REVIEW ARTICLE

Molecular and genetic basis of depression

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Abstract

Joyousness or sadness is normal reaction to state of life. If any of these lead to certain semi-permanent changes in daily life, then it is termed as mental disorder. Depression is one of the mental disorders with a state of low mood and aversion to activities that exerts a negative effect on a person's thoughts and behaviour. Adolescent group is probably the world's largest active group of people, who are getting prone to this state of mind leading to their diminished mental and physical abilities. Depression is closely linked to stress and thus a chronic stressful life can increase the risk of depression. Depression is a complex disease having both genetic and environmental components as contributing factors. In this study an attempt has been made to put forward the understanding of the known genes and their functional relationships with depression and stress with special reference to *BDNF* and *5-HTTLPR*. Analysis of common genetic variants associated with depression, especially in the members of a family who had a previous history, might help in identifying the individuals at risk prior to the onset of depression.

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Introduction

A clinically significant manifestation of behavioural, psychological or biological dysfunction that occurs in an individual with stress is considered as mental disorder according to DSM-5 (Vieta *et al.* 2014). Mental disorders have two opposite range of phenomena: (i) mania, characterized by intense, unrealistic feelings of excitement and euphoria while, (ii) depression, where individuals feel sad and dejected most of the day but may have normal mood from time to time. Depression is classified into three types: major, unipolar and bipolar.

Major depression / clinical depression

In major depression, individuals experience depressive mood or lose interest in pleasurable activities for at least two consecutive weeks. The heritability of major depression is 37% and it is approximately three times higher if a first degree family member is affected (Fava and Kendler 2000; Sullivan *et al.* 2000; Moreno *et al.* 2013). Depression is among the 10 disorders with the greatest global burden (Lopenz *et al.* 2006) and it is predicted to become the second leading cause of disability adjusted life years (DALYs) in 2020 (Murray and Lopenz 1997).

One of the major symptoms in most of the depressed patients is that they have recurring thoughts of suicide (Carson *et al.* 2007). Other symptoms associated with this disorder are called specifiers, can be grouped together under different names as follows:

(i) Melancholic features: early morning awakening, worsening of depression in the morning causing agitation or retardation, loss of appetite and weight loss, excessive guilt feeling and variably depressed moods.
(ii) Psychotic features: hallucinations, guilt and worthlessness.
(iii) Atypical features: mood reaction is better with positive events; increase in appetite and weight gain, hypersomnia (excessive sleepiness), leaden paralysis (heavy feelings in arms or legs) and acute sensitivity to rejections.
(iv) Seasonal pattern: two or more episodes and remissions occurring during the same time every year usually during spring or autumn.

Unipolar depression / chronic depression

Unipolar depression includes dysthymic disorder ranging from mild to moderate intensity. This is characterized by a person remaining persistently depressed almost throughout the day for at least one to two years with intermittent normal mood, and this period could last longer. This intermittent

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normal mood is the distinguishing feature of unipolar disorder from major depression. The incidence is much higher in women than in men, and frequency of its occurrence has increased in recent decades which are estimated to be between 31 and 42% (Kaelber *et al.* 1995; Kessler *et al.* 2003; Fabbri *et al.* 2013).

Bipolar depression

It is a severe mental disorder, characterized by at least two episodes of elevated level of depression, impulsiveness, interpersonal problems, violence and mania (Keck *et al.* 2001; Osby *et al.* 2001; Cruceanu *et al.* 2013). Such patients require hospitalization during manic episodes. It also includes cyclothymic disorder, i.e., becoming more creative due to increased physical and mental activities. The main distinguishing feature of bipolar depression or bipolar mood disorder from unipolar is the presence of manic or hypomanic condition.

Bipolar disorders have been further subdivided into bipolar I and bipolar II disorders. Bipolar I includes the presence of one or more manic or mixed episodes, while in bipolar II disorder, person experiences hypomanic condition along with the symptoms of depressive disorder. Bipolar II is more common than bipolar I. Bipolar disorders are distributed equally in males and females and usually gets initiated during adolescence (Winokur and Tsuang 1996), the heritability is estimated to be approximately 80% (Cruceanu *et al.* 2013). Recently, DSM-5 introduced a new category of other specified bipolar and related disorders to accommodate the hypomaniac episodes of shorter duration with insufficient symptoms, which do not meet the criteria of bipolar I and II.

Depression seen in adolescent commonly have a few of the above features with a risk of recurrence and remission which may or may not continue in adult life (Pine *et al.* 1999; Fombonne *et al.* 2001; Dunn and Goodyer 2006). There are studies documenting poverty, lower education status, experience of insecurity and hopelessness, rapid social change, risk of violence and physical illness as risk factors for adolescent depression; girls are more affected as they often face such situations in the society (Patel and Kleinman 2003; Jacob 2012). It has been suggested that middle-to-late adolescence (15–18 years) may be a critical time for studying vulnerability to depression as there is greater risk for depression onset during this period. A dramatic increase in gender differences in depression has been observed in this group also, young women being more affected (Hankin *et al.* 1998; Rohde *et al.* 2009). All the above mentioned risk factors are associated with stress, hence, an understanding of stress is also essential in the present context.

Stress

Stress is our body's reaction to adapt to a changing environment. It can be of two types: eustress and distress. Eustress or (mild) positive stress gives excited feeling, e.g., a stress or motivation when throwing a party or going out with friends, while distress or negative stress causes anxiety, decreased performance, etc. A few general symptoms of distress include headache, stomach ache, sweating, diarrhoea, sleeplessness, increased heart rate, rapid breathing, etc.

Stress response results in increased flow of adrenalin and cortisol in blood leading to increased heart rate and blood flow to all vital organs alerting the senses. Stress can also be categorized as physical and psychological. Physical stress arises as a result of our body's response to physical stressors, like work, illness, etc., while psychological stress occurs when our mind perceives an inability to cope with a challenge. Often both react and interact with each other to produce additional stress. Stress in prolonged and severe condition is believed to initiate several psychiatric illnesses including depression. The impact of severe stress has negative effects on brain volume and structure (Bremner 1999; Woon *et al.* 2010; Kang *et al.* 2012; Licznerski and Duman 2012).

Several neurotransmitters and endocrine system, such as hypothalamo–pituitary–adrenocortical axis (HPA), get activated during severe stress (Chaouloff 1993). Cortisol produced by the adrenal gland during high stress condition has been considered as one of the most reliable tests for biological abnormality and therefore, salivary cortisol level is used to assess the severity of depression (Mannie *et al.* 2007). Individuals (16–20 years) with increased level of salivary cortisol in the morning, have familial risk of depression (Mannie *et al.* 2007). Further, high amount of cortisol is secreted in individuals having first degree relatives with depression history than having nondepressed first degree relatives.

Globally, depression is ranked among the top three major causes of disability, except in high income countries of Asia Pacific, where it is ranked fourth (Murray *et al.* 2012; Institute for Health Metrics and Evaluation (IHME) 2013). The Global Burden of Disease (GBD) 2013 study showed anxiety as one of the top 10 causes while schizophrenia and bipolar disorder appear among the top 20 causes of disability in many regions. In 1990, noncommunicable disease accounted for 31% of DALYs among both sexes in India, but it increased to 53% by 2013 as reported by IHME.

Complexities of depression

Depression, which is closely associated with stress, is affected by a number of factors that form a network and influence the manifestation of depression. These factors are both environmental (e.g., condition at home, school/work place, diet, hormonal milieu, etc.) and genetic (figure 1), and are interlinked with each other. For example, the HPA that regulates the hormone levels is guided by certain sets of genes which, in turn, provide the conditions (environment) affecting mood and may be a causal factor for depression.

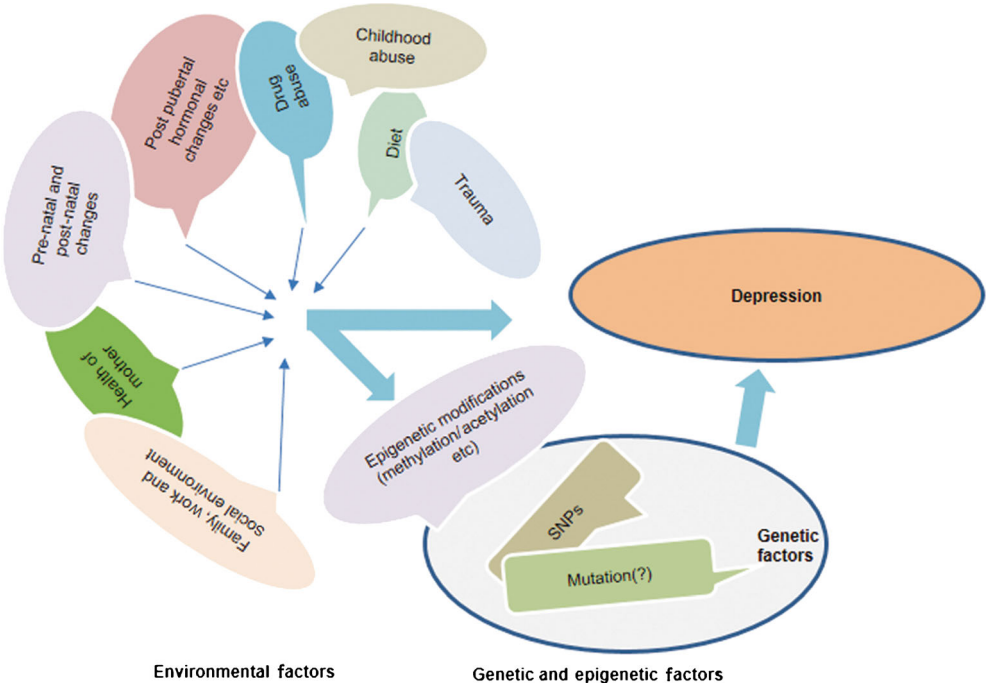

Figure 1. Environmental and genetic factors associated with depression. Environmental factors- prenatal and postnatal conditions: health of mother, etc.; postpubertal changes: hormonal changes, HPA axis regulation, etc.; drug, diet, condition at home, school, office includes a wide array of factors such as socio-economic status, IQ, education, etc. Genetic/epigenetic factors- mutations: insertions and deletions of nucleotides causing frame shifts, substitution, etc.; SNPs; epigenetic modification as methylation, acetylation, phosphorylation of DNA and histone proteins.

Genetic component in depression

Genes coding for neurotrophic factors and brain signalling molecules which play regulatory roles in many neuronal functions are, brain-derived neurotropic factor (*BDNF*) and 5-hydroxytryptamine (*5-HT*). These two factors are two different signalling molecules functioning in separate but overlapping pathways and play regulatory role in functions, like neuronal survival, neurogenesis, synaptic plasticity and also in regulation of depression. Since these two molecules are best studied, they have been dealt in more detail in this study.

BDNF and its receptors

BDNF is a widely distributed neurotrophin found in the brain and was first isolated as a secretory protein promoting the neuronal survival, phenotypic differentiation, axonal and dendritic growth and synapse formation (Lewin and Barde 1996; Huang and Reichardt 2001). The gene has a complex structure with multiple upstream promoters, and the primary transcript undergoes alternate splicing to form several isoforms (West *et al.* 2001; Lu 2003). The promoters of individual BDNF transcripts are regulated by various physiological factors and these transcripts are spatially distributed in different brain regions, different cell types and even different parts of the cell exhibiting complex regulation of neuronal function (Pattabiraman *et al.* 2005; Cunha *et al.* 2010; Park and Poo 2013).

BDNF function is mediated by two receptor systems, Trkβ (tropomyosin-receptor kinase beta) and p75NTR (p75 neurotrophin). These receptors are localized on the membrane of intracellular vesicles in the absence of signals. Electrical activity, cAMP level and Ca^{++} level stimulate exocytosis of these cytoplasmic vesicles into the cell surface, releasing Trkβ on the outer membrane with other receptors (Meyer-Franke *et al.* 1998; Du *et al.* 2000). Presence of p75NTR on the membrane enhances the specificity of Trkβ for the primary ligand, BDNF (Benedetti *et al.* 1993; Clary and Reichardt 1994; Lee *et al.* 1994; Bibel *et al.* 1999; Brennan *et al.* 1999; Mischel *et al.* 2001). Trkβ dimerizes and is autophosphorylated at several tyrosine residues after binding with BDNF leading to initiation of several pathways: regulation of channel functions, local axonal and dendritic growth, survival and proliferation of neurons, synaptic functions, assembly of cytoskeleton, retrograde signalling and receptor cross-talk (Park and Poo 2013). Phosphorylation of tyrosine at 490 position in Trkβ, activates phosphatidylinositol 3 kinase (PIK3) which through Akt1/2 increases transcription of Bcl-2, Bax, etc., responsible for neuronal survival. Phosphorylation of tyrosine at 785 position of Trkβ recruits phospholipase C-γ1 (PLC-γ1) (Kalpan and Miller 2000) which hydrolyses Ptd-Ins(4,5)P2 (phosphatidylinositol 4,5-bisphosphate), generating inositol triphosphate (IP3) and

diacylglycerol (DAG). IP3 promotes Ca^{++} release from endoplasmic reticulum and also activates protein kinase C (PKC) and Ca^{++}-calmodulin-regulated protein kinases. PKC is required for neurotrophic growth factor (NGF), to promote neurite outgrowth and also to activate Erk1 and Erk2 (Corbit *et al.* 1999). Activation of Erk/MAPK-Ras signalling cascade is essential for neurotrophin-promoted differentiation of neurons (Bekinschtein *et al.* 2008; Minichiello 2009).

BDNF signalling has been shown to regulate adultc neurogenesis (Lu and Chang 2004) as the basal rate of proliferation of new neurons in the dentate gyrus of the hippocampus is increased in BDNF heterozygous ($BDNF^{+}/BDNF^{-}$) mice as well as in mice with abnormal Trkβ function; however, the survival of these newly divided neurons/neuroblasts is significantly reduced, suggesting the requirement of normal BDNF–Trkβ signalling for the long-term survival of newborn neurons in the dentate gyrus (Sairanen *et al.* 2005).

Polymorphism in BDNF and the consequences

BDNF is translated and folded in the endoplasmic reticulum into a precursor protein (pro-BDNF) and then through several steps packed into secretary vesicles (Lu 2003). The polymorphic amino acid Val66Met located in the prodomain affects BDNF sorting and secretion thereby suggesting an important function of this domain. This SNP is associated with deficits in short-term episodic memory, abnormal hippocampal activation, neuropsychiatric disorders as Parkinson's and Alzhimer's diseases (Guerini *et al.* 2009; Pivac *et al.* 2011) and impairment of NMDA and GABAnergic neurons in their synaptic plasticity (Neves-Pereira *et al.* 2002; Sklar *et al.* 2002; Egan *et al.* 2003; Chen *et al.* 2005; Schumacher *et al.* 2005; Strauss *et al.* 2005; Chen *et al.* 2006; Okada *et al.* 2006; Pattwell *et al.* 2012). Altered BDNF when binds to p75NTR, activates a set of signalling cascade involving nuclear factor-kappa B (NFκB), c-jun kinase and sphingomylin hydrolysis (Huang and Reichardt 2003; Gentry *et al.* 2004; Teng *et al.* 2005). This leads to arrested cell cycle, activation of apoptotic pathway and also initiation of N-methyl-D-aspartic acid (NMDA) receptor-dependent synaptic depression in the hippocampus (Ibanez 2002; Lu and Je 2003; Barker 2004; Lu *et al.* 2005).

Val66Val BDNF polymorphism has been generalized with extraversion while Met66Met or Val66Met is shown to be associated with introversion (Terracciano *et al.* 2010). It has been hypothesized that BDNF depletion, particularly in the dentate gyrus of the hippocampus in adults, occurs as a result of defeat stress leading to cognitive dysfunction and depressive symptoms, which can be reverted by antidepressants (Duman *et al.* 1997; Shirayama *et al.* 2002; Duman and Monteggia 2006). From the experiments on animal models, BDNF has emerged as a modulator of brain reward system, and absence or ectopic presence causes depressive symptoms, cognitive dysfunctions, low energy and memory deficits (Nestler and Carlezon 2006; Monteggia *et al.* 2007; Pattwell *et al.* 2012).

BDNF plays prodepressive and antidepressive roles via two different pathways

Depression is generally characterized by two events: behavioural despair and the inability to experience pleasure (anhedonia). These sets of behaviours are likely to be controlled by two interacting brain systems: the brain stress system HPA pathway and the brain reward system (ventral tegmental area-nucleus accumbens (VTA-NAc)) and VTA-prefrontal cortex. VTA-Nac is the origin of dopaminergic neurons. The hippocampal circuitry includes functional components for learning and memory as well as negative regulation of the HPA-mediated stress pathway, and both are altered in depression. The dopaminergic VTA-NAc pathway plays a crucial role in reward and motivation. Experimental evidences indicate opposite effects of BDNF on these two systems. Intrahippocampal infusion of BDNF produces antidepressive effects (Siuciak *et al.* 1997; Shirayama *et al.* 2002), while in contrast, it appears to play a prodepressive role in the VTA-NAc reward system (Eisch *et al.* 2003). Inhibiting BDNF–Trkβ signalling using dominant-negative Trkβ-T1 (truncated Trkβ) in NAc, a dramatic antidepressive effect is seen in experimental animals (Eisch *et al.* 2003). In another experiment, Berton *et al.* (2006), tried to create a long-lasting social withdrawal in different genotypes of mice by repeated exposure to aggression. As expected, mice with wild-type *BDNF* showed social withdrawal, while mice with *BDNF* gene deletion prevented social defeat, similar to the effect seen with chronic antidepressant treatment (Berton *et al.* 2006). Blocking *BDNF* expression by RNAi also confirmed the above result of prevention of social defeat (Taliaz *et al.* 2010). It was also found that mice lacking Trkβ in hippocampal neural progenitor cells failed to produce antidepressant-induced proliferation and neurogenesis (Li *et al.* 2008).

BDNF regulates transmission at glutamatergic and GABAergic synapses by both presynaptic and postsynaptic mechanisms (Minichiello 2009; Fortin *et al.* 2012). Microarray and electron microscopic observations have shown downregulation of synaptic protein in major depressive disorders (Kang *et al.* 2012). The dichotomy of BDNF actions in the hippocampus and VTA-NAc demands separate investigation on the effects of BDNF manipulations on behaviour related to anhedonia and motivation, and despair and stress.

5-HT/serotonin

5-HT is produced in the raphe nuclei of brain stem region which innervate the cortical brain regions and regulate a wide repertoire of functions such as behaviour, cognition and mood. There are 15 genes encoding 5-HT receptors in mammalian brain (Bockaert *et al.* 2006). All the receptors, except 5-HT3 (ionotropic), are G-protein-coupled receptors (Bockaert *et al.* 2006). The 5-HT released by the serotonergic neurons into the synaptic cleft is removed by 5-hydroxytryptamine transporter (5-HTT) of the presynaptic neuron. This transporter determines the time and duration of

the response of 5-HT, and therefore plays an important role in serotonergic neurotransmission. It has been shown that longer the duration of serotonin present in the synaptic cleft, longer is the activation, leading to depression (Lesch and Mossner 1998). 5-HTT is encoded by a single gene *SLC6A4* and polymorphisms in this gene have been shown to be partly responsible for regulating serotonin function in brain (Lesch *et al.* 1999). *5-HTT* promoter region (*5-HTTLPR*) has a polymorphism resulting either in 14 or 16 repeats located about 1kb upstream of the transcription initiation site (Lesch *et al.* 1996). The wild-type, long (l) allele contains 16 repeats, whereas the short (s) allele contains 14 repeats. The allele 's' expresses at a lower level and therefore the homozygotes show less reuptake of serotonin from the synaptic cleft, leading to prolonged activity of serotonin and depressive symptoms (Lesch *et al.* 1996).

The 5-HTTLPR polymorphism or abnormal 5-HT signalling has been shown to be associated with anxiety, depression and aggression-related personality traits including suicides (Baumgarten and Grozdanovic 1995; Hen 1996; Lesch *et al.* 1996; Berman *et al.* 1997; Lesch and Mossner 1998; Mann 1998). It has been found that unipolar depression across the lifespan is associated with diminished serotonergic function in the brain via a series of complex neurochemical events that lead to warping in emotion and cognitive processing (Jans *et al.* 2007; Goodyer *et al.* 2010).

Studies conducted in preschoolers (age 5–8 years) have shown a correlation of BDNF and 5-HTTLPR polymorphisms in brain development and show high level of cortisol which could be a cause of depression (Dougherty *et al.* 2010). However, studies conducted in adults (age 18–81 years) showed mixed results. In adolescents, BDNF Met66Met and Val66Met as well as 5-HTTLPR s/s (homozygous for short form) and l/s (heterozygous) have shown to be more involved in episodic depression (Brumett *et al.* 2008; Goodyer *et al.* 2010).

In India, open pilot studies were carried out on *5-HTTLPR* (Guhathakurta *et al.* 2006) and treatment response to serotonin reuptake inhibitor (escitalopram) in depression in adults aged 40–50 years (Margoob *et al.* 2008). It was found that individuals with the short (s/s) variant showed a poor treatment response to the antidepressant, escitalopram (Margoob *et al.* 2008), however, the results require validation by analysing more samples.

Other candidate genes

An extensive information is available on the involvement of several genes in stress and depression, however, for many genes, almost equal number of studies show no association bringing the conclusion to its infancy. The limitations in all such studies being, small sample size and varying environmental factors. This demands studies on large-sized population covering wide geographical areas, classifying individuals of similar genetic makeup and assessing the polymorphisms, and gene activities in them. A recent large-sized *in silico* data analysis has prioritized 169 genes out of 5055 candidate genes for depression (Kao *et al.* 2011). Besides BDNF and 5-HTTLPR, a few of the top prioritized gene products are presented below and several of them are listed in table 1.

Dopamine beta hydroxylase (DBH): It catalyses the key steps in biosynthesis of neurotransmitter noradrenaline from dopamine. A low activity of this enzyme has been correlated with depression (Wood *et al.* 2002; Cubells and Zabetian 2004), however, there are also studies which do not show association.

Tumour necrosis factor (TNF): It plays an important role in altering neuronal and immune interactions as a result of the level of cytokines changes. Further, there is an increase in pain sensitivity and inflammation with altered functioning of TNF (Euteneuer *et al.* 2010). In recent studies, it was shown that the proinflammatory cytokines, TNF-alpha and interleukins, IL6 and IL10, were increased in patients with depression (Dowlati *et al.* 2010; Ertenli *et al.* 2010; Euteneuer *et al.* 2010). Receptors of IL, tachykinin receptors NK1 and NK2 expressed in monocytes are increased in recurrent major depression.

Glycogen synthase kinase 3β (GSK3β): Is an enzyme which is involved in neural cell development and energy metabolism, and therefore, has been considered as an important factor involved in depression (Zhang *et al.* 2010). It also plays an important role in mood stabilization (Jope and Bijur 2002). This gene is regulated by 5-HT or drugs acting on 5-HT neurotransmission, and GSK3β inhibition rescues the behavioural abnormalities in 5-HT deficient mice. Postnatal inactivation of this enzyme in forebrain pyramidal neurons showed anxiolytic and prosocial effect (Latapy *et al.* 2012) showing the possibility that drugs (e.g. lithium, clozapine, fluoxetine and ketamine) regulating GSK3β activity may serve as a good treatment strategy for major depressive disorders.

Glutamate receptor, ionotrophic, AMPA3 (GRIA3): Depressive disorder is almost invariably accompanied by disturbed sleep, typically with early morning awakenings, leading to decrease in sleep duration (Leventhal and Rehm 2005); but in some forms of depression (e.g. seasonal affective disorder), sleep duration can be modulated (Partonen and Lonnqvist 1998). In bipolar mood disorder, a decrease in sleep duration can lead to mania (Doghramji 2003). A significant association of rs687577 of GRIA3 on the X chromosome with sleep duration was found in women. In this, 'A' allele plays a dominant role and was shown to be associated with normal or longer sleep duration, while C/C was associated with decreased sleep duration and with increased risk of depression in women.

Table 1. Important variants involved in stress and depression.

Gene	Susceptible variant	Location	Description	Reference
Serotonergic				
SLC6A4	14–16 repeats upstream to transcript initiation site	17q11.2	Serotonin transporter	Lesch *et al.* 1996; Goodyer *et al.* 2010; Brumett *et al.* 2008
HTR1A	rs6295 rs878567	5q11.2-q13	Serotonin receptor subfamily	Kishi *et al.* 2013; Benedetti *et al.* 2011; Kim *et al.* 2011; Angles *et al.* 2012*; Kishi *et al.* 2011*
HTR2A	rs6311 rs6313	13q14.2	Serotonin receptor	González-Castro *et al.* 2013; Jin *et al.* 2013*
TPH2	rs4570625	12q21.1	Rate limiting enzyme in serotonin biosynthesis	Gao *et al.* 2012; Serretti *et al.* 2011*; Campos *et al.* 2010
Dopaminergic				
DBH	rs6271 rs5320	9p34	Enzyme converting dopamine to nor epinephrin	Ates *et al.* 2013; Punia *et al.* 2010; Bhaduri and Mukhopadhyay 2008
DRD2	rs6277	11q22-23	Dopamine G-coupled receptor inhibits adenylyl cyclase activity	Whitmer and Gotlib 2012
DRD4	C616G C521T	11p15.5	Dopaminergic D4 receptor	Ambrósio *et al.* 2004*
Neurotrophin				
BDNF	rs6265	11p13	Protein involved in brain development	Pattwell *et al.* 2012; Terracciano *et al.* 2010
NGFR	rs2072446	17q21-22	Trk receptor	Fujii *et al.* 2011
Others				
COMT	rs4680	22q11.21	Enzyme degrading catecholamines	Lachman *et al.* 1996; Hosak 2007; Kocabas *et al.* 2010
GNB3	rs5443	12p13	G-protein, involved in signal transduction	Cabadak *et al.* 2011; Lu *et al.* 2012*; Lee *et al.* 2004
DTNBP1	rs760761 rs26019522	6p22.3	Important for biosynthesis of lysozyme-related organelles	Breen *et al.* 2006; Kim *et al.* 2008; Raybould *et al.* 2005*
MAO-A	rs1137070	Xp11.3	Mitochondrial enzyme catalysing oxidative deamination of amines	Słopień *et al.* 2012
MTHFR	rs1801133	1p36.3	Folate and homocysteine metabolism	Chojnicka *et al.* 2012; Ward *et al.* 2011; Lizer *et al.* 2011; Morris *et al.* 2003
GRIA3	rs687577	3q11.9	Neuronal development	Doghramji 2003
APOE	Epsilon-4	19q13.2	Associated with the late life depression including Alzheimer's and Parkinson's diseases etc.	Butters *et al.* 2003; Steffens *et al.* 2003
FKBP5	rs9296158	12p13.33	Protein folding and trafficking	Binder *et al.* 2008; Roy *et al.* 2012; Appel *et al.* 2011

*Papers showing no association in contrast to others which showed association. *DRD*4 did not show association with depression.

Tryptophan hydroxylase 2 (TPH2): Is exclusively detected in central nervous system, mainly in the raphe nuclei and also in the peripheral myenteric neurons of small intestine. It catalyses the conversion of tryptophan to 5-hydroxytryptophan (5-HTP) and thus considered as a rate-limiting enzyme of serotonin biosynthesis. TPH2 has been shown to be associated with the pathophysiology of several psychiatric disorders such as anxiety, aggression, depression-associated personality traits, suicidal behaviour, bipolar disorder, attention deficit hyperactivity disorder and deficits in cognitive control and emotion (Waider *et al.* 2011). A rare variant of TPH2 (rs120074175) showed its association with the psychiatric disorders (Zhang *et al.* 2005), however, several studies failed to establish this association (Delorme *et al.* 2006; Ramoz *et al.* 2006; Sacco *et al.* 2007).

TPH1 is an isoform of TPH2 sharing 70% homology in amino acid sequence and expressed in the gastrointestinal tract and pineal gland (Walther and Bader 2003). It was found that rs2108977 of TPH1 is associated with hyperphagia and posttraumatic stress disorder (PTSD) and females with this isoform showed significantly higher level of anxiety and depression.

FK506-binding proteins 5 (FKBP5): Is a member of immunophilin protein family which plays role in immunoregulation, protein folding and trafficking. It interacts with mature corticoid receptors (e.g., progesterone, glucocorticoid, mineralocorticoid receptor complexes), HSP90 and P23. Genetic studies have identified its role in PTSD, depression and anxiety. Several SNPs of *FKBP5*, such as, rs9296158, rs3800373, rs1360780 and rs9470080 have been shown to be associated with childhood trauma (Binder *et al.* 2008). It is also found that this protein is less expressed in PTSD and is associated with higher rate of depressive disorders (Binder *et al.* 2004; Appel *et al.* 2011). An increase in FKBP51 has also been correlated with anxiety phenotype in mice, and when deleted, showed antidepressant type effects. Therefore, drug discovery efforts focussing on depleting FKBP51 levels may yield novel antidepressant therapies (O'Leary *et al.* 2011).

Catechol-O-methyltransferase (COMT): Is one of the several enzymes that degrade catecholamines, like dopamine, epinephrine and norepinephrine, and therefore, is involved in the inactivation of catecholamine neurotransmitters. rs4680 is a common SNP of COMT and corresponds to Val108Met (soluble form) and Val158Met (membrane bound form) (Lotta *et al.* 1995; Spielman and Weinshilboum 1981). Homozygotes for this variant have 3–4 fold lower enzyme activity compared to the wild-types, while it is intermediate for the heterozygotes (Lachman *et al.* 1996). rs4680 has been associated with schizophrenia (Saqud *et al.* 2010), bipolar disorder (Hosak 2007), major depressive disorder (Kocabas *et al.* 2010), obsessive compulsive disorder (Pooley *et al.* 2007) and Parkinson's disease (Williams-Gray *et al.* 2008). However, there are studies which did not find any association between this polymorphism and cognition in depressed adults (Potter *et al.* 2009) or in children (6–7 years) (Evans *et al.* 2009). Recently, a meta-analysis showed no association between this polymorphism and suicidal behaviour in Mexican population (Tovilla-Zarate *et al.* 2011).

Antidepressants and modulation of gene activities

Antidepressants normally work in two ways – (i) prevent reuptake of serotonin, (ii) block degradation of serotonin by inhibiting monoamine oxidase (Duman *et al.* 1997; Nestler *et al.* 2002; Castren 2005). Serotonin and nor-epinephrine reuptake inhibiting drugs (SRIs) are used for the treatment of depression and anxiety with several weeks of observation (Kreiss and Lucki 1995; Duman *et al.* 1997; Hervas and Artigas 1998; Trillat *et al.* 1998; Malagie *et al.* 2001; Nestler *et al.* 2002). Thus, over a period of time, the amount of serotonin and nor-epinephrin increases and they help in improving mood and reduce anxiety.

In the studies with antidepressants, the BDNF pathway was also found to be modulated. An increase in the transcript level of BDNF in hippocampus and cortex region of brain following antidepressant treatment was shown in rodents (Nibuya *et al.* 1995, 1996). Studies in human patients with antidepressant treatment also showed increased BDNF level (Chen *et al.* 2001b; Dwivedi *et al.* 2003; Karege *et al.* 2005). Some studies have shown that direct incorporation of BDNF in hippocampus of rodents mimics antidepressant treatment (Siuciak *et al.* 1997; Shirayama *et al.* 2002). However, on the other hand, another study on BDNF knockdown mice did not show depressive behaviour and did not respond to antidepressants (Monteggia *et al.* 2004). Administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), enhanced BDNF expression and also enhanced neurogenesis, which in turn led to the enhancement of long term potentiation (LTP) in dentate gyrus (Wang *et al.* 2008; Bianchi *et al.* 2010). The Val66Met polymorphism in BDNF showed interference with SSRI and neurogenesis (Bath *et al.* 2012), however, the molecular mechanism of BDNF-mediated neurogenesis is not understood (Ninan *et al.* 2010).

Antidepressants alter the expression or activation of cAMP response element binding protein (CREB), a transcription factor, which gets activated by phosphorylation and in turn activates three pathways: (i) cAMP-pkA, (ii) Ca-calmodulin, (iii) MAP-K pathway (Shaywitz and Greenberg 1999). BDNF acts through CREB pathway (Nibuya *et al.* 1996; Conti *et al.* 2002). Mouse having CREB overexpression, showed decreased depressive behaviour (Chen *et al.* 2001a).

Lithium compounds are antidepressants and mood stabilizers, elicit increased hippocampal neurogenesis (Chen *et al.* 2000; Malberg *et al.* 2000) and this antidepressant-induced survival is lost in mice when BDNF signalling is disrupted (Sairanen *et al.* 2005). Further, stress-induced depressive behaviours have been correlated with a decrease in

hippocampal BDNF level (Nibuya *et al*. 1995; Smith *et al*. 1995; Vaidya *et al*. 1997; Duman 2004; Duman and Monteggia 2006) and antidepressant treatment enhanced the expression of BDNF (Nibuya *et al.* 1995; Russo-Neustadt *et al.* 1999; Duman and Monteggia 2006).

Epigenetic modifications have a long lasting effect in mature neurons and may be implicated in complex neurological disorders (Tsankova *et al.* 2007). Stress can regulate histone methylation which in turn downregulates BDNF transcripts III and IV. Histone demethylase can also downregulate BDNF but when antidepressants (like imipamine) are administered, it promotes histone acetylation and downregulates histone deacetylation (Tsankova *et al.* 2006).

Conclusion

This study gives an indication that compared to the other diseases, the genetics of depression and stress is less explored even though significant proportion of the population are sufferers. It has already been indicated in the previous section that the main limitations of such studies is the small sample size in isolated localities and the genetic and environmental heterogeneity observed across individuals in any population. With the advent of sophisticated technologies, many research groups have shifted their research from candidate gene approach, i.e. studying the association of individual genes with the trait or disease, to the whole genome analysis approach like genomewide association studies (GWAS) and next generation sequencing (NGS), etc. One such study by Georgi *et al.* (2014) in recent years carried out microsatellite genotyping and high density SNP-array genotyping of 388 members of an extended family having 18 parent child trios. As the individuals were family members especially, parent child trios, the chances of genetic heterogeneity were less. The analysis revealed a large number of SNPs in the entire genome, and many of them showing close association with bipolar disorder. This leaves a wide scope in validating the association of these SNPs which will lead in understanding several genes and pathways involved in depressive disorders.

With the intention of reducing genetic and environmental heterogeneity of the subjects under study for depression, studies on twins, specially the monozygotic ones residing in same or two different environmental conditions, or adoption studies, where the children are of different genetic makeup but residing in a given environment, may reveal the heritability of a given polymorphism and its interaction with the environmental components (McAdams *et al.* 2012). In an appropriate study, Byrne *et al.* (2013) assessed the role of epigenetic modifications (methylation) in CpG sites in 12 monozygotic twins discordant for major depressive disorder (MDD) and another 12 monozygotic twins concordant for no MDD. They report a sex specific difference in CpG methylation predicting higher susceptibility of females for depressive disorders. Such studies have paved the ways for taking up further studies in the given direction.

Variability in the genome also arises due to copy number variation (CNV) of a segment of DNA (containing one or more genes) in the genome and they have potential involvement in the psychiatric diseases. In a study by Saus *et al.* (2010), at least 14 genes with CNVs have been correlated with the psychiatric disorders. This has opened a new dimension of studies and further explorations.

Physical exercise is another factor which improves cognition (Laske *et al.* 2010). In mice, voluntary wheel running was shown to increase BDNF levels (Johnson *et al.* 2003). High physical activities induced CREB enhancement which improved synaptic function and enhanced learning and memory (Vaynman *et al.* 2004). Running too showed improvement in cognitive functions, hippocampal neurogenesis, dendritic plasticity and behaviour (Yau *et al.* 2011) and human studies in recent years have shown that physical exercise improves depressive symptoms (Guiney and Machado 2013; Silveira *et al.* 2013) and this aspect needs further exploration for therapeutic purposes.

Study on mood disorder during childhood and adolescence needs special attention for reasons like: (i) young people with a history or with current depressive symptoms are more likely to generate social adversities in their own lives (Cole *et al.* 2006); (ii) nearly 50% of adolescent onset depression occurs spontaneously without any acute life event, but nearly 95% occur in those with a background of chronic (more than 12 months) psychosocial difficulties (Rueter *et al.* 1999; Goodyer *et al.* 2000) and (iii) first episode and recurrent depressive disorders over the lifespan show different strengths depending on prior social adversities (Kendler *et al.* 2000, 2001). An early understanding of an individual's genetic susceptibility to mood disorders may help design management strategies and manipulation of the social environment which may help alleviate the risk of the disorder.

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