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Review Article

Tryptophan hydroxylase gene polymorphism and 5HT transporter gene promoter region polymorphism in anxiety and depressive disorder- comprehensive literature review

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ABSTRACT

Anxiety and depressive disorders are multifactorial conditions influenced by genetic and environmental factors. Research has highlighted the role of genetic polymorphisms, particularly in the tryptophan hydroxylase (TPH) and serotonin transporter or 5-HTT (5-hydroxy tryptamine transporter), which regulate serotonin, a key neurotransmitter in mood regulation. Polymorphisms in TPH1 and TPH2, enzymes involved in serotonin biosynthesis, have been linked to depression and anxiety, though findings are inconsistent. While certain TPH1 polymorphisms, like T27224C, may offer protection, TPH2 variants, such as rs1386494, have been associated with major depression in specific populations. The 5-HTTLPR (serotonin-transporter-linked promoter region shows varying associations with anxiety and depressive disorders. The short (S) allele of 5-is associated with reduced serotonin uptake, higher neuroticism, and increased risk for anxiety and depression, particularly when combined with stressful life events. However, gene-environment interactions and population differences complicate these associations, as treatment responses vary across different genotypes. Despite the inconclusive results, these studies underscore the importance of serotonergic genes in mood disorders, emphasizing the need for further research into genetic, environmental, and psychological interactions to improve understanding and treatment of anxiety and depressive disorders.

Keyword: 5-HTTLPR (serotonin-transporter-linked promoter region), Tryptophan hydroxylase (TPH), Anxiety and depressive disorders

INTRODUCTION

Genetic research in psychiatry focuses on the impact of genetic polymorphisms, which can alter molecular functions and influence behaviour. Mutation and polymorphism are the main sources of genetic variation, with the latter maintaining the presence of two or more alleles of a gene in a population exposed to a similar environment. The maintenance of genetic polymorphisms plays a central role in the study of psychiatric disorders, as these polymorphisms may influence susceptibility to mental illness.[1]

ANXIETY AND DEPRESSIVE DISORDERS

Anxiety and depression are the most prevalent psychiatric disorders, and they frequently co-occur. The first multivariate genetic analysis of anxiety and depression was carried out by Kendler et al in 1987 in 3798 twins from Australia. The study revealed that symptoms of anxiety and depression were moderately influenced by genetic factors and that environmental factors appeared to be either anxiogenic or depressogenic. Kendler later reported that major depression and generalized anxiety disorder (GAD)were the result of same genetic factors

and that environmental factors to pure GAD may be relatively distinct.[2] Anxiety and depressive symptoms often co-occur together and the scientific community is veering to the view that these are interconnected illnesses.[3,4]

SEROTONIN IN ANXIETY AND DEPRESSION

Serotonin also known as 5-hydroxy tryptamine (5-HT) is a neurotransmitter that is distributed widely through the central nervous system. The role of the receptors in the causation of mental disorder gained prominence over past 2 decades. Until the nineties, the psycho-pharmacological management consisted of administering GABAergic drugs (e.g. Benzodiazepines) for anxiety disorders and mono-amine reuptake inhibitor drugs (e.g., Tricyclic Antidepressant drugs) for depressive disorders. A significant departure from convention happened when anti-depressant drugs were found to be effective in anxiety disorders like panic disorder, obsessive compulsive disorder, phobic anxiety disorder and post-traumatic stress disorder. It was found that depletion of serotonin levels may precipitate depression. Further, low concentrations of 5HIAA, a metabolite of serotonin, were found in the cerebrospinal fluid of people with suicidal impulses.[5]

TRYPTOPHAN HYDROXYLASE GENE POLYMORPHISMS IN ANXIETY AND DEPRESSION

The gene of tryptophan hydroxylase, the rate limiting enzyme in the synthesis of serotonin, is widely recognized as a major candidate gene in many psychiatric disorders. Tryptophan hydroxylase (TPH) catalyses monooxygenation of tryptophan to 5- hydroxy tryptophan which gets decarboxylated to form 5 hydroxy tryptamines also called as serotonin. By means of somatic cell hybridization. TPH gene was located on to the short arm of chromosome 11. Recently a new isoform of the enzyme (TPH2) has been identified. TPH2 is predominantly expressed in the brain stem where the serotonergic raphe nuclei are located. Studies implicate TPH2 as a possible factor in the etiology of anxiety and depression.6

TRYPTOPHAN HYDROXYLASE 2 (TPH2) GENE POLYMORPHISMS IN ANXIETY AND DEPRESSION

Walthers et al 2003 found that genetically TPH deficient mice expressed normal amounts of 5HT in their brains which lead them to the discovery of an isoform of TPH. They identified the new isoform as TPH2 or neuronal TPH.7 The original TPH came to be called as TPH1. Zill et al 2004 demonstrated that except in brain stem TPH1 and TPH2 are nearly equally distributed in several brain regions but TPH1 is exclusively expressed in peripheral tissues. Both the genes are highly homologous proteins with 75% of amino acid identity. All-important structural and functional sequences of TPH1 are conserved in TPH2. TPH2 is located on chromosome 12Q15, comprises of 11 exons, and covers a region of 93.5 kilo bases. Zill et al 2004 investigated 300 unrelated Caucasian patients of major depression (114 males and 186 females) and 265 ethnically matched healthy controls[6]. Song et al studied 138 Chinese patients with generalised anxiety disorder and 90 healthy controls for 5HTTLPR and TPH2 gene A218C polymorphism and found association with TPH2 gene.

They however found that the SS genotype of 5HTTLPR was significantly associated with generalised anxiety disorder.[8] Mossner et al studied 134 unrelated patients of panic disorder, female 85 male 49, and same number of unrelated healthy controls. All were of German descent. Mean age of patients was 45.7 while that of controls was 45.2 years. They selected rs 4570625 and rs4565946 SNPS for study. They did not find any associations and concluded that factors other than rate of synthesis perhaps had greater importance in pathogenesis.[9] Lin et al studied 117 Han Chinese post-partum women with depression and 83 healthy controls.

They found that 2775A allele was present only in post-partum women with major depression and anxiety disorder. Illi Ari et al 2009 studied many SNPS related to 5HT receptors as well as TPH1 rs 1800532 and rs 1386494 0f TPH2 in 86 patients of major depression and 345 controls. They found that none of the SNPS were associated with major depression.[10] Hermann et al 2007 related early post negativity (EPN) ERPs after exposure to high and low arousing pictures to 47 healthy adults and genotyped them for 5HTTLPR and TPH2 polymorphisms. They found highest neural activity to emotional stimuli in individuals carrying S variant of 5HTTLPR and T variant of TPH2.[11,12] Gizatullin et al 2008 studied 194 patients of stress induced major depression and 246 healthy controls of of North European descent and analysed 5 TPH2 polymorphisms for genotype, allele and haplotype association. They found no association on any parameter with depression and concluded that TPH1 may be more relevant for major depression.[13] Canli et al assessed personality of 29 healthy adults by NEO-P self-report questionnaire and profile of mood states (POMS) and genotyped them for G703T polymorphism.

They allowed the patients to scan 18 second blocks of neutral, happy, and fearful facies under fMRI scan. They observed the genotype GT and TT showed greater amygdale activation for positive as well as negative emotions.[14] Mushtaq et al studied 60 patients of anxiety and 60 patients of depressive disorders and 40 healthy controls of North India and analysed TPH2 polymorphism for genotype association and found no association with MDD and anxiety disorder in Indian population.[15] Mushtaq et al studied 60 patients of anxiety, 60 patients of depressive disorders and 40 healthy controls of North India and analysed TPH1 A779C. A

gene polymorphism and found association with major depressive disorder (MDD) in North Indian) population.[16] Tao et al studied One hundred and eighty five MDD patients of China and found TPH-2 gene variant rs4290270 could potentially serve as a reliable biomarker to identify MDD patients with early wakening symptom.[17]

5HT TRANSPORTER POLYMORPHISMS IN ANXIETY AND DERESSION

The human 5HTT gene (SLC6A4) has been cloned and mapped on to chromosome 17q11.1-q12. A polymorphism has been identified in the promoter region of SLC6A4, called as 5HT transporter linked promoter region(5HTTLPR) polymorphism which consists of different lengths of repetitive sequences, containing GC-rich 20-23 base pairs long repeat elements. A deletion/insertion in the promoter region creates a short (S) allele and a long (L) allele (14 and 16 repeat alleles), which alters the promoter activity.[1]

The S variant has been reported to be associated with lower basal and transcription efficiency of the SLC6A4, resulting in lower serotonin uptake activity, when compared with L-variant 1) This 5HTTLPR polymorphism has been studied in various psychiatric disorders with positive and negative reports of association.[7] Individuals carrying 1 or 2 copies of the S allele noted to exhibit elevated neuroticism, a personality trait involved in the propensity to depression.[10] It was also reported that S carriers exhibit elevated amygdala reactivity to threatening stimuli.[6] Most of the psychotropic drugs effective against a broad range of psychotic, mood, anxiety and impulse control disorders act directly or indirectly act through serotonergic mechanisms.[8]

In 2003, it was reported that S carriers exhibited elevated depressive symptoms, depressive disorders and suicidality after experiencing stressful life events and childhood maltreatment. With the reports of Hariri et al, and Caspi et al 5HTTLPR has become the most investigated gene variant in psychiatry. The study of Gene-By-Environment (G-E) has since gained momentum.[18,19]

The S allele has been postulated to manifest with higher depression score, when life events are more severe Killpatrick et al found that the S-genotype was associated with increased risk of post-traumatic stress disorder but only under high environmental stress e.g. Hurricane.[20-22] Mushtaq et al et al in a study of 57 subjects having major depression, found that the L-type homozygotes responded much better to antidepressant treatment. Levinson 2006 estimated that 55% of genetic risk of major depression was shared by neuroticism.[23] In a metanalysis of 23 studies Srijan Sen et al found a significant association between 5HTTLPR and neuroticism as measured by NEO-P. some association was also found for harm avoidance. Zalsman et al 2006 studied 5HTTLPR and stressful life events. They found that SS genotype predicted greater depression severity particularly in association with moderate and severe life events.[24] Tibrewal et al studied 93 OCD patients and 92 healthy controls from South India. They found S allele frequency was 60% which was higher than white Europeans.

However, they found no association with 5HTTLPR and OCD.[25] Margoob et al reviewed the link between 5HTTLPR and psychiatric disorders.[26] Mushtaq et alstud ied 30 patients of anxiety and 30 patients of depressive disorders and 40 healthy controls of North India and analyzed 5HTT polymorphism for genotype association and found 5HTTLPR association with anxiety and not with depression. Further it was found that SS genotype was found to be significantly high in patients with anxiety. Further comparison of anxiety scores between the 5HTTLPR genotypes revealed no statistically significant differences in the anxiety scores between SS genotype and LL/LS genotypes.[27]

Miozzo et al, in 2020 in a community study comprising 628 participants found out that S allele carrier state was associated with increased prevalence of panic disorder and there was an increased risk for comorbidity in homogenous cases of major depressive disorder.[28] Simonyte et al studied 353 participants of Lithuania aged 65 years and found that lifetime or current stressful life events and their modification by 5HTTLPR genotypes are risks factors for late life depression.[29] However Gillispie et al 2007 reported that in 1206 twins stress predicted depression but there was no interaction with 5HTTLPR.[30] Mandelli et al 2007, studied 5HTTLPR and life events of preceding one year in 685 subjects of depression and bipolar disorder and found positive interaction mainly in women.[31] Eley et al 2004 in a study of 990 subjects found that environment risk was a non-significant predictor and TPH predicted depression.

They also found gene-environment effect in women only.[32] Belsky et al 2009 were of the view that genes act plasticity factors rather than vulnerability factors rendering some individuals more susceptible to positive or negative factors.[33] There are only a few studies on 5HTTLPR and TPH interactions. Neumeister et al reported that SS genotype was associated with an increased risk of developing depression during tryptophan derivation.[33] Herman et al noted high neural activity to emotional stimuli in individuals carrying the S allele of 5HTTLPR and the T variant of TPH2.[34]

GENE ENVIRONMENT INTERACTION

Life events can occur in variety of domains. A given life event may be a turning point for one individual but not for another individual. Life events can be classified into polar categories viz. desirable-undesirable; pleasant-unpleasant; major-minor and so on.[35] Even though life change units do seem to provide a quantitative measure

of overall life change they may not reflect the actual amount of stress resulting from experiencing of specific events. Individuals perceive events differently. 5HT transporter polymorphism and its relation to neuroticism and the consequent propensity for depression, that S carriers of 5HTTLPR exhibit elevated symptoms of depression and diagnosable depression after experiencing stressful life events and that S carriers exhibit elevated amygdale reactivity, have been instrumental in making 5HTTLPR the most investigated polymorphism in psychiatry and neuroscience.[36,37] Caspi et al in a comprehensive review of observational, experimental, and animal studies evidence to elaborate on the '5HTT stress sensitivity' hypothesis and offered recommendations for gene- environmental research.[37]

CONCLUSION

It appears that the serotonin system, plays important role in the onset of several psychopathologies and depression and anxiety disorders. 5HTTLPR polymorphisms by their effect on expressiveness of the serotonin transporter and consequent effect on reuptake and availability of serotonin in synapses and tryptophan hydroxylase gene polymorphisms by their effect on the availability of the rate limiting enzyme in the pathway of serotonin synthesis seem to affect the system directly or indirectly by interacting with environmental variables which ultimately result in the onset or exacerbation of anxiety and depressive disorders.

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