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Genetic factor of Depression-concept of Ayurvedic management

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ABSTRACT

Globally, depression, one of the neurological disorders has been described as millennia linked with neurobiology associated with direct neurochemicals and biochemical incredible factors interact with "gene-gene", "gene –environment"as long as a scaffold for future for better exploration. For the depth knowledge and management of depression we can consult with traditional Indian medicine system i.e. Ayurveda. According to Ayurveda the term depression is correlated with Vishada (Depression=Vishada). In the manner of conceptual and etymological study of depression, Ayurveda has firstly described depression as Vishada means depressed mood. Ayurvedic Acharyas described depression at many places as one of the symptoms of a various diseases and etiological factor of many psychological as well as physical diseases. In this review article we have outlined the upshot of altered regulation of particular neuro-chemical markers, molecular biology, genetics with significant role of Ayurveda which has great evidence to study the mechanisms, plasticity and neuronal survival in depression and biggest impact of Indian classical therapy in the management of depression.

Key Word- Depression, Clock gene, COMT gene, DISC-1 gene, Genetics, MTHFR gene, NRG-1 gene, Polymorphism.

Introduction:

Epidemiological study suggest that frequency of depression is 350 million people / year in Indian population and on average about 1 in 20 individual is reported by World Mental Health survey. The lifetime prevalence was estimated to be approximately 17% in the United States, with similar rates being reported on the European countryl[1,2]. Depression is an extensive neurological life -threatening disorder, has been linked to abnormal circadian rhythm or clock that affects individual in all communities. Depression frequently reduces the activity of person and causes disability with mood off, loss of interest or pleasure, decreased energy level, low self-worth, disturbed sleep, reduce appetite and poor concentration with symptoms of anxiety and depression. Approximately 15% of depression cases commit to suicide [3,4].

It is widely accepted that a neurochemical imbalance underlies in the path way involved with mood disorders. Neuro chemical imbalances like synthesis & secretion of nor-epinephrine and serotonin, are thought to underlie depression. Since a whole spectrum of behavior is disrupted during depressive episodes, it is unlikely that dysregulation of a single neuro chemicall substrate, that can account for the depressive disorder.

Networking exist between different anatomical and neurochemical substrates in the onset of depression and recovery from depression, is well defined as a psychiatric disorder characterized by an inability to concentrate, insomnia, loss of appetite,feelings of extreme sadness, guilt, helplessness and hopelessness, thoughts of death and is also known as "clinical depression". However, recent studies demonstrate genetic alterations which are responsible for depression and recovery could occur by induction of appropriate plasticity and genetic remodeling through acting as antidepressant.

In Ayurveda the commentators like *Chakrapanidatta*, *Dallhana* has elaborated the term depression as"Vishada" (fear and weakness) is derived from the Sanskrit root which signifies stupor, inactiveness, dejection, depression and despondency, mentioned in the Monniere William"s dictionary.According to Mahabharata and Maitreya Upanishada the meaning of Vishada is dejection, depression, despondency and is a persistent feeling of sadness and inappropriate guilt which are the cardinal signs of depression.

GENETIC OF DEPRESSION

In 1986, Wender et al reported the "adoption studies" having some important evidents of genetic impact over depression but some have accepted with limited success[5]. **A**lthough some other studies are based on heritability of depression that varies from 40-50% showing with higher involvement of genes[6,7].A large number of environmental and genestic factors are involved in the severity of depressive disorder including early birth, prenatal infections, chromosomal abnormalities and mutations[8].The genetic heterogeneity and variable gene penetrance are responsible for phenotypic expression in hereditary syndromes. Marazita reported that Mendalian principle is unfit to mode of inheritance of depression[9]. Molecular mechanism have shown the relationship between genetics and depression[10].

The interaction between "gene – gene" and "gene – environment" are influenced by the severity of depression[11,12].It is commonly combined with other psychiatric disorders and act as a "risk factor" for many other neurodegenerative disorder including obesity, cardiovascular disorders etc [13,14]. However, there are various hypotheses of depression but there are only two major hypotheses described in the etiological status of depression. First, monoamine deficiency hypothesis as monoamine is a key component of the neurological system and is involve in the biosynthesis of neurotransmitters which is regulated by several gene whereas their deficiency leads to depression [15,16,17]. Another important hypothesis is stress hypothesis in which hypothalamic-pituitary-adrenal(HPA) axis alters the pathological response towards the depression [18,19]. Multiple genes act randomly on neural cell and impaired their functional activity, lead to psychiatric symptoms but no any specific symptoms appear with modulation of gene expression in the development of depression. However, the genetic factors alters the activity of neurochemical parameter and in impairs the cellular plasticity and elasticity of depression[20]. The symptoms appear into a single phenotype either with trait scores such as neuroticism or by using categorical diagnoses involved in the depression and anxiety[21].

Recent studies have described, there are 169 genes which are responsible for depression while only four genes are directly associated with the impairment of activity of neurotransmitter such as Clock gene, COMT gene, DISC-1 and NRG-1 gene. However, monoaminergic, polyaminergic and folic acid metabolism regulatory gene showing polymorphism in the depression have also significant association with depressive disorders. The most of genetic studies on depression have been focused on "Gene polymorphisms" in which genomic sequences are modified through single mutation , resulting change in the expression and functional activity of translational product[22].

1.1Candidate Genes and Gene-Environment interactions involved in the regulation of monoamines:-

1.1.1Clock genes:

Biological clock regulate and control the physiological processes such as sleep timing, feeding, behavior, lipid and carbohydrate metabolism, blood pressure[23].Therfore, circadian rhythmicity has significance for intracellular molecular mechanisms through clock genes. It has a property of feedback mechanism (regulation of own expressional pattern) and show two type of feedback mechanisms – negative and positive. During negative feedback mechanism different clock gene [per and cry gene] inactivate the transcriptional process while positive feedback mechanism complete the process in the presence of histone acetyltransferases (HATs). It is able to "open-up" of chromatin for promoting the transcription of Bmal and clock gene involve in the circadian clock system. However, the inactive stage of HATs is "close'to the chromatin,unable to transcript [24]. Clock gene also controls the phosphorylation, stability, localization of clock proteins and regulation of the oscillation. In mammals, Clock and Bmal1 are heterodimers, encode transcription factors CLOCK and BMAL1 (brain and muscle ARNT-like protein are also known s ARNTL or MOP3 [23,25] involved in activation of transcription of three Period genes (PER1, 2 and 3) and two Cryptochrome genes (CRY1 and 2),[25] Rorand Rev-Erb26 . Clock proteins is phosphorylated by casein kinase I epsilon (CKIε) and delta (CKIδ)27. Ubiquitin ligase complexes like FBXL3 and β-TRCP1 degrade the clock gene [28 ,29].Translational products and enzymes act together in controlling of clock functioning and abnormalities causing the synchronization of emotional, physiological ,behavioral processes[30] including chromatin remodeling process, important for " phase shifting effects" of light

on circadian rhythms. Besides these, clock gene also controls the biosynthesis of melatonin, plays an important role in circadian sleep. It is synthesized primarily in the pineal gland and regulated by the environmental light／dark cycle via the suprachiasmatic nucleus.

1.1.2 COMT gene (catechol-O-methyl transferase):

Catechol-O-methyl transferase (COMT) gene lies on chromosome 22q1132 was identified in 1950s, which is involved in catabolism of monoamines that are influenced by psychotropic medications, including neuroleptics and antidepressant agents. COMT-1 gene exhibit two isoforms; one soluble cytoplasmic (S-COMT) and another one membrane bound form (MB-COMT)[31,33,34]. It is also showing a common G>A polymorphism, a valine methionine (Val/Met) substitution at 108 and 158 codon of S-COMT and MB-COMT, respectively. The polymorphism are modified 3- to 4-fold times through enzymatic activity and these variation are directly associated with depression[35]**.** The translational product of COMT gene is largely expressed in the hippocampal part of brain and the prefrontal cortex [36]**.** Guldberg & Marsden, has reported expressional pattern of COMT because their level is high in embryonic development but gradually decline with decreasing age linked to depression [37-40].

1.1.3 Disrupted-In-Schizophrenia 1 (DISC1)

DISC1 gene is located at chromosome 1q42.1 with multiple isoforms but no one is identical to other isoforms. It consist 854 amino acids but exhibit non-enzymatic activity[41]**.** DISC1 is highly expressed during the embryonic and adult neurogenesis specifically in the embryonic ventricular, sub ventricular and hippocampus area of the brain with neural progenitor cells[42,43].DISC1gene have breakpoints of a balanced [(1: 11)(q42.1;q14.3)] chromosomal translocation so, it generate the risk of severe mental illnesses and depression[44]**.** Genetic variants are also associated with neurocognitive dysfunction, influences the activity of hippocampus with level of grey matter in the brain [45]**.** Therefore, DISC genes is responsible in causing susceptibility to psychiatric illness.

1.1.4 Neuregulin 1 (NRG1)

Neuregulin 1 is the member of the neuregulin family encode proteins of epidermal growth factor (EGF)-like domain, activate ErbB receptor tyrosine kinases. It regulates the developmental processes, plasticity, and oncogenesis. It is known to be important in many organs, including heart, breast, and nervous system. NRG1 has different functional activity in the nervous system [46]. A psychiatric relevance of NRG1 has emerged with the increasing evidence is susceptible gene for schizophrenia.

1.2 The action of Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism associated with depression:-

1.5 **MTHFR-**Numerous studies have showing the associations between MTHFR gene polymorphisms and major psychiatric disorders including schizophrenia (SZ), bipolar disorder (BPD) and unipolar depressive disorder (UDD) etc[47]. MTHFR is a crucial enzyme involved with folate-mediated pathway which is one-carbon metabolism and essential requirement for the biosynthesis of purine and thymidylate [48]. The methylation of both DNA and amino acids involved in the formation of neurotransmitters and regulation of brain function and neurodevelopment [49, 50].

MTHFR located on chromosome 1p36.3, with two common polymorphisms: (1) a CT transition at nucleotide 677 and (2) an AC transition at nucleotide 1298. C677T located at exon 4 and results in a transition from an alanine into a valine amino acid (Ala222Val) in the catalytic domain, with each copy of the 677T allele causing a 35% reduction of enzyme activity. A1298C is located in exon 7 and changes the glutamate into an alanine amino acid (Glu429Ala). This results in enhanced the binding of enzyme inhibition, with each copy of the 1298C allele decreasing the enzyme activity[51-53].. Some recent reports are showing the ethnicity and sex may influence the relationship between MTHFR variants and psychiatric disorders [54-55]**.**

MTHFR gene polymorphisms reduces the enzymatic activity including decrease the level of L-methylfolate and then decline accessibility of methyl groups which elevated homocysteine levels (i.e.,

hyperhomocysteinemia). In recent study, the low production of L-methylfolate gives rise to a lack of monoamine while low availability of methyl group have epigenetic effects on the expression of many genes[56-57]with reduced methylation associated with aberrant building of cell membranes and has damaging effects on myelin structure, which lead to impaired neurotransmission[58].Hypercysteinemia modulate the activity of N-methyl-D-aspartate receptors (NMDAR), that have properties in the long-term potentiality means learning and memory. The action of homocysteine on NMDAR may impair learning and memory and can even be excitotoxic, find in cell death [59].

Because L-methylfolate is essential for the production of biopterin, a cofactor required by tyrosine and tryptophan hydroxylases for the synthesis of monoaminergic neurotransmitters, such as dopamine and norepinephrine. It also converts the amino acid homocysteine (Hcy) into methionine by reducing homocysteine levels and leading to the production of s-adenosylmethionine (SAMe), the major methyl (CH3) donor in the brain and also provides methyl to the DNA and histone methyltransferase enzymes that mediate the epigenetic in the controling of gene expression [57,59].Thus, modified levels of homocysteine is required in the assembly of SAMe allows for normal nerve conductance, plasma membrane formation, and the synaptic transmission that underlies long-term potentiation.

1.3 **Mechanism of gene in depression:**

Yet, no one studies have cleared the exact action of gene in the impairment of brain function which lead to mental illness. However, recent report have examined several molecular cascade mechanism which causes the disturbances associated with mental diseases such as schizophrenia, bipolar disease and mild to major depression. All neurodisorders are associated with neural circuit formation and neuro developmental factors play a key role in the pathogenesis of mental diseases [60].

1.4 Association of Chromosomal abnormalities:

Chromosomal abnormalities are directly linked to mental illness, and help in the characterization of phenotypes, identification of candidate genes and linkage areas of gene [61].Due to the lack of clear mode inheritance of neruoillness associated with other common disorders to be complex with Mendelian and non-Mendelian principles. According to the hypothesis "additive or interactive" are showing the effects of numerous genes, with quantitative trait model, observed the phenotype with small functional effect so, this complexity is showing the linkage in the difficult to interpret. However, it is involved in the completion of statistics with strong linkage by using nonparametric "model free" approaches[61].

Chromosomal aberrations have been reported in many of the linkage **hot spots** that are candidate susceptibility loci. The powerful cytogenetic techniques have great ability to find out the etiology of psychiatric illness through banding of chromosome that can quickly trace the location of the gross morphological areas which disrupted by chromosomal aberrations and rearrangement such as 1q42 ,5q22–3,7q21,9q34,10p12 ,13q32 ,15q13 ,15q24 ,18p11,18q21–22 and 22q11–13 associated with depression. Some chromosomal rearrangements are documented in table-1,which is directly linked to depression mental illness and hence, the candidate genes may be identified[62].Microsatellite markers or single nucleotide polymorphisms (SNPs) can be used to map chromosome areas linked with disequilibrium with the causative gene and thereby identify the risk of haplotypes including those for psychiatric illness [63].The haplotype have been identified, the candidate genes in the distinct area, can be screened for mutations and the function of the disease gene involved in the depression can be identified[64].

1.5 Antidepressant:

Antidepressants drugs are capable to treat depression including other anxiety, neurotic compelling disorder, abnormality in eating, chronic- neuropathic pain, dysmenorrhea, snoring, migraines, attention deficit hyperactivity disorder (ADHD) sleep disorder etc [65]. Numerous antidepressants are discovered on the basis of their biological activity such as the selective serotonin reuptake inhibitors (SSRIs) serotonin–norepinephrine

reuptake inhibitors (SNRIs) including buprenorphine ,tryptophan, low-dose antipsychotics and other like norepinephrine reuptake inhibitors (NRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs) ,norepinephrine-dopamine releasing agents (NDRAs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs),and monoamine oxidase inhibitors (MAOIs) [65-68] documented in Table-2 as per their availability.

medicine .

1.5.1 Mechanisms of antidepressant action :

Globally, a large number of antidepressant are being used in the management of depression which acts through specific pathway to treat neuropsychiatric disorder and enhance the synthesis of various neurotransamine. Bioavailability of monoamines in brain is essential to make proper balance of neurotransamine.

A] "Neurogenic Adaptations hypothesis" – This hypothesis based on the molecular and cellular mechanisms, during the action of antidepressants decline the effect of depression through modulating the expression of genes involved in the regulation of neurogenesis and it may be increased in the hippocampus, depends how long the antidepressant agent are used [69-70].Because antidepressants have different response due to genetic variability of individual and heterogeneitic etiological effect. The consequent interaction between "gene- gene and "gene-environment" involved in the implication of different etiological pathways in response of

antidepressant treatment for depression. Thus, "Gene-environment" interaction are play major role in the management of depressiont[71-73].

B] "Hypothalamic-Pituitary-Adrenal Axis"- Antidepressant are also able to regulate hypothalamicpituitary-adrenal axis (HPA axis) similar to mechanism showed in neuroendocrine function like production of control, suppressing the effect of stress and consequently preventing negative feedback mechanism and result repressed the expression of depression [74].

C] "Monoamine hypothesis"- This hypothesis is based on action of Mono Amine Oxidase Inhibitor, its present increase the availability of different essential monoamine neurotransmitters such as dopamine(DA), 5-hydroxytryptamine (5-HT) and nor epinephrine (NE). During the mechanism MAOI blocks the action of monoamine oxidase which prevent the catabolism of monoamine. Conventionally, MAOIs are non selective and irreversible example of tranylcypromine whereas two most important mammalian MAOI are their isforms reported such as MAO-A and MAO-B both selective as well as reversible [75].

1.5.2 Side effect of antidepressant:

For the management of depression a group of various antidepressant drug are used but they are frequently releasing redundant compound which arise a range of unfavorable condition or side effects including blurred vision, sleep disruption , sexual dysfunction, weight gain ,anxiety, headache, constipation, nausea, and sedation. Zhang et al (2005) reported that constant utilization of antidepressant illustrated unwanted changes due to synthesis of 3, 5-cyclic adenosine monophosphate (cAMP) from adenosine 5-triphosphate (ATP) by adenylyl cyclase [76]. Therefore, chronic use of different types of antidepressant including serotonin and norepinephrine uptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, lithium and electroconvulsions increases the level of the 3, 5-cyclic adenosine monophosphate (cAMP) and this system induced adverse condition. Single-nucleotide polymorphisms (SNPs) in several genes are associated with adverse effects with the use of SSRI antidepressant like citalopram or antidepressants in combinations of other. These included FK506-binding protein-5 (FKBP5), glutamate receptor ionotropic kainate-1 (GRIK1) and 4 (GRIK4), n-methyld- aspartate receptor-2A (GRIN2A), 5-hydroxytryptamine receptor-2A (HTR2A),potassium channel subfamily-K member-2 (KCNK2) (six SNPs), and the serotonin transporter (SLC6A4) variants[77].

Therefore, that reason is enough for exploration of the knowledge of herbal formulations and their beneficial effect on the recovery of depressive disorder. Ayurveda science is depends upon herbal based product which have been claimed to have property of antidepressant which able to renovate the depression such product

are Asparagus racemosus, Nordostachys jatamansi, Gotu kola and Tinospora cordifolia etc. Because herbal medicine has a long, and respected history in the treatment of depression.

Conclusion:

We conclude that depression is monoaminergic dysfunction by the lack of a uniform level of neurotransmitter but the pathogenetic mechanisms still not more understand at the neuronal and molecular level. Genetic studies of depression and related disorders reflects the involvement of various genes and their protein. They interact to different neuromolecules of brain to implicate the neurocircuitries which affected circadian rhyme or clock of both animal and human. The interaction between "gene-gene" and "gene-environment" have either directly or indirectly influence the level of different neurotransmitter. Therefore, herbal based antidepressant drugs are beneficial in the management of depressive disorder because it has no any side effect like modern medicine and completely safe in use.

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S.No	Classification of Antidepressant	Name of drug/medicine
	Selective serotonin reuptake inhibitors (SSRIs)	Citalopram (Celexa),Escitalopram (Lexapro, Cipralex), Paroxetine ,(Paxil, Seroxat),Fluoxetine (Prozac),Fluvoxamine (Luvox),Sertraline etc
	Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Desvenlafaxine (Pristiq),Duloxetine (Cymbalta), Milnacipran (Ixel, Savella),Venlafaxine etc
	Serotonin antagonist and reuptake inhibitors (SARIs)	Etoperidone (Axiomin, Etonin),Lubazodone ,Nefazodone (Serzone, Nefadar),Trazodone (Desyrel) etc
	Norepinephrine reuptake inhibitors (NRIs)	Atomoxetine (Strattera),Reboxetine (Edronax), Viloxazine (Vivalan) etc
	Norepinephrine-dopamine reuptake inhibitors (NDRIs)	Bupropion (Wellbutrin, Zyban),Dexmethylphenidate (Focalin),Methylphenidate (Ritalin, Concerta) etc

Site	Abnormality	Diagnosis	Reference
11q23.1	Reciprocal translocation t(9;11)(p24;q23.1)	Bipolar disorder, unipolar depression	Baysal 1998
2q11.2	Insertion, insertion of 2q11.2–q21.1 into 8p21.3 leading to a partial trisomy of 2q	Schizoaffective disorder, psychotic illness and learning disability	Glass 1998I
1q42	Reciprocal translocation, t(1;11)(q42;q14.3)	Schizophrenia, bipolar disorder and recurrent major depression	Blackwood 2001
13q13	Reciprocal translocation,t(13;14)	Depression	Nielsen 1973
18p11	Ring chromosome (18)(p11q23)	Manic-depressive psychosis and learning disability	Christensen 1970
21	Trisomy	Depression	Collacott 1992;

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Table 1.Rearrangements and anomalies of chromosome associate with psychiatric disorder such as depression.

	Norepinephrine-dopamine releasing agents (NDRAs)	Amphetamine (Adderall),Dextroamphetamine (Dexedrine),Dextromethamphetamine (Desoxyn),Lisdexamfetamine (Vyvanse) etc
	Tricyclic antidepressants (TCAs)	Amitriptyline (Elavil, Endep),Butriptyline (Evadene),Clomipramine (Anafranil),Desipramine (Norpramin, Pertofrane),Dosulepin [Dothiepin] (Prothiaden),Doxepin (Adapin, Sinequan),Imipramine (Tofranil),Iprindole (Prondol),Lofepramine (Feprapax, Gamanil, Lomont),Melitracen (Melixeran),Nortriptyline (Pamelor),Opipramol (Insidon),Protriptyline (Vivactil),Trimipramine (Surmontil) etc
	Tetracyclic antidepressants (TeCAs)	Amoxapine (Asendin),Maprotiline (Ludiomil),Mianserin (Bolvidon, Norval, Tolvon),Mirtazapine (Remeron) etc
	Monoamine oxidase inhibitors (MAOIs)	Isocarboxazid (Marplan),Moclobemide (Aurorix, Manerix),Phenelzine (Nardil),Pirlindole (Pirazidol),Selegiline [L-Deprenyl] (Eldepryl, Zelapar, Emsam),Tranylcypromine (Parnate) etc

Table-2 showing the globally classified antidepressant and their respective market available medicine.