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Original article

Association between the 5-methyl tetrahydrofolate reductase (*5-MTHFR*) and integrin B3 subunit (*ITGB3*) genes polymorphism and major depressive disorder

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ABSTRACT

Background and objectives: Major depression disorder (MDD) is a common condition and syndromic sickness with devastating psychological, social, and economic effects. In general, it is a widespread problem, and the prevalence of MDD varies by country. The genetic contribution to MDD is estimated to be around 35%. This study was done to explore the association between 5-methyl tetrahydrofolate reductase (*5-MTHFR*) and integrin β3 subunit (*ITGB3*) genes polymorphism for development of major depressive disorder.

Materials and methods: The current study comprised thirty MDD patients, ranging in age from 18 to 52 years. All of the individuals were diagnosed using the Diagnostic and Statistical Manual of Mental Axis I Disorder in the outpatient departments of Taif Psychiatry Health Hospital (DSM-IV). The three polymorphic markers, C667T and A1298C of the *5-MTHFR* gene and T1565C of the *ITGB3* gene, were genotyped using the PCR-RFLP method.

Results: The C667T single nucleotide polymorphism was found to be in heterozygous state in ten patients, while the A1298C single nucleotide polymorphism was not found in any of them. Twenty-one patients had the T1565C single nucleotide polymorphism in the *ITGB3* gene, five of whom were homozygous state and 16 of whom were heterozygous state. Seven patients were discovered to have compound mutations in both genes.

Interpretation & conclusion: The current findings could point to a link between MDD and the T allele of the C667T polymorphism in the *5-MTHFR* gene and the C allele of the T1565C polymorphism in the *ITGB3* gene.

1. Introduction

Major depressive disorder (MDD) is a mental disorder that affects sufferers' moods. MDD is a recurrent, syndromic disorder with devastating psychological, social, and economic implications (Asdaq and Yasmin, 2020, Asdaq et al., 2020). It's a common occurrence, affecting large number of adults during their lifetime (Salari et al., 2020). The prevalence rate of MDD is different in various parts of the world. It was 2% in China (Lu et al., 2008), 6.7% in South Korea (Cho et al., 2015), 20.5% in Chile (Markkula et al., 2017), and 21% in France (Bromet et al., 2011). Depressed people experience

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mood swings that affect their lives in a variety of ways, including how they feel, think, conduct, and interact with others. MDD is thought to have a 35% genetic contribution, with higher heritability demonstrated in family and twin studies (Otte et al., 2016).

The association between food or nutrients and mood has piqued people's interest in recent years. As previously reported, nutritional variables have a role in its origination, and progression and also it affects the outcome of the antidepressant therapies (Young, 1993). Folic acid, often known as folate, has shown the most consistent and persuasive outcomes of all the micronutrients studied (Arinami et al., 1997). The link between folate deficiency and depression is documented in the literature (Gilbody et al., 2007).

Patients with folate deficiency anemia, as well as other patient populations at high risk for folate deficiency, such as alcoholics (Abou-Saleh and Coppen, 1982) and epileptics on anticonvulsants, have a high rate of occurrence of depression (Froscher et al., 1995).

Depressed adults have a higher prevalence of folate insufficiency and low folate status than other adults (Reynolds et al., 1984; Carney et al., 1990). Some studies have suggested that a lack of folate in the diet, or folate malabsorption may be the cause of depression (Botez et al, 1984).

Mood disorders are assumed to be linked to a lack of neurotransmission, or a dysfunctional biological signal transduction (Podell, 1983). A neurotransmitter (such as serotonin, norepinephrine, or dopamine) is released into the synaptic gap when a signal entering the brain or moving from one brain cell to another arrives at a synapse. It was suggested that that depression is caused by a neurochemical imbalance of neurotransmitters such as serotonin and norepinephrine (Groff et al, 1995).

One carbon metabolism is crucial for the function of neurotransmitters through its role in methylation.

Neurotransmission is known to be affected by one-carbon metabolism (Podell, 1983). Folate, in the monoglutamate form of 5-methyl tetrahydrofolate (*5-MTHF*), passes the blood–brain barrier. The *5-MTHF* reductase (*5-MTHFR*) gene produces *5-MTHF*, which gives methionine synthetase the methyl group that it needs to methylate homocysteine to methionine (Miner et al., 1997). As a result, various potential abnormalities in one-carbon metabolism may play a role in the pathophysiology of depression.

Additionally, there is link between etiology of mood and developmental disorders including changes in serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. The integrin 3 subunit gene (*ITGB3*) has been implicated as a regulator of serotonergic systems via genetic interactions with the 5-HT transporter gene (Whyte et al., 2013).

In the present research, as depression is a hereditary disease, the proportion of depression patients with genetic mutations of a key regulatory enzymes of *5-MTHFR* and *ITGB3* genes were analyzed.

2. Materials and methods

2.1. Participants

The Taif University Ethics Committee accepted this study, which was carried out in collaboration with the Taif Psychiatry Health Hospital's outpatient department. Thirty individuals with Major Depressive Disorder (MDD) in an age group of 18 and 52 years took part in the study.

All the individuals were diagnosed using the Diagnostic and Statistical Manual of Mental Axis I Disorder (DSM-IV) in the outpatient departments of Taif Psychiatry Health Hospital.

2.2. Genotyping

Peripheral blood samples were used to obtain genomic DNA. Table 1 lists the polymorphic markers of *5-MTHFR* and *ITGB3* genes, as well as their positions, PCR primer information, and the annealing temperature utilized for PCR.

The three polymorphic markers were genotyped using the PCR-RFLP technique. For C667T and A1298C polymorphisms of the *5-MTHFR* gene, the PCR products were digested for two hours at 37 °C with 5 units of *HinfI* and *MboII* restriction enzymes, respectively. The *ITGB3* gene was cut using the *NciI* restriction enzyme in the case of T1565C. 2% ethidium bromide agarose gels were used to examine the digestion products.

3. Results

Thirty Saudi individuals with MDD were included in this study, all of them were diagnosed at the Taif Psychiatry Health Hospital. The average age was 36 ± 4 years, the average weight was 62 kg, and the average BMI was 24 ± 4. The goal was to see if there were any gene variations in two essential genes, *5-MTHFR* and *ITGB3*, that are linked to depression in some way. Table 2 shows the geno-

Table 1
Details of *5-MTHFR* and *ITGB3* polymorphic markers, their locations, PCR primer details and the annealing temperature used for PCR.

Gene symbol	SNP	Location	Primer sequence 5′-3′	Ann. Temp (°C)
5-MTHFR	C667T	Exon 4	F: GAAGGAGAAGGTGTCTGCGGGA R: AGGACGGTGCGGTGAGAGTG	58
	A1298C	Exon 7	F: CTTTGGGGAGCTGAAGGACTACTAC R: ACTTTGTGACCATTCCGGTTTG	55
ITGB3	T1565C	Exon 3	F: GAGTCGCCATAGCTCTGATTG R: ACCTCCACCTTGTGCTCTATG	55

Table 2
Details of genotyping analysis for SNPs of *5-MTHFR* and *ITGB3* genes using RFLP analysis.

SNP	PCR productSize (bp)	Restriction Enzyme	Genotypes and restriction fragment sizes (bp)
5-MTHFR			
C667T	198	*HinfI*	CC:198, CT: 198 + 171 + 27, TT: 171 + 27
A1298C	163	*MboII*	AA: 56, 31, 30, 28, 18; AC/CC: 84, 31, 30, 18
ITGB3			
T1565C	313	*NciI*	TT: 330, TC: 330 + 210 + 120, CC: 210 + 120

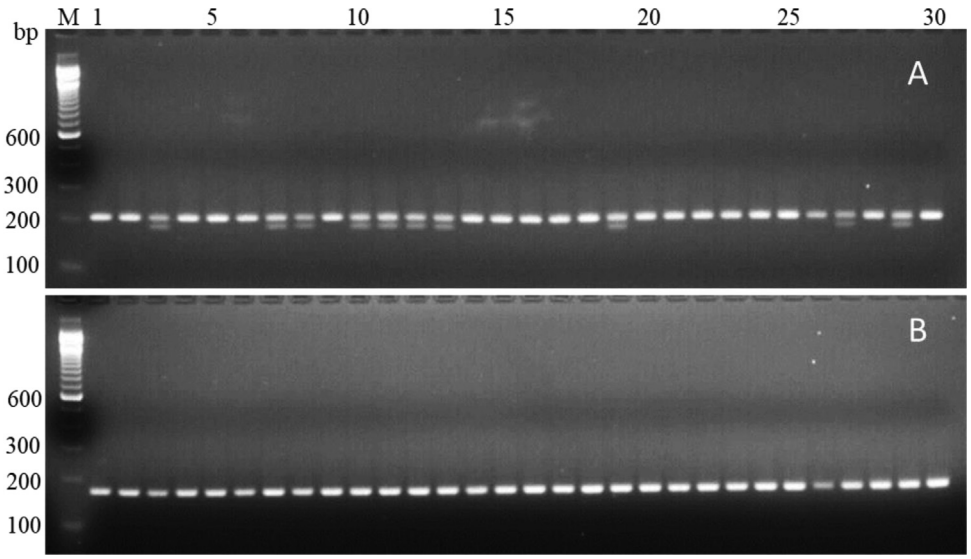

Fig. 1. RFLP analysis for the single nucleotide polymorphism of *5-MTHFR* gene (A; C667T and B: A1298C) mutations on PCR fragments cutting with *HinfI* and *MboII*, respectively (Table 2). The 27 bp fragment of C667T single nucleotide polymorphism has been run off the gel.

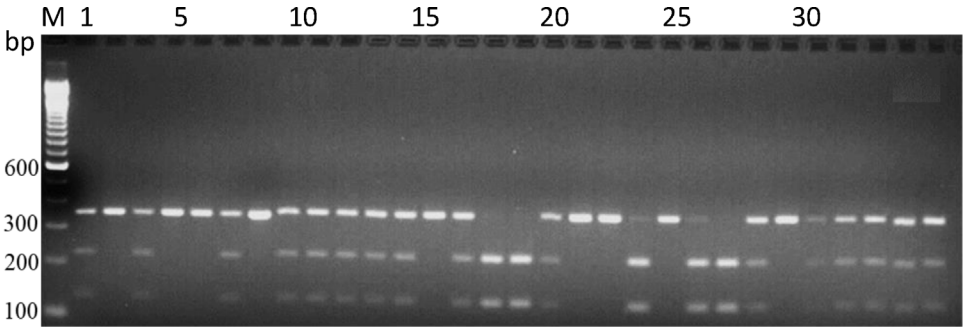

Fig. 2. RFLP analysis for the single nucleotide polymorphism of *ITGB3* gene (T1565C) mutation on PCR fragments cutting with *NciI* respectively (Table 2).

types of the two well-known polymorphisms C667T and A1298C of 5-MTHFR and T1565C of ITGB3 genes.

DNA collected from 30 patients was subjected to PCR-RFLP analysis. For the C667T and A1298C single polymorphisms in the *5-MTHFR* gene, the PCR amplified product was digested with *HinfI* and *MboII*, respectively. In a 2% agarose gel, the results are determined (Fig. 1). The C667T single nucleotide polymorphism was found to be in heterozygous state in ten patients, while the A1298C single nucleotide polymorphism was not found in any of all patients (Fig. 1A and B). Twenty-one patients had the T1565C single nucleotide polymorphism in the *ITGB3* gene, five of whom were homozygous state and 16 of whom were heterozygous state (Fig. 2).

Seven patients were discovered to have compound mutations in the *5-MTHFR* and *ITGB3* genes (Fig. 1A and Fig. 2).

4. Discussion

The most prevalent psychiatric problem for which people seek help or suffer without seeking care is mood disorders, which include sadness and mania. MDD is a recurrent, heritable syndrome condition that has both psychological and biological aspects. There are numerous lines of evidence that support depression's heredity. First-degree relatives of patients with severe depression are 1.5–3 times more likely than the general population to suffer from depression (American Psychiatric Association, 1994).

In the last three decades, researchers have been attempting to find genetic markers of depression (Oved K et al., 2013; Yusup et al., 2013). Polymorphisms on chromosomes 11, 18, and 21 (Berrettini, 1995) have been linked to depression. The significance of folate in neuropsychiatric diseases has gotten a lot of attention (Wan et al., 2018). The importance of DNA methylation and folate in mental wellness cannot be overstated. Reduced 5-MTHFR activity or a lack of folate have been linked to the beginning of psychiatric disorders such schizophrenia, bipolar disorder, depression, autism, and ADHD (Klengel et al., 2014).

There are 14 common or rare single nucleotide polymorphisms in the *5-MTHFR* gene that have been linked to enzymatic deficiency (Liew and Gupta, 2015). The most common are rs1801133 (C677T) and rs1801131 (A1298C), which may lower 5-MTHFR activity to varying degrees. The enzyme activity of heterozygous and homozygous mutant persons of C677T is 67 and 25% of that of wild-type individuals, respectively (van der Put et al., 1998).

In the present study, the genotyping analysis of *5-MTHFR* revealed 33.33% (10/30) of MDD patients who have heterozygous single nucleotide polymorphism in C667T, but no patients have the A1298C mutation. According to the findings of a Japanese study, *5-MTHFR* may be impacted in depression (Arinami et al., 1997). The odds ratio of carrying the C677T variant in depressed

patients was 2.8 when compared to healthy controls ($p < 0.005$), demonstrating an increased incidence of *5-MTHFR* mutations in major depressive disorder (Arinami et al., 1997). Additionally, The *5-MTHFR* polymorphism was shown to be more prevalent in depressed patients than in healthy controls in a cohort study of depressive patients and healthy controls (Kelly et al., 2004).

While a study of depressed patients over a 60-month period found that those with the CC genotype of *5-MTHFR* C677T were more likely to have more severe symptoms than those with the TT genotype (Bousman et al., 2013). Another study found a link between hyperhomocysteinemia and the TT *5-MTHFR* genotype and depression, but not concomitant anxiety disorder (Folate, 2003). More research has found a link between *5-MTHFR* C677T and depression risk, including postmenopausal depression (Słopien et al., 2008) and childhood trauma-related major depression disorder (Lok et al., 2013).

According to a one of the interesting study, increasing the frequency of mutant T alleles in the C677T gene increases stress risk for depression (Lok et al., 2013). Additionally, A meta-analysis that included 26 published research found a connection between the 5-MTHFR C677T polymorphism and an elevated risk of depression (Wu et al., 2013).

As a result of the interaction between genetic and environmental factors, all these studies imply that *5-MTHFR* mutations may increase the environmental risks for MDD (poor folate intake, early traumatic stress).

All of these studies point to a link between serious depression and a genetic polymorphism of the *5-MTHFR* C677T mutation.

Additionally, the role of the serotoninergic *ITGB3* gene in the genesis of depression is highlighted in the present work. Serotonin, in addition to being a neurotransmitter, is also a neurotrophic factor that plays a role in early brain development and behavioral regulation. It has been demonstrated via different neurophysiological, biochemical, and pharmacological research that serotonin dysregulation plays a significant role in a variety of neurological illnesses (Probst-Schendzielorz et al., 2015; Whyte et al., 2013). In platelets and mouse brain, a functional interaction of ITGB3 protein with the serotonin transporter was examined, revealing a lower serotonin absorption capability in *ITGB3* knockout mice's platelets and brain (Whyte et al., 2013). As a result, individuals with a high baseline *ITGB3* expression level may benefit from antidepressants, particularly serotonin reuptake inhibitors and tricyclic antidepressants (Probst-Schendzielorz et al., 2015). However, ITGB3 appears to interact with CHL1, a member of the L1 family of cell adhesion molecules, in addition to serotonin transporter. Neuronal differentiation, migration, and neurite outgrowth are all influenced by L1 and CHL1 (Huang et al., 2011). L1 was shown to be expressed at higher levels in PBMCs from bipolar disorder patients compared to healthy donors (Wakabayashi et al., 2008), while CHL1 polymorphisms were linked to a higher risk of schizophrenia (Shaltout et al., 2013) and antidepressant side effects (Clark et al., 2012).

All of these studies highlight the importance of ITGB3 and CHL1 for the neurological system, as well as their likely role in depression disorders. A direct link between ITGB3 and CHL1 has also been proposed to be involved in the control of serotonin absorption (Probst-Schendzielorz et al., 2015).

As a result, this could explain the link between the *ITGB3* gene and depressive illnesses, as well as confirm our findings about the *ITGB3* gene point mutation and depression.

5. Conclusion

The current study's findings may point to a link between MDD and the T allele of the C667T polymorphism in the 5-MTHFR gene and the C allele of the T1565C polymorphism in the ITGB3 gene. However, our findings are limited by the fact that the number of donors was insufficient. This finding can be investigated further by including other depressed patients in the study. Furthermore, the functional significance of these two mutations in major depressive disorder has yet to be determined.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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