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Influence of interactions between genes and childhood trauma on refractoriness in psychiatric disorders

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ABSTRACT

Psychiatric disorders are excellent disease models in which gene–environmental interaction play a significant role in the pathogenesis. Childhood trauma has been known as a significant environmental factor in the progress of, and prognosis for psychiatric illness. Patients with refractory illness usually have more severe symptoms, greater disability, lower quality of life and are at greater risk of suicide than other psychiatric patients. Our literature review uncovered some important clinical factors which modulate response to treatment in psychiatric patients who have experienced childhood trauma. Childhood trauma seems to be a critical determinant of treatment refractoriness in psychotic disorder, bipolar disorder, major depressive disorder, and post-traumatic stress disorder. In patients with psychotic disorders, the relationship between childhood trauma and treatment-refractoriness appears to be mediated by cognitive impairment. In the case of bipolar disorder, the relationship appears to be mediated by greater affective disturbance and earlier onset, while in major depressive disorder the mediating factors are persistent, severe symptoms and frequent recurrence. In suicidal individuals, childhood maltreatment was associated with violent suicidal attempts. In the case of PTSD patients, it appears that childhood trauma makes the brain more vulnerable to subsequent trauma, thus resulting in more severe, refractory symptoms. Given that several studies have suggested that there are distinct subtypes of genetic vulnerability to childhood trauma, it is important to understand how gene–environment interactions influence the course of psychiatric illnesses in order to improve therapeutic strategies.

1. Introduction

Both genetic disposition and environmental factors contribute to the development of psychiatric disorders, especially severe disorders such as schizophrenia, bipolar disorder (BD), severe depression, and post-traumatic stress disorder (PTSD) (Uher, 2014).

Childhood trauma has been regarded as the most important environmental determinant of the occurrence of psychiatric illness. In fact, stress and maltreatment in the early life are thought to interact with genomic traits and can alter neurodevelopment (Brietzke et al., 2012). Childhood trauma is associated with development of psychiatric illness and more generally with poor functioning and cognitive deficits (Lee and Hoaken, 2007). Furthermore, in individuals who have experienced maltreatment psychiatric disorders present with more severe symptoms and more comorbidity, and the response to treatment is worse (Alvarez et al., 2011; Nanni et al., 2012). On this basis one can speculate that interactions between genes and childhood trauma influence progress and prognosis in psychiatric disorders as well as their occurrence.

"Refractoriness" is an important concept in clinical psychiatry. The word "refractory" can be used to imply greater resistance (Souery et al., 1999) and it has been suggested that the terms "refractory" and "resistant" can be used interchangeably (Berlim and Turecki, 2007). Treatment resistant patients have more severe symptoms, greater disabilities, higher suicidal risk and lower quality of life than non-treatment resistant patients (Kane et al., 1988; Mamo, 2007; Hassan and De Luca, 2015), making treatment refractoriness an important issue which deserves greater clinical attention.

In this article, we review the literature on how interactions between genes and childhood trauma affect refractoriness in psychiatric disorders. We focus on four themes: 1) gene–environment interactions involved in mental illness, 2) the effects of childhood stress and trauma on psychopathology, 3) gene–childhood trauma interactions in psychiatric disorders and 4) gene–childhood trauma interactions with respect to refractoriness in several psychiatric disorders.

Abbreviations: 5-HTTPLR, 5-hydroxy-tryptamine transporter-linked polymorphic region; APOE-ε4, Apolipoprotein 4; BD, Bipolar disorder; BDNF, Brain-derived neurotrophic factor; MAOA, Monoamine oxidase A; MDD, Major depressive disorder; MMN, Mismatch negativity; MTHFR, Methylenetetrahydrofolate reductase; PACAP, Pituitary adenylate cyclase-activating polypeptide; PTSD, Post-traumatic stress disorder; SNP, Single nucleotide polymorphism; αCaM kinase II, α-calcium/calmodulin-dependent protein kinase.

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2. Gene–environment interactions in severe psychiatric disorders

Both genetic disposition and environmental factors are important in the development of psychiatric disorders, particularly severe psychiatric disorders such as schizophrenia, BD and severe depression (Uher, 2014). It is because the overall contribution of genetic influence might be stronger for those severe mental disorders (Shih et al., 2004), and a number of environment exposures appear to be responsible for substantial proportion of cases of severe mental illness (Varese et al., 2012; Uher, 2014). The large "heritability gap" – the difference between twin study heritability and molecular single nucleotide polymorphism (SNP) heritability – in severe mental disorders indicates that gene–environmental interactions may account for large proportion of cases (Uher, 2014). Several researchers have used proxy methods (e.g. adoption studies; twin studies) to assess gene–environment interactions, but such methods are also limited because of unequal familial relatedness and because specific environmental factors may interact with specific genetic variants. In this regard, the investigation of the interactions involving specific molecular genetic variants is important to explain the causal relationships developing to severe mental illness (Uher, 2014).

A gene–environment interaction is involved when two different genotypes respond to environmental variation in different ways. It can be defined as the dependence of the effects of an environmental factor on an individual's genotype and vice versa (Duncan and Keller, 2011). Recent studies have demonstrated specific gene–environment interactions in severe psychiatric disorders including psychosis, BD, MDD and PTSD (Fig. 1). Although a number of environmental factors are thought to play a role in psychiatric disorders, it has been suggested that childhood trauma has a critical impact on brain development which produces permanent functional changes that may increase the risk of developing mental health problems (Heim and Binder, 2012).

3. The influence of childhood stress and trauma on psychopathology

Psychological trauma is the unique individual experience of an event or enduring conditions, in which the individual's ability to integrate his/her emotional experience is overwhelmed, or the individual experiences a threat to life, bodily integrity, or sanity (Pearlman and Saakvitne, 1995). Childhood trauma could be regarded as psychological trauma which the individuals have experienced during his/her childhood. Childhood abuse is defined as the "physical and mental injury, sexual abuse, negligent treatment, or maltreatment of a child under the age of 18 years by a person who is responsible for the child's welfare under circumstances which indicate that the child's health or welfare is harmed or threatened" (Child Abuse Prevention and Treatment Act, 2010). In this study, childhood trauma includes any difficult conditions that affects physically and psychologically to children such as accidents, natural disaster and childhood abuse.

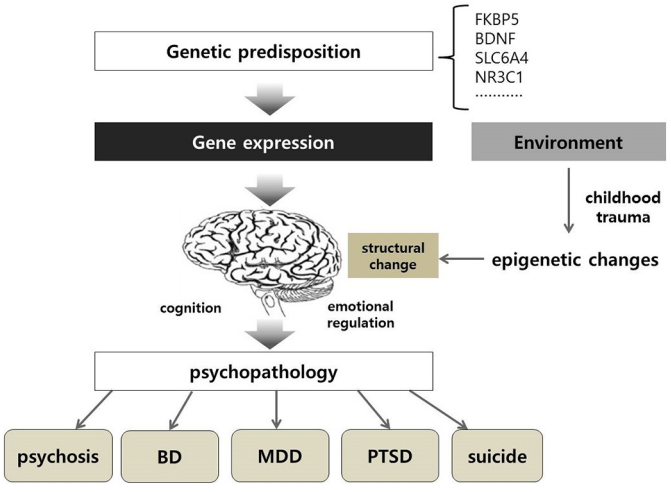

Fig. 1. Gene–childhood trauma interactions affect gene expression. The gene expression affected by a specific gene–environmental interaction leads to structural and functional changes in the brain including changes in cognition and emotional regulation. These changes mediate genetic predisposition to psychopathology associated with psychosis, mood disorders and post-traumatic stress disorder.

Childhood stress and trauma can produce long-term changes in brain development (Kaufman et al., 2000). Neuroimaging studies suggest that experience of trauma in early life may lead to structural as well as functional changes in the brain (Bremner, 2006). Childhood stress is also associated with adult psychopathology via its effects on specific brain systems (Mello et al., 2003). Fig. 1 shows how childhood trauma can lead to adult psychopathology.

The brain regions most consistently reported to be affected by childhood trauma are the corpus callosum and hippocampus (Teicher and Samson, 2013). There have also been reports linking childhood adversity to structural changes in anterior cingulate cortex (Cohen et al., 2006a, b), orbitofrontal cortex (Hanson et al., 2010), dorsolateral prefrontal cortex (Tomoda et al., 2009) and the striatum/basal ganglia (Dillon et al., 2009). These brain regions are all associated with emotional regulation, however most studies report that childhood maltreatment is not associated with volumetric changes in the amygdala (Andersen et al., 2008; Teicher and Samson, 2013), which is one of the regions critically involved in emotional regulation. Smaller amygdala volumes have, however, been observed in patients with borderline personality disorder or PTSD and a history of childhood trauma (Brambilla et al., 2004; Veer et al., 2015).

There are also reports of correlations between childhood trauma and cognitive functioning. In particular, some studies have reported negative correlations between childhood maltreatment and general cognitive abilities, memory or executive function in psychotic patients (Schenkel et al., 2005; Aas et al., 2011; Shannon et al., 2011). Parlar et al. (2014) reported that women with PTSD showed reduced ability to identify the social cognitive perspective of others compared with patients who did not have any history childhood trauma.

It has also been reported that children with a history of childhood abuse are more likely to have difficulties with emotion regulation than children without such a history (Shipman et al., 2000, 2005). Children who had suffered abuse showed deficits or delays in understanding and regulating emotions and tended to anticipate negative reactions to display of sadness and anger (Shipman et al., 2000). Childhood trauma has also been associated emotional non-acceptance (Gratz et al., 2007) and it has been reported that childhood trauma can lead to emotional avoidance and suppression (Krause et al., 2003).

A number of studies have shown that adults with a history of childhood trauma are vulnerable to various psychiatric disorders, such as affective disorders, psychotic disorders, anxiety disorders, substance abuse, PTSD and suicidal behavior (Brietzke et al., 2012). Emotional dysregulation is implicated in many psychiatric disorders, but it is the central feature of BD (Garno et al., 2005; Dvir et al., 2014). In patients with a history of childhood trauma BD tends to manifest earlier and produce more severe symptoms (Kauer-Sant'Anna et al., 2007; Etain et al., 2008). Exposure to childhood trauma has also been associated with development of major depressive disorder (MDD) (Felitti et al., 1998). One study reported that risk for depression increased dose-dependently with the number of adverse childhood experiences (Anda et al., 2002). The course of MDD is also worse in patients with a history of childhood adversity: onset tends to be earlier and the duration of the illness tends to be longer than in patients without a history of early adversity (Nanni et al., 2012). Childhood trauma also increases the risk of developing psychosis, including hallucinations and delusions (Freeman and Fowler, 2009; Alvarez et al., 2011; Galletly et al., 2011). In one study about 94% of patients with schizophrenia retrospectively reported childhood trauma (Kilcommons and Morrison, 2005), and childhood maltreatment is reported to be caused about 33% of cases of psychosis (Varese et al., 2012). Importantly, psychotic symptoms have been associated

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with higher rates of childhood trauma and emotional disturbances (Galletly et al., 2011). The lifetime prevalence of PTSD is more than four times higher (odds ratio = 4.86) in individuals with a history of childhood trauma than in those without such a history (Scott et al., 2010). PTSD patients with history of childhood maltreatment are more likely to be classed as having "complex PTSD" because they tend to have more severe symptoms and comorbid mood disorders (van der Kolk et al., 2005; Sher, 2008; Cloitre et al., 2009). The criteria for complex PTSD include features such as loss of control, helplessness and deformations of identity and sense of self as well as the standard PTSD symptoms (Cloitre et al., 2013; Maercker et al., 2013).

4. Gene–childhood trauma interactions in psychiatric disorders

Most research on interactions between childhood trauma and specific genes with respect to psychotic disorders has investigated single candidate genes. There is a gene–environment interaction involving the SNPs in glucocorticoid receptor co-chaperone (FKBP5) and childhood trauma with respect to risk of experiencing psychotic symptoms in young adulthood (Collip et al., 2013). Another study reported that brain-derived neurotrophic factor (BDNF) *Met* allele carriers with a history of childhood maltreatment were more likely to develop psychotic symptoms than carriers without such a history of childhood maltreatment (Alemany et al., 2011). Recently Aas et al. (2014) demonstrated that the lower BDNF mRNA levels in which are a feature of psychosis may be associated with both a history of childhood trauma and the BDNF *val66met* variant.

A number of studies have attempted to identify genetic variations that interact with childhood adversity to increase risk of developing depression. First, Caspi et al. (2003) showed that a gene–childhood trauma interaction modulated the risk of developing depression. It has been shown that a functional polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4*), known as the 5-hydroxytryptamine transporter-linked polymorphic region (5-HTTLPR) moderates the effects of childhood maltreatment on depression (Uher et al., 2011; Brown et al., 2013). Additionally, several studies have provided evidence that the BDNF *Val66Met* polymorphism interacts with childhood trauma to influence risk of developing depression (Gatt et al., 2009; Hornung and Heim, 2014). Aguilera et al. (2009) reported the impact of childhood adversity on depressive symptoms in *Met* allele carriers and in *S* carriers of BDNF gene. It has also been reported that there is an interaction between *22/23EK*, *9ß* in the NR3C1 gene and childhood adversity such that co-occurrence increases risk of depression (Bet et al., 2009; Lopizzo et al., 2015).

A recent study reported that interactions between early life trauma and genotype may have a significant effect on the development and manifestation of BD through the genes involved in calcium signaling (Anand et al., 2015). There has been less research into gene–environment interactions in BD than in depression (Uher, 2014). Childhood abuse was known to interact with BDNF polymorphisms to increase the risk of developing BD (Liu, 2010), however Miller et al. (2013) found no significant interaction between the BDNF *met* allele carrier genotype and childhood trauma with respect to incidence of BD.

Various genetic polymorphisms appear to modulate risk for PTSD in patients with a history of childhood adversity. Binder et al. (2008) found that *FKBP5* polymorphisms coding a do-chaperone of the glucocorticoid receptor sensitized individuals to the effects of childhood maltreatment with respect to the development of PTSD. The risk of developing PTSD in adulthood in individuals with the TT genotype of rs9470080 in FKPB5 was greatest amongst those who also had a history of childhood abuse (Xie et al., 2010). In the context of anxiety and anxiety-related disorders, Baumann et al. (2013) found that adverse childhood experiences were associated with greater sensitivity to anxiety in subjects homozygous for the Catechol-O-methyltransferase (COMT) *met* allele. There was also a trend towards greater anxious apprehension in the presence of childhood abuse in male carriers of low-activity monoamine oxidase A (MAOA) alleles (Baumann et al., 2013). Stein et al. (2008) showed that in individuals with a history of childhood abuse the *S/S* 5-HTTLPR genotype was associated with greater anxiety sensitivity than other 5-HTTLPR genotypes. In contrast, Klauke et al. (2011) reported an interaction between maltreatment and the 5-HTTLPR *L* allele with respect to anxiety sensitivity, more specifically, somatic anxiety sensitivity was influenced by an interaction between the *L/L* genotype and childhood trauma. Hemmings et al. (2008) also found an interaction between childhood emotional abuse and the BDNF *Met* allele with respect to the development of obsessive–compulsive disorder in adulthood. However a study of gene–environment interactions involved in panic disorder found no evidence of interactions between childhood trauma and the HTR1A, HTR2A and 5-HTTLPR genes, which have been implicated in etiology of panic disorder (Blaya et al., 2010).

Taken together these results suggest that interactions between specific genes and childhood trauma do play a role in the pathogenesis of severe psychiatric disorders.

5. Gene–childhood trauma interactions with respect to refractoriness in psychiatric disorders

Emerging evidence suggests that gene and environment act synergistically, with specific genetic factors rendering individuals more or less vulnerable to environmental stress (Caspi et al., 2010). Childhood trauma alone may worsen the course of psychiatric disorders, but there is also accumulating evidence that certain genes and early childhood trauma act synergistically and this interaction affects the clinical course of the illness. Fig. 2 shows how gene–childhood trauma interactions influence treatment refractoriness in several psychiatric disorders. Several groups of researchers have investigated and identified specific gene and childhood trauma interactions that play a role in the refractoriness of psychiatric illness (Table 1). We will discuss the gene and childhood trauma interactions with respect to refractoriness in

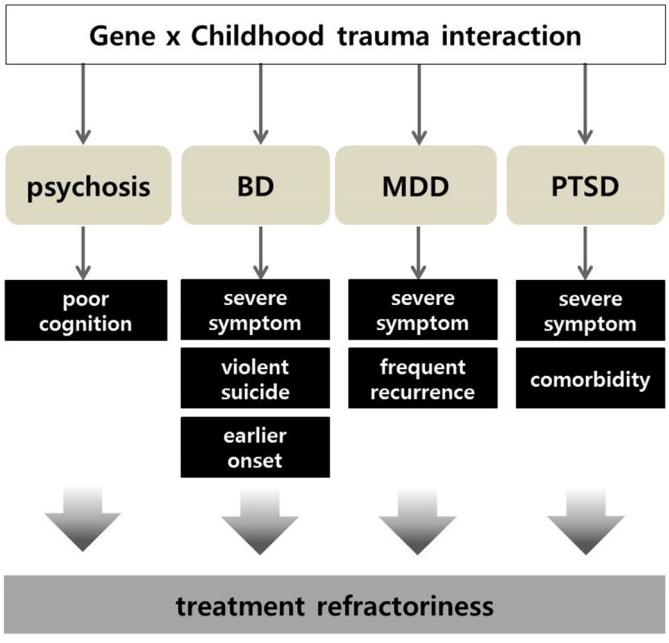

Fig. 2. Gene–childhood trauma interactions influence not only the development of psychiatric disorders, but also their progress and prognosis. In psychotic disorders, cognitive impairment appears to mediate the association between exposure to childhood trauma and treatment refractoriness. The deteriorating symptom such as persistent and severe symptom, and frequent recurrence could be mediating factors in depressive disorder. The greater affective disturbance, violent suicide and earlier onset could be mediating factors in bipolar disorder. In the case of PTSD exposure to childhood trauma appears to cause changes in the brain which render individuals more vulnerable to subsequent trauma, resulting in more severe symptoms and more comorbid disease and hence treatment refractory illness.

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Table 1
Gene–childhood trauma interactions on refractoriness in psychiatric disorders.

Gene	Environmental factor	Psychiatric disorder	Factors mediating refractoriness	Reference
SLC6A4	Childhood maltreatment-	Psychosis	Poor cognitive function	Aas et al., 2012
BDNF	Childhood maltreatment	Schizophrenia	Reduced working memory/executive function	Aas et al., 2013
SLC6A4	Sexual abuse	Depression	Persistent symptom	Uher et al. (2011); Fisher et al. (2013)
BDNF	Sexual abuse	Depression	Symptom severity	Aguilera et al., 2009
MTHFR	Childhood maltreatment	Depression	Recurrence	Lok et al., 2013
GR & MR	Childhood maltreatment	Depression	Recurrence	Juruena, 2014 Hardeveld et al., 2015
APOE-o4	Childhood maltreatment	Depression	Symptom in old age	Park et al., 2015
TPH 2	Childhood maltreatment	Depression	Non-response to treatment	Xu et al., 2012
GRIA 3	Childhood maltreatment	Depression	Poor treatment outcome	Pu et al., 2013
BDNF	Early life stress	BD	greater affective disturbance	Miller et al., 2013
TLR2	Childhood maltreatment	BD	more severe clinical course	Oliveira et al., 2015
TLR2	Sexual abuse	BD	earlier onset	Oliveira et al., 2015
Genes coding for CCA (GWAS)	Childhood maltreatment	BD	earlier onset	Anand et al., 2015
BDNF	Early life stress	BD	Violent suicide attempt	Perroud et al., 2008
ADARB1& HTR2C	Childhood maltreatment	Depression, BD, schizophrenia	Suicide attempt	Karanovic et al., 2015
FKBP5	Childhood maltreatment	PTSD	Increased symptom severity	Binder et al., 2008
ADRB2	Childhood maltreatment	PTSD	Increased symptom severity	Liberzon et al., 2014
ADCYAP1R1	Childhood maltreatment	PTSD	increased symptom severity	Almli et al., 2013

SLC6A4, serotonin transporter; BDNF, brain-derived neurotrophic factor; MTHFR, methylenetetrahydrofolate reductase; GR & MR, glucocorticoid receptor and mineralocorticoid receptor; APOE-o4, apolipoprotein4; TPH 2, tryptophan hydroxylase2; GRIA 3, glutamate receptor subunit 3 gene; TLR2, Toll-like receptor 2 gene; CCA, calcium channel activity; GWAS, genome wide association study; ADARB1, adenosine deaminases acting on RNA B1 gene; HTR2C, serotonin receptor 2C; FKBP5, glucocorticoid receptor co-chaperone; ADRB2, adrenergic receptor $_{B}$2 gene; ADCYAP1R1, Human type I pituitary adenylate cyclase-activating polypeptide receptor 1; BD, bipolar disorder.

psychosis and bipolar disorder which have been regarded as major psychiatric illness with higher degree of genetic influence on its etiology (Weissman et al., 1984; Kendler et al., 1985; Cuesta et al., 2015). Additionally, we include depression, PTSD and suicide that could have been developed by exposure to early life trauma or extreme early life stressors (Kendler et al., 1995; Heim and Nemeroff, 2001; Cohen et al., 2006a,b; Weber et al., 2008; Schoedl et al., 2010) in our discussion. We also focus on "suicide" in this section to differentiate it as major psychiatric events to the refractory results other psychiatric illness such as psychosis or mood disorders.

5.1. Psychosis

An interaction between BDNF SNPs and childhood trauma may influence cognitive functions in patients with psychotic symptoms. It has been shown that an interaction between the serotonin transporter gene polymorphism (SLC6A4/5-HTT) and childhood trauma influence several cognitive functions. Individuals with the *S/S* version of the 5-HTTLPR gene who had been exposed to high levels of childhood trauma had significantly worse cognitive functioning than both patients without childhood trauma and patient with the *L/L* version of the gene (Aas et al., 2012). Patients with schizophrenia who were also BDNF *met* carriers and had been exposed to childhood sexual abuse showed reduced working memory/executive function and general cognition, larger lateral ventricles, and decreased hippocampal volume compared with all other divided sub-groups according to the genotype and presence of childhood sexual abuse. (Aas et al., 2013).

Cognitive dysfunction is one of the core abnormalities in schizophrenia spectrum disorders (Flashman and Green, 2004) and persists following successful treatment of psychotic symptoms (van Os and Kapur, 2010). It is possible that neurocognitive functioning influences prognosis and predicts functional outcome in schizophrenia. Patients with schizophrenia in remission were reported to have better overall neurocognitive functioning than those who did not meet remission criteria (Torgalsboen et al., 2014). Fervaha et al. (2014) also reported that neurocognitive deficits independently contributed to functional outcomes assessed 1 year later amongst patients with schizophrenia. Interestingly, neurocognitive indicators predicted early remission and social and occupational functioning in young adults with first-episode psychosis (Torgalsboen et al., 2014). These findings suggest that patients with specific gene polymorphisms and a history of childhood trauma might have a particularly poor prognosis and poor functioning and that these effects are mediated by neurocognitive impairments.

5.2. Depression

Aguilera et al. (2009) showed that childhood sexual abuse has more causative effect on adult depressive symptoms in carriers of an *S*-allele version of the 5-HTTLPR polymorphism (5-HTT gene) than in the *L/L* group, and similarly that it has more effect on symptoms in carriers of a *Met* allele version of the *Val66Met* polymorphism (BDNF gene) than in individuals with the *Val/Val* version. Other studies have also reported interactions between 5-HTTLPR and childhood maltreatment with respect to persistent depression (Uher et al., 2011; Fisher et al., 2013). Another study investigated whether an interaction between C677T methylenetetrahydrofolate reductase (MTHFR) variants and exposure to traumatic childhood influenced recurrence of MDD during a 5.5-year follow-up (Lok et al., 2013) and found that *T*-allele carriers of C677T polymorphism (*rs1801133*) were at increased risk of developing depressive symptoms or MDD recurrence if they had also been exposed to childhood trauma (Lok et al., 2013). Childhood trauma can induce changes in the adult hypothalamic–pituitary-adrenal (HPA) axis stress response by reducing the ability of cortisol to bind to glucocorticoid receptors and mineralocorticoid receptors (Juruena, 2014). It has been postulated that an imbalance in functioning of these two receptors may be a risk factor for depression (Juruena, 2014; Hardeveld et al., 2015). Such a mechanism might also lead to higher awakening cortisol levels, which are thought to reflect impaired circadian rhythm (Pruessner et al., 1997; Clow et al., 2010; Hardeveld et al., 2014). Hardeveld et al. (2014) also found that elevated awakening cortisol levels were associated with recurrence of MDD. The gene–childhood trauma interaction affecting depression symptoms was also found in an elderly population. Childhood adversity was only associated with higher rates of depression in elderly people with the apolipoprotein4 (APOE-o4) allele (Park et al., 2015).

Gene–childhood trauma interactions can affect response to treatment in the case of depression. Animal research (Musazzi et al., 2010) suggested that gene–environment interactions during early development in rodents caused life-long synaptic changes affecting the course of depressive-like behavior and the response to drug treatment. Rats subjected to maternal separation in the first 2 weeks of life showed baseline differences in the activation of synapsin I and Erk1/2, as well

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as in α-calcium/calmodulin-dependent protein kinase (αCaM kinase II)/syntaxin-1 and αCaM kinase II/NMDA-receptor interactions in hippocampal synaptosomes. These marked alterations in key regulators of presynaptic release and neurotransmission suggest that the maternal separation procedure induced synaptic dysfunction (Musazzi et al., 2010). Treatment with escitalopram reversed some but not all of the effects of maternal separation. This study showed that early life stress may interact with genes encoding synaptic proteins to cause life-long synaptic changes which influence response to antidepressants drugs (Musazzi et al., 2010). A human study of the interaction between specific genes and childhood trauma (Xu et al., 2012) reported that in the context of childhood trauma the *G/G* genotype of *rs7305115*(TPH2), one of the SNPs in the coding regions of serotonergic genes, was associated with a reduced response to antidepressants. Genetic polymorphisms in glutamatergic and GABAergic genes and their interactions with childhood trauma were also reported in another human study. SNPs in GRIA3 were found to interact with childhood adversity to influence the treatment outcome (Pu et al., 2013).

Taken together, these findings support the hypothesis that gene–childhood trauma interactions influence the severity and clinical course of depression.

5.3. Bipolar disorder

It is well established that childhood trauma is associated with more severe BD symptoms; however there has been little research into gene–childhood trauma interactions that might influence refractoriness in BD. Oliveira et al. (2015) observed a combined effect of both genetic variant of Toll-like receptor 2 (TLR2) and childhood sexual abuse on the age of onset of BD. They found that the presence of both TLR2 rs3804099 TT risk genotype and low to severe sexual trauma had a significant effect on determining early onset age. The psychiatric and somatic symptoms of BD are more severe in early onset cases (Etain et al., 2012).

Evidence shows that BDNF *Met* allele carriers experience greater affective disturbance as a result of exposure to stress in early life (Miller et al., 2013). The risk of violent suicide attempts is also influenced by an interaction between the BDNF *met* allele and childhood trauma (Perroud et al., 2008; Pregelj et al., 2011). Moreover, the general negative effect of childhood sexual abuse on age of BD onset appears to be due mainly to the subgroup of patients carrying the BDNF *met* allele (Miller et al., 2013). There is extensive longitudinal evidence associating earlier onset of BD with worse outcomes (Leverich et al., 2007; Perlis et al., 2009; Post et al., 2010). Miller et al. (2013)'s results suggest that childhood sexual abuse may lead to earlier onset of BD in BDNF *met* allele carriers and hence to more severe and persistent symptoms.

Specific genetic factors and traumatic events may influence the clinical severity of psychiatric disorders through their effects on cognitive function. Previous studies reported that childhood sexual abuse was negatively correlated with performance on a memory task and that the association was moderated by the presence of the *Met66* BDNF allele (Savitz et al., 2007; Liu, 2010). TLR2 genetic susceptibility is a candidate genetic factor for a gene–childhood trauma interaction affecting the clinical course of BD. An adverse TLR2 genotype may affect neuroimmunological responses to prenatal and perinatal infections, leading to a lower threshold for stress-triggered pathological responses and hence to more severe clinical manifestations of BD (Oliveira et al., 2015).

Recent exploratory analysis using genome-wide association studies (GWAS) showed that age of onset of BD was influenced by gene–early life trauma interactions; SNPs in or near genes coding for proteins related to calcium channel activity were implicated (Anand et al., 2015). Anand et al. (2015) detected a negative association between age of onset of BD and a number of traumatic events experienced in childhood. Further research is needed to confirm the direction of the gene–childhood trauma interactions on age of onset of BD, but the evidence currently available suggests that certain gene–early–life trauma interactions worsen the manifestation of BD.

5.4. Suicide

The majority of suicidal individuals have a psychiatric disorder, mainly a mood disorder (Beautrais et al., 1996). It has also been suggested that childhood trauma modifies early brain development in ways which confer a vulnerability to suicidal behavior that is expressed in adulthood (Perroud et al., 2008). The stressful situations such as childhood trauma have been linked to abnormalities in serotonin (5-HT) regulation in animal and human studies (Hariri et al., 2002; Barr et al., 2003). In other words, both genes associated with 5-HT regulation and abnormal brain development caused by stressful childhood events increase vulnerability to suicide. BDNF plays an important role in the regulation and growth of 5-HT neurons during childhood (Altar et al., 1997); a recent study showed that the effect of childhood maltreatment on the violence of suicide attempts was moderated by the BDNF *Val66Met* allele. In individuals reporting severe childhood sexual abuse, the incidence of violent suicide attempts was higher amongst those with the *Val/Val* genotype than those carrying a *Met* allele (Perroud et al., 2008).

Adenosine deaminases acting on RNA enzymes (ADAR and ADARB1) mediate A-to-I RNA editing (Nishikura, 2010), through which some cells can make discrete changes to specific nucleotide sequences within a RNA molecule. Increased expression of deficient ADARB1 mRNA variant has been described in the post-mortem brains of suicide victims with schizophrenia and BD (Silberberg et al., 2012; Karanovic et al., 2015). Decreased expression of ADARB1 mRNA has been reported in suicide victims with MDD (Lyddon et al., 2013). Karanovic et al. (2015) investigated the moderating effects of variants of the ADARB1 and HTR2C genes, lifetime history of stressful experiences and psychiatric disorders such as MDD, BD and schizophrenia on risk for suicidal behaviors, and showed that in patients with major psychiatric disorders vulnerability to suicide was related to the joint effects of ADARB1 and HTR2C variants, the existing mood disorder and cumulative exposure to various stressful events. These evidences suggest that specific gene–childhood trauma interactions may also influence suicidal behavior.

Refractory depression can be one of risk factors for suicidal behavior (Oquendo et al., 1997). The interaction between gene and early life stress affecting the suicidal behavior should be investigated in further studies.

5.5. PTSD

Several studies suggest that the difference between PTSD patients with and without a history of childhood trauma is due to a gene–environment interaction. The *FKBP5* gene is the gene most consistently shown to interact with childhood trauma to increase vulnerability to PTSD (Binder et al., 2008). Binder et al. (2008) observed an additive interaction involving 4 SNPs (*rs9296158*, *rs3800373*, *rs1360780* and *rs9470080*) in the *FKBP5* locus and there appears to be a "dose-dependent" genetic protection against the increase in severity of adult PTSD associated with severe childhood abuse. Individuals homozygous for the protective *G* allele of *rs9296158* had the least severe PTSD symptoms whereas those homozygous for the risk allele *A* had the most severe symptoms. Binder et al. (2008) also reported that interactions between the four *FKBP5* SNPs and total score on the Childhood Trauma Questionnaire (Bernstein et al., 2003) could be used to predict PTSD symptom severity. In summary, this research indicates that specific *FKBP5* alleles interact with childhood trauma to protect against or aggravate PTSD. It has been suggested that there is a robust interaction between specific SNPs within the *FKBP5* locus and childhood abuse which leads to greater symptom complexity and results in cases being classed as "complex PTSD" (Cloitre et al., 2009).

Recent research on systems implicated in PTSD, such as the adrenergic and noradrenergic systems, showed that an interaction between specific genes and childhood abuse influences PTSD symptom severity (Liberzon et al., 2014). An association between PTSD symptom severity

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and the interaction of *rs2400707* on the ADRB2 gene with childhood adversity was found in a cohort of male soldiers of European American ancestry. An *rs2400707*–childhood trauma interaction predicting adult PTSD symptoms was replicated in an independent, predominantly female African American cohort (Liberzon et al., 2014). The *rs2400707 A* allele was associated with resilience to childhood adversity. Liberzon et al. (2014) found no interaction between the ADRB2 gene and lifetime exposure to adulthood trauma, suggesting that genetic variance in interaction with childhood trauma alone can influence adult PTSD symptom severity. More efficient transcription and hence greater expression of ADRB2 may exacerbate the negative biological consequences of chronic activation of adrenergic and noradrenergic systems in individuals with a history of childhood trauma; such a mechanism could account for the refractoriness of PTSD symptoms in this population.

Ressler et al. (2011) have shown that levels of pituitary adenylate cyclase-activating polypeptide (PACAP) protein in the blood are associated with PTSD symptom severity in women, and that differential methylation of the PAC1 receptor (PAC1R) was correlated with PTSD symptoms. They also found an association between a SNP in a putative estrogen response element within the *ADCYAP1R1* gene (PAC1R) and PTSD symptoms in women who had experienced trauma (Ressler et al., 2011). Uddin et al. (2013) found an interaction between the *ADCYAP1R1* gene and childhood maltreatment in a cohort of women. In a related research, Almli et al. (2013) found a childhood trauma and genotype interaction, predicting PTSD symptom severity in carriers of the *C* allele of *ADCYAP1R1* gene. This body of research indicates that interactions between specific genotypes and certain measures of childhood trauma, such as the number, severity and type of traumatic events may moderate symptom severity in PTSD.

Mehta et al. (2013) proposed that the biological modification associated with PTSD vary between individuals with and without a history of childhood trauma. The gene expression profiles of PTSD patients matched for adult exposure to trauma but with or without a history of childhood trauma were almost completely non-overlapping. They had distinct genomic and epigenetic profiles. The extend of epigenetic modifications linked to these gene expression changes occurred at a rate up to 12 times higher in the PTSD group exposed to trauma in childhood. They raise the possibility that there are two distinct subtypes of PTSD, with different symptoms, course and refractoriness to treatment, according to whether or not the patient experienced abuse in early life. This suggests that childhood maltreatment results in the presence of distinctive genetic biomarkers which are expressed in PTSD.

6. Conclusion

Both genetic and environmental factor play critical roles in the development of several psychiatric disorders. Gene–environment interactions, especially those involving exposure to childhood trauma as the environmental factor, are regarded as an important factor in the development of severe psychiatric illness. The extant research indicates that interactions between specific genotypes and childhood abuse contribute not only to the incidence of various psychiatric disorders but also to their course, prognosis and refractoriness to treatment.

Biological responses to environmental variables such as childhood trauma are influenced by genetic susceptibility; risky genotypes can lower the threshold for pathological responses leading to more severe clinical presentations of psychiatric disorders. Childhood trauma may influence the trajectory of psychiatric disorder by inducing epigenetic changes. Given that there is evidence that the presence or absence of childhood trauma is associated with specific subtypes of illness, research into the mechanisms by which gene–environment interactions influence the course of psychiatric disorders has the potential to bring about substantial improvements in treatment.

To date, there has been relatively little research considering specifically how gene–childhood trauma interactions influence refractoriness in psychiatric illness. However, evidences to date show that the mediating factors through pathway from childhood trauma to treatment refractoriness include symptom severity, cognition deficit, earlier onset, suicidal behavior, recurrence and recovery and comorbidity. This issue is interesting and should be subject to further research.

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