorable antidepressant responses (Binder *et al*, 2004; Zou *et al*, 2010) and that FKBP5 can promote antidepressant activity (Gassen *et al*, 2014; Gassen *et al*, 2015). These questions related to potency, mechanism, and safety of SAFit remain to be examined and extended to humans.

CONCLUSIONS AND FUTURE DIRECTIONS

Since the discovery of FKBP5 20 years ago (Baughman *et al*, 1995), converging evidence from human and animal studies has advanced our understanding into how gene–stress–epigenetic interactions may regulate FKBP5 responsivity, and how FKBP5 disinhibition may contribute to stress-related phenotypes, thus serving as potential therapeutic target (O'Leary *et al*, 2011; Schmidt *et al*, 2012). Below we discuss remaining open questions and potential future directions for this line of research.

First, can we infer strategies for stress-disorder biomarker research from the example of FKBP5? As we discussed, complex phenotypes are likely shaped by the effects of gene–stress–epigenetic interactions on tissues that are involved in disease pathogenesis. Given the inherent limitations of examining such tissues, for example, brain in living humans, it is essential to identify peripheral markers that correlate with similar markers in the tissues of interest. This is true for genetic polymorphisms but not for epigenetic modifications, which show substantial tissue specificity. Endeavors to identify biomarkers may benefit from the translation of findings from living human cohorts with detailed data on timing and type of stressor exposure to molecular findings

from postmortem human studies and animal models. For instance, changes in *Fkbp5* methylation in mouse blood have been suggested to be a promising biomarker that reflects chronic glucocorticoid exposure burden and similar changes in the brain (Ewald *et al*, 2014; Lee *et al*, 2011); similarly, glucocorticoid exposure affects methylation in a neuronal progenitor cell line of the same CpGs showing changes with early trauma in blood. However, it remains to be determined whether FKBP5 methylation levels also reflect the effects of chronic stress across tissues and whether this finding holds true in humans.

Second, can FKBP5 serve as a target for individualized treatment modalities? The development of SAFit has been an important step towards modulating phenotypes where FKBP5 disinhibition may be a contributing factor. A central question will be whether FKBP5 antagonism leads to symptom improvement only in patients with genetic and epigenetic changes associated with FKBP5 disinhibition or whether it could be beneficial to all patients showing similar symptoms. The use of biomarkers reflecting FKBP5 disinhibition, such as 'risk' FKBP5 polymorphisms or low FKBP5 methylation levels at CpG sites near functional GREs, may prove useful for guiding these studies. Furthermore, the timing of treatment initiation may be critical. Will inhibition of FKBP5 only be beneficial early in disease risk development, shortly after trauma exposure, when symptoms may not have fully developed, or will it also reduce symptoms once the disease has fully manifested? The first possibility may again require biomarkers of increased risk for efficient preventive strategies. In addition, different molecular interactions of FKBP5 may contribute to different phenotypes and these specific molecular events may need to be selectively targeted in order to maximize efficacy and safety, necessitating the development of even more specific antagonists. Finally, we will need to understand whether FKBP5 antagonists may be used as monotherapy *vs* augmentation strategy in addition to established treatment, including psychotherapy.

Finally, while valuable lessons may be learned from the example of FKBP5, it is clear that risk for stress-related disorders is shaped by complex interactions among multiple environmental stressors and many genes with small individual effects on expressed phenotypes. Elucidating these interactions at a systems level is a daunting task but may contribute to a more holistic understanding of stress-related disorders.

FUNDING AND DISCLOSURE

This work was supported by an ERC starting grant to EBB and FP7 framework grant number 281338 (GxE molmech) and a Marie-Sklodowska Curie fellowship (H2020 grant no. 653240) to ASZ. EBB is co-inventor of the patent application 'FKBP5: a novel target for antidepressant therapy' (European Patent no. EP 1687443 B1). The other authors declare no conflict of interest.

REFERENCES

- Albu S, Romanowski CP, Letizia Curzi M, Jakubcakova V, Flachskamm C, Gassen NC *et al* (2014). Deficiency of FK506-binding protein (FKBP) 51 alters sleep architecture and recovery sleep responses to stress in mice. *J Sleep Res* **23**: 176–185.
- Almli LM, Duncan R, Feng H, Ghosh D, Binder EB, Bradley B *et al* (2014). Correcting systematic inflation in genetic association tests that consider interaction effects: application to a genome-wide association study of posttraumatic stress disorder. *JAMA Psychiatry* **71**: 1392–1399.
- Anacker C, Zunszain PA, Cattaneo A, Carvalho LA, Garabedian MJ, Thuret S *et al* (2011). Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Mol Psychiatry* **16**: 738–750.
- Appel K, Schwahn C, Mahler J, Schulz A, Spitzer C, Fenske K *et al* (2011). Moderation of adult depression by a polymorphism in the FKBP5 gene and childhood physical abuse in the general population. *Neuropsychopharmacology* **36**: 1982–1991.
- Attwood BK, Bourgognon JM, Patel S, Mucha M, Schiavon E, Skrzypiec AE *et al* (2011). Neuropilin cleaves EphB2 in the amygdala to control anxiety. *Nature* **473**: 372–375.
- Balsevich G, Uribe A, Wagner KV, Hartmann J, Santarelli S, Labermaier C *et al* (2014). Interplay between diet-induced obesity and chronic stress in mice: potential role of FKBP51. *J Endocrinol* **222**: 15–26.
- Bamberger CM, Schulte HM, Chrousos GP (1996). Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. *Endocr Rev* **17**: 245–261.
- Barent RL, Nair SC, Carr DC, Ruan Y, Rimerman RA, Fulton J *et al* (1998). Analysis of FKBP51/FKBP52 chimeras and mutants for Hsp90 binding and association with progesterone receptor complexes. *Mol Endocrinol* **12**: 342–354.
- Baughman G, Wiederrecht GJ, Campbell NF, Martin MM, Bourgeois S (1995). FKBP51, a novel T-cell-specific immunophilin capable of calcineurin inhibition. *Mol Cell Biol* **15**: 4395–4402.
- Belleville G, Marchand A, St-Hilaire MH, Martin M, Silva C (2012). PTSD and depression following armed robbery: patterns of appearance and impact on absenteeism and use of health care services. *J Traum Stress* **25**: 465–468.
- Belsky J, Hartman S (2014). Gene–environment interaction in evolutionary perspective: differential susceptibility to environmental influences. *World Psychiatry* **13**: 87–89.
- Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R (2009). Vulnerability genes or plasticity genes? *Mol Psychiatry* **14**: 746–754.
- Belsky J, Pluess M (2013). Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. *Dev Psychopathol* **25**: 1243–1261.
- Bertolino E, Singh H (2002). POU/TBP cooperativity: a mechanism for enhancer action from a distance. *Mol Cell* **10**: 397–407.
- Bevilacqua L, Carli V, Sarchiapone M, George DK, Goldman D, Roy A *et al* (2012). Interaction between FKBP5 and childhood trauma and risk of aggressive behavior. *Arch Gen Psychiatry* **69**: 62–70.
- Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB *et al* (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA* **299**: 1291–1305.
- Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Putz B *et al* (2004). Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat Genet* **36**: 1319–1325.
- Blair LJ, Nordhues BA, Hill SE, Scaglione KM, O'Leary JC 3rd, Fontaine SN *et al* (2013). Accelerated neurodegeneration through chaperone-mediated oligomerization of tau. *J Clin Invest* **123**: 4158–4169.
- Boscarino JA, Erlich PM, Hoffman SN, Zhang X (2012). Higher FKBP5, COMT, CHRNA5, and CRHR1 allele burdens are associated with PTSD and interact with trauma exposure: implications for neuropsychiatric research and treatment. *Neuropsychiatr Dis Treat* **8**: 131–139.
- Bouwmeester T, Bauch A, Ruffner H, Angrand PO, Bergamini G, Croughton K *et al* (2004). A physical and functional map of the human TNF- α /NF- κ B signal transduction pathway. *Nat Cell Biol* **6**: 97–105.
- Buchmann AF, Holz N, Boecker R, Blomeyer D, Rietschel M, Witt SH *et al* (2014). Moderating role of FKBP5 genotype in the impact of childhood adversity on cortisol stress response during adulthood. *Eur Neuropsychopharmacol* **24**: 837–845.
- Chrousos GP, Gold PW (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* **267**: 1244–1252.
- Cohen S, Janicki-Deverts D, Miller GE (2007). Psychological stress and disease. *JAMA* **298**: 1685–1687.
- Collip D, Myin-Germeys I, Wichers M, Jacobs N, Derom C, Thiery E *et al* (2013). FKBP5 as a possible moderator of the psychosis-inducing effects of childhood trauma. *Br J Psychiatry* **202**: 261–268.
- Dackis MN, Rogosch FA, Oshri A, Cicchetti D (2012). The role of limbic system irritability in linking history of childhood maltreatment and psychiatric outcomes in low-income, high-risk women: moderation by FK506 binding protein 5 haplotype. *Dev Psychopathol* **24**: 1237–1252.
- Davies TH, Ning YM, Sanchez ER (2002). A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *J Biol Chem* **277**: 4597–4600.
- Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG (2000). Squirrel monkey immunophilin FKBP51 is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology* **141**: 4107–4113.
- Dick DM, Agrawal A, Keller MC, Adkins A, Aliev F, Monroe S *et al* (2015). Candidate gene–environment interaction research: reflections and recommendations. *Perspect Psychol Sci* **10**: 37–59.
- Dunn EC, Solovieff N, Lowe SR, Gallagher PJ, Chaponis J, Rosand J *et al* (2014). Interaction between genetic variants and exposure to Hurricane Katrina on post-traumatic stress and post-traumatic growth: a prospective analysis of low income adults. *J Affect Disord* **152–154**: 243–249.
- Ellsworth KA, Eckloff BW, Li L, Moon I, Fridley BL, Jenkins GD *et al* (2013a). Contribution of FKBP5 genetic variation to gemcitabine treatment and survival in pancreatic adenocarcinoma. *PLoS One* **8**: e70216.
- Ellsworth KA, Moon I, Eckloff BW, Fridley BL, Jenkins GD, Batzler A *et al* (2013b). FKBP5 genetic variation: association with selective serotonin reuptake inhibitor treatment outcomes in major depressive disorder. *Pharmacogenet Genomics* **23**: 156–166.
- Ewald ER, Wand GS, Seifuddin F, Yang X, Tamashiro KL, Potash JB *et al* (2014). Alterations in DNA methylation of Fkbp5 as a determinant of blood-brain correlation of glucocorticoid exposure. *Psychoneuroendocrinology* **44**: 112–122.
- Fabian AK, Marz A, Neimanis S, Biondi RM, Kozany C, Hausch F (2013). InterAKtions with FKBP5–mutational and pharmacological exploration. *PLoS One* **8**: e57508.
- Fani N, Gutman D, Tone EB, Almli L, Mercer KB, Davis J *et al* (2013). FKBP5 and attention bias for threat: associations with hippocampal function and shape. *JAMA Psychiatry* **70**: 392–400.
- Feil R, Fraga MF (2011). Epigenetics and the environment: emerging patterns and implications. *Nat Rev Genet* **13**: 97–109.
- Franklin TB, Russig H, Weiss IC, Graff J, Linder N, Michalon A *et al* (2010). Epigenetic transmission of the impact of early stress across generations. *Biol Psychiatry* **68**: 408–415.
- Fries E, Hesse J, Hellhammer J, Hellhammer DH (2005). A new view on hypocortisolism. *Psychoneuroendocrinology* **30**: 1010–1016.
- Fujii T, Hori H, Ota M, Hattori K, Teraishi T, Sasayama D *et al* (2014a). Effect of the common functional FKBP5 variant (rs1360780) on the hypothalamic–pituitary–adrenal axis and peripheral blood gene expression. *Psychoneuroendocrinology* **42**: 89–97.
- Fujii T, Ota M, Hori H, Hattori K, Teraishi T, Matsuo J *et al* (2014b). The common functional FKBP5 variant rs1360780 is associated with altered cognitive function in aged individuals. *Sci Rep* **4**: 6696.
- Gaali S, Gopalakrishnan R, Wang Y, Kozany C, Hausch F (2011). The chemical biology of immunophilin ligands. *Curr Med Chem* **18**: 5355–5379.
- Gaali S, Kirschner A, Cuboni S, Hartmann J, Kozany C, Balsevich G *et al* (2015). Selective inhibitors of the FK506-binding protein 51 by induced fit. *Nat Chem Biol* **11**: 33–37.
- Galea S, Nandi A, Vlahov D (2005). The epidemiology of post-traumatic stress disorder after disasters. *Epidemiol Rev* **27**: 78–91.
- Gallo LI, Ghini AA, Piwien Pilipuk G, Galigiani MD (2007). Differential recruitment of tetratricopeptide repeat domain immunophilins to the mineralocorticoid receptor influences both heat-shock protein 90-dependent retrotransport and hormone-dependent transcriptional activity. *Biochemistry* **46**: 14044–14057.
- Gassen NC, Hartmann J, Zschocke J, Stephan J, Hafner K, Zellner A *et al* (2014). Association of FKBP51 with priming of autophagy pathways and mediation of antidepressant treatment response: evidence in cells, mice, and humans. *PLoS Med* **11**: e1001755.
- Gassen NC, Hartmann J, Zannas AS, Zschocke J, Maccarrone G, Hafner K *et al* (2015). FKBP51 inhibits GSK3 β and augments the effects of distinct psychotropic medications. *Mol Psychiatry* (in press).
- Gee DG, Casey BJ (2015). The impact of developmental timing for stress and recovery. *Neurobiol Stress* **1**: 184–194.
- Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* **160**: 636–645.
- Hartmann J, Wagner KV, Lieb C, Scharf SH, Wang XD, Wolf M *et al* (2012). The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. *Neuropharmacology* **62**: 332–339.
- Hernaus D, van Winkel R, Gronenschild E, Habets P, Kenis G, Marcelis M *et al* (2014). Brain-derived neurotrophic factor/FK506-binding protein 5 genotype by childhood trauma interactions do not impact on hippocampal volume and cognitive performance. *PLoS One* **9**: e92722.
- Hohne N, Poidinger M, Merz F, Pfister H, Bruckl T, Zimmermann P *et al* (2014). FKBP5 genotype-dependent DNA methylation and mRNA regulation after

- psychosocial stress in remitted depression and healthy controls. *Int J Neuropsychopharmacol* **18**: 1–9.
- Holz NE, Buchmann AF, Boecker R, Blomeyer D, Baumeister S, Wolf I et al (2014). Role of FKBP5 in emotion processing: results on amygdala activity, connectivity and volume. *Brain Struct Funct* **220**: 1355–1368.
- Huang MC, Schwandt ML, Chester JA, Kirchhoff AM, Kao CF, Liang T et al (2014). FKBP5 moderates alcohol withdrawal severity: human genetic association and functional validation in knockout mice. *Neuropsychopharmacology* **39**: 2029–2038.
- Hubler TR, Denny WB, Valentine DL, Cheung-Flynn J, Smith DF, Scammell JG (2003). The FK506-binding immunophilin FKBP51 is transcriptionally regulated by progesterone and attenuates progesterone responsiveness. *Endocrinology* **144**: 2380–2387.
- Hubler TR, Scammell JG (2004). Intronic hormone response elements mediate regulation of FKBP5 by progesterone and glucocorticoids. *Cell Stress Chaperones* **9**: 243–252.
- Ising M, Depping AM, Siebertz A, Lucae S, Unschuld PG, Kloiber S et al (2008). Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neurosci* **28**: 389–398.
- Jaaskelainen T, Makkonen H, Palvimäki JJ (2011). Steroid up-regulation of FKBP51 and its role in hormone signaling. *Curr Opin Pharmacol* **11**: 326–331.
- Jacobson L, Sapolsky R (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Rev* **12**: 118–134.
- Jensen KP, Herman AL, Morean ME, Kranzler HR, Gelemtier J, Sofuoglu M (2014). FKBP5 variation is associated with the acute and chronic effects of nicotine. *Pharmacogenomics J* **15**: 340–346.
- Jin Y, Xu J, Liu H, Liu D (2014). Posttraumatic stress disorder and posttraumatic growth among adult survivors of Wenchuan earthquake after 1 year: prevalence and correlates. *Arch Psychiatr Nurs* **28**: 67–73.
- Jinwal UK, Koren J 3rd, Borysov SI, Schmid AB, Abisambra JF, Blair LJ et al (2010). The Hsp90 cochaperone, FKBP51, increases Tau stability and polymerizes microtubules. *J Neurosci* **30**: 591–599.
- Kaltsas G, Zannas AS, Chrousos GP (2012) Hypothalamic-pituitary-adrenal axis and cardiovascular disease. In: Hjemdahl P, Rosengren A, Steptoe A (eds). *Stress and Cardiovascular Disease*. Springer: London, UK.
- Keller MC (2014). Gene x environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. *Biol Psychiatry* **75**: 18–24.
- Kelly MM, King EM, Rider CF, Gwozd C, Holden NS, Eddleston J et al (2012). Corticosteroid-induced gene expression in allergen-challenged asthmatic subjects taking inhaled budesonide. *Br J Pharmacol* **165**: 1737–1747.
- Kendler KS, Karkowski LM, Prescott CA (1999). Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* **156**: 837–841.
- Kim YS, Kim YJ, Lee JM, Kim EK, Park YJ, Choe SK et al (2012). Functional changes in myeloid-derived suppressor cells (MDSCs) during tumor growth: FKBP51 contributes to the regulation of the immunosuppressive function of MDSCs. *J Immunol* **188**: 4226–4234.
- Kinouchi S, Iga J, Ueno S, Yamauchi K, Numata S, Song H et al (2008). FKBP5, SERT and COMT mRNA expressions in the peripheral leukocytes during menstruation cycle in healthy reproductive females. *Neurosci Lett* **434**: 124–128.
- Klengel T, Binder EB (2013a). Allele-specific epigenetic modification: a molecular mechanism for gene-environment interactions in stress-related psychiatric disorders? *Epigenomics* **5**: 109–112.
- Klengel T, Binder EB (2015). FKBP5 allele-specific epigenetic modification in gene by environment interaction. *Neuropsychopharmacology* **40**: 244–246.
- Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM et al (2013b). Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* **16**: 33–41.
- Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, Miller A et al (2005). Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. *Mol Psychiatry* **10**: 1058–1059.
- Kohrt BA, Worthmann CM, Ressler KJ, Mercer KB, Upadhyaya N, Koirala S et al (2015). 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* **27**: 180–196.
- Kraft P, Aschard H (2015). Finding the missing gene-environment interactions. *Eur J Epidemiol* **30**: 353–355.
- Kress C, Thomassin H, Grange T (2006). Active cytosine demethylation triggered by a nuclear receptor involves DNA strand breaks. *Proc Natl Acad Sci USA* **103**: 11112–11117.
- Lee RS, Tamashiro KL, Yang X, Purcell RH, Harvey A, Willour VL et al (2010). Chronic corticosterone exposure increases expression and decreases deoxyribonucleic acid methylation of Fkbp5 in mice. *Endocrinology* **151**: 4332–4343.
- Lee RS, Tamashiro KL, Yang X, Purcell RH, Huo Y, Rongione M et al (2011). A measure of glucocorticoid load provided by DNA methylation of Fkbp5 in mice. *Psychopharmacology* **218**: 303–312.
- Lessard J, Holman EA (2014). FKBP5 and CRHR1 polymorphisms moderate the stress-physical health association in a national sample. *Health Psychol* **33**: 1046–1056.
- Levrán O, Peles E, Randesi M, Li Y, Rotrosen J, Ott J et al (2014). Stress-related genes and heroin addiction: a role for a functional FKBP5 haplotype. *Psychoneuroendocrinology* **45**: 67–76.
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M et al (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **329**: 959–964.
- Li TK, Baksh S, Cristillo AD, Bierer BE (2002). Calcium- and FK506-independent interaction between the immunophilin FKBP51 and calcineurin. *J Cell Biochem* **84**: 460–471.
- Lu NZ, Cidlowski JA (2005). Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. *Mol Cell* **18**: 331–342.
- Luijk MP, Velders FP, Thamer A, van Ijzendoorn MH, Bakermans-Kranenburg MJ, Jaddoe VW et al (2010). FKBP5 and resistant attachment predict cortisol reactivity in infants: gene-environment interaction. *Psychoneuroendocrinology* **35**: 1454–1461.
- Lv J, Xin Y, Zhou W, Qiu Z (2013). The epigenetic switches for neural development and psychiatric disorders. *J Genet Genomics* **40**: 339–346.
- Magee JA, Chang LW, Stormo GD, Milbrandt J (2006). Direct, androgen receptor-mediated regulation of the FKBP5 gene via a distal enhancer element. *Endocrinology* **147**: 590–598.
- Markman B, Dienstmann R, Tabernero J (2010). Targeting the PI3K/Akt/mTOR pathway—beyond rapalogs. *Oncotarget* **1**: 530–543.
- Meaburn EL, Schalkwyk LC, Mill J (2010). Allele-specific methylation in the human genome: implications for genetic studies of complex disease. *Epigenetics* **5**: 578–582.
- Menke A, Arloth J, Putz B, Weber P, Klengel T, Mehta D et al (2012). Dexamethasone stimulated gene expression in peripheral blood is a sensitive marker for glucocorticoid receptor resistance in depressed patients. *Neuropsychopharmacology* **37**: 1455–1464.
- Menke A, Klengel T, Rubel J, Bruckl T, Pfister H, Lucae S et al (2013). Genetic variation in FKBP5 associated with the extent of stress hormone dysregulation in major depression. *Genes Brain Behav* **12**: 289–296.
- Minelli A, Maffioletti E, Cloninger CR, Magri C, Sartori R, Bortolomasi M et al (2013). Role of allelic variants of FK506-binding protein 51 (FKBP5) gene in the development of anxiety disorders. *Depress Anxiety* **30**: 1170–1176.
- Munafò MR, Zammit S, Flint J (2014). Practitioner review: a critical perspective on gene-environment interaction models—what impact should they have on clinical perceptions and practice? *J Child Psychol Psychiatry* **55**: 1092–1101.
- Nelson ED, Kavalali ET, Monteggia LM (2008). Activity-dependent suppression of miniature neurotransmission through the regulation of DNA methylation. *J Neurosci* **28**: 395–406.
- Nicolaides NC, Charmandari E, Chrousos GP, Kino T (2014). Recent advances in the molecular mechanisms determining tissue sensitivity to glucocorticoids: novel mutations, circadian rhythm and ligand-induced repression of the human glucocorticoid receptor. *BMC Endocr Disord* **14**: 71.
- Nillini YI, Nosen E, Williams PA, Tracy M, Coffey SF, Galea S (2013). Unique and related predictors of major depressive disorder, posttraumatic stress disorder, and their comorbidity after Hurricane Katrina. *J Nerv Ment Dis* **201**: 841–847.
- O’Leary JC 3rd, Dharia S, Blair LJ, Brady S, Johnson AG, Peters M et al (2011). A new anti-depressive strategy for the elderly: ablation of FKBP5/FKBP51. *PLoS One* **6**: e24840.
- Paakinaho V, Makkonen H, Jaaskelainen T, Palvimäki JJ (2010). Glucocorticoid receptor activates poised FKBP51 locus through long-distance interactions. *Mol Endocrinol* **24**: 511–525.
- Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC et al (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology* **39**: 1245–1253.
- Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC et al (2015). HPA axis genetic variation, pubertal status, and sex interact to predict amygdala and hippocampus responses to negative emotional faces in school-age children. *Neuroimage* **109c**: 1–11.
- Pei H, Li L, Fridley BL, Jenkins GD, Kalari KR, Lingle W et al (2009). FKBP51 affects cancer cell response to chemotherapy by negatively regulating Akt. *Cancer Cell* **16**: 259–266.
- Pelleymounter LL, Moon I, Johnson JA, Laederach A, Halvorsen M, Eckloff B et al (2011). A novel application of pattern recognition for accurate SNP and indel

- discovery from high-throughput data: targeted resequencing of the glucocorticoid receptor co-chaperone FKBP5 in a Caucasian population. *Mol Genet Metab* **104**: 457–469.
- Pereira MJ, Palming J, Svensson MK, Rizell M, Dalenback J, Hammar M *et al* (2014). FKBP5 expression in human adipose tissue increases following dexamethasone exposure and is associated with insulin resistance. *Metabolism* **63**: 1198–1208.
- Romano MF, Avellino R, Petrella A, Bisogni R, Romano S, Venuta S (2004). Rapamycin inhibits doxorubicin-induced NF-kappaB/Rel nuclear activity and enhances the apoptosis of melanoma cells. *Eur J Cancer* **40**: 2829–2836.
- Romano S, D'Angelillo A, Pacelli R, Staibano S, De Luna E, Bisogni R *et al* (2010). Role of FK506-binding protein 51 in the control of apoptosis of irradiated melanoma cells. *Cell Death Differ* **17**: 145–157.
- Roy A, Gorodetsky E, Yuan Q, Goldman D, Enoch MA (2010). Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology* **35**: 1674–1683.
- Roy A, Hodgkinson CA, Deluca V, Goldman D, Enoch MA (2012). Two HPA axis genes, CRHBP and FKBP5, interact with childhood trauma to increase the risk for suicidal behavior. *J Psychiatr Res* **46**: 72–79.
- Russell GM, Henley DE, Leendertz J, Douthwaite JA, Wood SA, Stevens A *et al* (2010). Rapid glucocorticoid receptor-mediated inhibition of hypothalamic-pituitary-adrenal ultradian activity in healthy males. *J Neurosci* **30**: 6106–6115.
- Russo SJ, Murrrough JW, Han MH, Charney DS, Nestler EJ (2012). Neurobiology of resilience. *Nat Neurosci* **15**: 1475–1484.
- Sabbagh JJ, O'Leary JC 3rd, Blair LJ, Klengel T, Nordhues BA, Fontaine SN *et al* (2014). Age-associated epigenetic upregulation of the FKBP5 gene selectively impairs stress resiliency. *PLoS One* **9**: e107241.
- Sapolsky RM, Armanini MP, Packan DR, Sutton SW, Plotsky PM (1990). Glucocorticoid feedback inhibition of adrenocorticotrophic hormone secretagogue release. Relationship to corticosteroid receptor occupancy in various limbic sites. *Neuroendocrinology* **51**: 328–336.
- Scammell JG, Denny WB, Valentine DL, Smith DF (2001). Overexpression of the FK506-binding immunophilin FKBP51 is the common cause of glucocorticoid resistance in three New World primates. *Gen Comp Endocrinol* **124**: 152–165.
- Scharf SH, Liebl C, Binder EB, Schmidt MV, Müller MB (2011). Expression and regulation of the Fkbp5 gene in the adult mouse brain. *PLoS One* **6**: e16883.
- Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, Baldwin AS Jr (1995). Characterization of mechanisms involved in transrepression of NF-kappa B by activated glucocorticoid receptors. *Mol Cell Biol* **15**: 943–953.
- Schiene-Fischer C, Yu C (2001). Receptor accessory folding helper enzymes: the functional role of peptidyl prolyl cis/trans isomerases. *FEBS Lett* **495**: 1–6.
- Schmidt MV, Paez-Pereda M, Holsboer F, Hausch F (2012). The prospect of FKBP51 as a drug target. *ChemMedChem* **7**: 1351–1359.
- Schmidt U, Buell DR, Ionescu IA, Gassen NC, Holsboer F, Cox MB *et al* (2015). A role for synapsin in FKBP51 modulation of stress responsiveness: convergent evidence from animal and human studies. *Psychoneuroendocrinology* **52**: 43–58.
- Shibuya N, Suzuki A, Sadahiro R, Kamata M, Matsumoto Y, Goto K *et al* (2010). Association study between a functional polymorphism of FK506-binding protein 51 (FKBP5) gene and personality traits in healthy subjects. *Neurosci Lett* **485**: 194–197.
- Shrestha S, Sun Y, Lufkin T, Kraus P, Or Y, Garcia YA *et al* (2015). Tetratricopeptide repeat domain 9A negatively regulates estrogen receptor alpha activity. *Int J Biol Sci* **11**: 434–447.
- Sinclair D, Fillman SG, Webster MJ, Weickert CS (2013). Dysregulation of glucocorticoid receptor co-factors FKBP5, BAG1 and PTGES3 in prefrontal cortex in psychotic illness. *Sci Rep* **3**: 3539.
- Sinha R (2007). The role of stress in addiction relapse. *Curr Psychiatry Rep* **9**: 388–395.
- Sriram K, Rodriguez-Fernandez M, Doyle FJ 3rd (2012). Modeling cortisol dynamics in the neuro-endocrine axis distinguishes normal, depression, and post-traumatic stress disorder (PTSD) in humans. *PLoS Comput Biol* **8**: e1002379.
- Stechschulte LA, Sanchez ER (2011). FKBP51-a selective modulator of glucocorticoid and androgen sensitivity. *Curr Opin Pharmacol* **11**: 332–337.
- Suzuki A, Matsumoto Y, Sadahiro R, Enokido M, Goto K, Otani K (2014). Relationship of the FKBP5 C/T polymorphism with dysfunctional attitudes predisposing to depression. *Compr Psychiatry* **55**: 1422–1425.
- Teles F, Gamliel A, Skowronska-Krawczyk D, Garcia-Bassets I, Rosenfeld MG (2013). 'Seq-ing' insights into the epigenetics of neuronal gene regulation. *Neuron* **77**: 606–623.
- Thomassin H, Flavin M, Espinas ML, Grange T (2001). Glucocorticoid-induced DNA demethylation and gene memory during development. *EMBO J* **20**: 1974–1983.
- Touma C, Gassen NC, Herrmann L, Cheung-Flynn J, Bull DR, Ionescu IA *et al* (2011). FK506 binding protein 5 shapes stress responsiveness: modulation of neuroendocrine reactivity and coping behavior. *Biol Psychiatry* **70**: 928–936.
- Tsolaki M, Kounti F, Karamavrou S (2009). Severe psychological stress in elderly individuals: a proposed model of neurodegeneration and its implications. *Am J Alzheimers Dis Other Dement* **24**: 85–94.
- U M, Shen L, Oshida T, Miyauchi J, Yamada M, Miyashita T (2004). Identification of novel direct transcriptional targets of glucocorticoid receptor. *Leukemia* **18**: 1850–1856.
- Uchida S, Hara K, Kobayashi A, Otsuki K, Yamagata H, Hobara T *et al* (2011). Epigenetic status of Gdnf in the ventral striatum determines susceptibility and adaptation to daily stressful events. *Neuron* **69**: 359–372.
- van Winkel R, Stefanis NC, Myin-Germeys I (2008). Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr Bull* **34**: 1095–1105.
- VanZomeren-Dohm AA, Pitula CE, Koss KJ, Thomas K, Gunnar MR (2015). FKBP5 moderation of depressive symptoms in peer victimized, post-institutionalized children. *Psychoneuroendocrinology* **51**: 426–430.
- Vermeer H, Hendriks-Stegeman BI, van der Burg B, van Buul-Offers SC, Jansen M (2003). Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: a potential marker for glucocorticoid sensitivity, potency, and bioavailability. *J Clin Endocrinol Metab* **88**: 277–284.
- Watts AG (2005). Glucocorticoid regulation of peptide genes in neuroendocrine CRH neurons: a complexity beyond negative feedback. *Front Neuroendocrinol* **26**: 109–130.
- Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR *et al* (2004). Epigenetic programming by maternal behavior. *Nat Neurosci* **7**: 847–854.
- Wei XE, Zhang FY, Wang K, Zhang QX, Rong LQ (2014). Assembly of the FKBP51-PHLPP2-AKT signaling complex in cerebral ischemia/reperfusion injury in rats. *Brain Res* **1566**: 60–68.
- Weiwad M, Edlich F, Kilka S, Erdmann F, Jarczowski F, Dorn M *et al* (2006). Comparative analysis of calcineurin inhibition by complexes of immunosuppressive drugs with human FK506 binding proteins. *Biochemistry* **45**: 15776–15784.
- White MG, Bogdan R, Fisher PM, Munoz KE, Williamson DE, Hariri AR (2012). FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes Brain Behav* **11**: 869–878.
- Wiederrecht G, Hung S, Chan HK, Marcy A, Martin M, Calaycay J *et al* (1992). 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* **267**: 21753–21760.
- Wilker S, Pfeiffer A, Kolassa S, Elbert T, Lingenfelder B, Ovuga E *et al* (2014). The role of FKBP5 genotype in moderating long-term effectiveness of exposure-based psychotherapy for posttraumatic stress disorder. *Transl Psychiatry* **4**: e403.
- Willour VL, Chen H, Toolan J, Belmonte P, Cutler DJ, Goes FS *et al* (2009). Family-based association of FKBP5 in bipolar disorder. *Mol Psychiatry* **14**: 261–268.
- Wochnik GM, Ruegg J, Abel GA, Schmidt U, Holsboer F, Rein T (2005). FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *J Biol Chem* **280**: 4609–4616.
- Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S *et al* (2007). Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci USA* **104**: 15858–15863.
- Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Farrer LA *et al* (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology* **35**: 1684–1692.
- Yang X, Ewald ER, Huo Y, Tamashiro KL, Salvatori R, Sawa A *et al* (2012). Glucocorticoid-induced loss of DNA methylation in non-neuronal cells and potential involvement of DNMT1 in epigenetic regulation of Fkbp5. *Biochem Biophys Res Commun* **420**: 570–575.
- Yehuda R, Daskalakis NP, Desarnaud F, Makotkine I, Lehmer AL, Koch E *et al* (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Front Psychiatry* **4**: 118.
- Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL Jr, Mason JW (1990). Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* **178**: 366–369.
- Zannas AS, Binder EB (2014a). Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes Brain Behav* **13**: 25–37.
- Zannas AS, West AE (2014b). Epigenetics and the regulation of stress vulnerability and resilience. *Neuroscience* **264**: 157–170.
- Zimmermann P, Bruckl T, Nocon A, Pfister H, Binder EB, Uhr M *et al* (2011). Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. *Am J Psychiatry* **168**: 1107–1116.
- Zou YF, Wang F, Feng XL, Li WF, Tao JH, Pan FM *et al* (2010). Meta-analysis of FKBP5 gene polymorphisms association with treatment response in patients with mood disorders. *Neurosci Lett* **484**: 56–61.