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Research Article

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The Role Bio-Psychological Factors in Genes ESR1, COMT & SERT on Premenstrual Dysphoric Disorder

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Abstract

Premenstrual dysphoria is a mood disorder that occurs before the menstrual cycle. While the symptoms of PMDD are similar to premenstrual syndrome (PMS), it is much more severe and can lead to extreme mood swings that can interfere with daily life and functioning. Research shows that women with PMS may have changes in genes that affect how the body processes stress and sex hormones. Research into the causes and treatment of PMDD is emerging, but evidence has shown that the condition is strongly influenced by genetic sensitivity to sex hormones. While PMDD is believed to have biological causes, research has shown that environmental variables such as perceived stress can also increase the risk and severity of the condition.

Keywords: PMDD, PMS, Genetic Disorder, SERT, COMT, ESR1 Genes, Psychological Disorder

1. Introduction

Premenstrual dysphoria is a mood disorder that occurs before the menstrual cycle. While the symptoms of PMDD are similar to premenstrual syndrome (PMS), it is much more severe and can lead to extreme mood swings that can interfere with daily life and functioning. Research shows that women with PMS may have changes in genes that affect how the body processes stress and sex hormones. These differences mean that women with PMDD are more sensitive to hormones that affect both mood and general health. While PMS can affect a woman's life and performance, it is not classified as a disorder and symptoms can usually be managed by the person themselves. Premenstrual dysphoric disorder is classified as a mental disorder by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). It's worth noting that premenstrual irritability and PMS are very common, but approximately 3 to 8 percent of menstruating women experience PMDD symptoms [1].

1.1. Symptoms of Premenstrual Dysphoric Disorder

Some of the main symptoms of PMDD include:
Feeling sad
Food cravings and overeating
Irritability and anger directed at others
Lack of interest in activities
Lack of energy and fatigue
Physical symptoms, including breast tenderness, bloating, and headaches
Severe mood swings
sleep disorders
Difficulty concentrating or thinking
Symptoms begin in the luteal phase or after ovulation and end shortly after menstruation begins [2].

1.2. Etiology of Premenstrual Dysphoric Disorder

Research into the causes and treatment of PMDD is emerging, but evidence has shown that the condition is strongly influenced by genetic sensitivity to sex hormones. While PMDD is believed to have biological causes, research has shown that environmental variables such as perceived stress can also increase the risk and severity of the condition. It is estimated that this condition is about 50% hereditary. Research suggests that PMDD may be associated with changes in cellular responses involved in estrogen and progesterone metabolism [3].

1.3. Diagnosis of Premenstrual Dysphoric Disorder

Diagnosis of premenstrual syndrome usually begins with a doctor taking a health history and performing a physical examination. In most cases, you should keep a calendar to track your symptoms for at least two periods.

To be diagnosed with PMDD, people must:
Experience at least five symptoms in two domains, one related to mood and the other to physical symptoms. Experience these symptoms in the pre-menstrual phase and the symptoms should be gone by one week after the period. These symptoms must also interfere with functioning at work, school, relationships, and other important areas of life and must not be related to an existing condition or caused by substance use [3].

1.4. Treatment of Premenstrual Dysphoric Disorder

Treatment for PMDD focuses on reducing and managing the symptoms of the disease. Some treatment options include: Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are effective in treating PMDD symptoms [4].

1.5. Oral Contraceptives

Lifestyle adaptations including changes in diet, exercise and stress management techniques Medicines to treat physical symptoms, including diuretics for fluid retention and anti-inflammatory drugs for pain Changes in menstrual products, especially if these cause discomfort or irritation. Medications approved by the FDA for the treatment of PMDD include the SSRIs sertraline, fluoxetine, and paroxetine HCI. The oral contraceptives drospirenone and ethinyl estradiol are also approved for the treatment of this condition.

Cognitive behavioral therapy (CBT) may also be used alone or in combination with other therapies. Over-the-counter pain relievers may also help relieve symptoms such as joint pain, muscle cramps, headaches, muscle aches, and breast tenderness [4].

1.6. Coping with Premenstrual Dysphoric Disorder

The mood swings and physical symptoms of PMDD can make it difficult to cope with everyday life and manage your relationships. You may feel irritable, depressed, and angry, which can lead to taking out these feelings on those around you. In addition to receiving treatment from a medical professional, there are self-care steps you can take to manage your symptoms. Natural therapies such as meditation, regular exercise and yoga can be effective in managing stress. Such actions may help you cope with symptoms of anxiety and depression.

Herbal supplements such as St. John's wort may be helpful. However, you should be cautious and talk to your doctor before using herbal remedies to relieve symptoms. Some herbal supplements, such as milk thistle, can have side effects when taken with other medications [5].

Getting plenty of rest and eating a healthy diet can also help. Avoiding salty foods may help prevent bloating and water retention. Minimize the consumption of sugar and simple carbohydrates to avoid fluctuations in blood sugar levels. Focus on eating complex carbohydrates, getting plenty of fiber and protein, and drinking enough fluids. Some research has also found that acupuncture may be a promising treatment for reducing symptoms associated with PMDD, but more research is needed. Coping strategies can be helpful, but you should contact your health care provider if your symptoms do not improve with self-treatment or if your symptoms interfere with your daily functioning, including your mental well-being, relationships, or job [5].

2. Materials and Methods

In this study, blood samples were taken from 60 women suffering from PMDD, and 70 women Health, and with their written consent, molecular genetic testing was performed to assessment the changes in these genes. Individual information (such as age, gender, medical history) was recorded. The subjects were selected after final diagnosis by a child and adolescent psychiatrist according to DSM-V criteria, signed a written consent for blood sampling, and filled out an interview form designed to understand the contribution of genetic influence. 5 cc of blood was taken from each person and in Falcons containing EDTA as an anticoagulant; It was poured and then the falcons were gently shaken to mix to prevent blood clots from forming. Finally, the samples were stored in a -20 ° C freezer to extract DNA from blood. Saturated salt method was used to extract genomic DNA from whole blood samples. After DNA extraction, its concentration must be determined so that a certain concentration of DNA is subjected to the PCR reaction. In this case, the concentration of DNA used is constantly maintained. Two methods are used to determine the concentration and quality of the extracted DNA.

1- Spectrophotometric method
2- Electrophoresis method

Spectrophotometry is a quantitative method and electrophoresis is a qualitative method. Molecular Real Time-PCR technique was used for this study. This technique is commonly used to examine different alleles of a gene in a population. The sequence diversity of the respective gene alleles creates different cleavage sites for the restriction enzymes, resulting in fragments of different lengths. Depending on the length of the DNA fragments obtained from the cut, the change in nucleotides can be detected. One of the advantages of this method is that it is fast and does not require a probe.

Gene	Primer name	Primer Sequence (5' to 3')	Length (bp)	TM (°C)	Product length(bp)
ESR1	Forward	TCTCAGAATAAGAGGTGGCG	20		
	Reverse	AGATGATCATGGCAGCGTCG		64	177
			20		
				64	156
COMT		CGTCAGAATAAGAGGTGGCG	20		
SERT		GCATGATCATGGCAGCGTCG	20		
		GCTCAGAATAAGAGGTGGCG	20	64	165
		CGATGATCATGGCAGCGTCG	20		

Table 1: Specifications of Primers Used in this Study

2.1. Genotype Determination: ESR1, SERT, COMT

To determine the ESR1, SERT, COMT genes, the intron 4 regions was amplified by PCR. The characteristics of the primers are given in Table 2, the PCR reaction concentration in Table 2, and the PCR steps in Table 2. PCR products were isolated on 2% agarose gel. Alleles were identified as 177, 156, 165 bps band after staining the gel with safe stain.

2.2. Investigation of ESR1, SERT, COMT Genes by Real-Time PCR Method

After PCR reaction using the mentioned primers according to the optimal PCR conditions, a fragment with a length of 177, 156, 165 bps was amplified. To ensure the performance of the PCR reaction for all samples, their PCR products were electrophoresed on 2% agarose gel and stained with Safe stain. PCR products were then cut using Nla III enzyme according to the following steps:

First, all the materials needed for the Real-Time PCR reaction, which include double ionized distilled water, a specific buffer of Nla III enzyme, Nla III enzyme, are poured into microtubes containing the PCR product. Then place the microtubes in a pan at 37 ° C for 16 hours. The concentrations of the materials used to break down the Nla III enzyme site are shown in Table 2.

After this period, some of the product containing the enzyme was cut, loaded on agarose gel and electrophoresed. And in the last step, that photo was taken.

Nla III enzyme and its cleavage site
Nla III enzyme is a highly functional restriction enzyme and its cleavage site is as follows:
5 '... A C G C ... 3'
3 '... T G C G ... 5'

The final volume in volume 30µl	Reaction material
14/5 µl	ddH2O
4 µl	Buffer(10x)
0.7 µl	*Nla* III
12 µl	PCR Product

Table 2: Concentration of Components Used to Break Down the Nla III Enzyme Site

TCTAACTGTTCTCCGGTTACAACAAGTGGTCCCGACCCGTGGCCAACATCTCGGACGTGGTCCTCGTCCG
GATGGGCCTGTCCATCGCTCAGCTCATTGA[CGTGGTAGGTGAGGGCGTGGCCATCGTGCACTGTGACTGA
CCTCGCCCTGCAAGG]AGCACAGGGGTCTGGGTGGGCAGAGGGGACACAGCCATCAACACTCCCCGTGGCT
CAGTGTGTCCGGCCCGGGCTGGTACGTCAGAACGACAGCCACCAGCTCTGCCCCGCCTGAGCCCCAGCCA

Figure : The primers bindings site in the ESR1, SERT, COMT genes and the Nla III enzyme identification and cleavage site: Arrow indicates the primer forward binding site; Has been).

3. Results

Real-Time PCR technique was used to investigate these genes. The results of electrophoresis of PCR products related to amplification of this genes using appropriate specific primers and fragments of amplification of these genes are shown in Figure 3. PCR fragments contain fragments of length 177, 156, 164 bps and fragments from Real-Time-PCR with the effect of Nla III restriction enzyme in the presence of G allele at the enzyme identification site located at the site of the relevant this genes; It is cut into two pieces with lengths of 120 and 170 bps and in the presence of A allele it is cut into one piece 210 bps and in the presence of GC allele it is cut into three pieces with lengths of 210, 120 and 170 bps.

In this study, the association of ESR1, SERT, COMT genes with Real-Time PCR technique was investigated. In this regard, 60 women with PMDD and 70 healthy women without a history of PMDD as a control group in the northwestern region of Iran were studied.

Based on statistical calculations and genotypic distribution between patients and controls, no correlation was found because the calculated P-value for different genotypes is greater than 0.05, which means that the hypothesis of the association of these genes with PMDD is rejected (0.5 = P-value). The genotypic frequency distribution of ESR1, SERT, COMT genes was calculated in the whole patient and control groups.

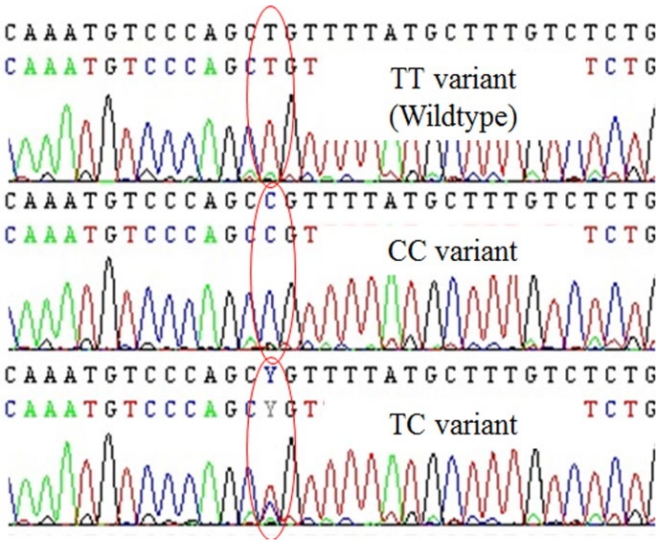

Figure 1: Schematic of the example of nucleotide mutation in ESR1 gene in women with PMDD.

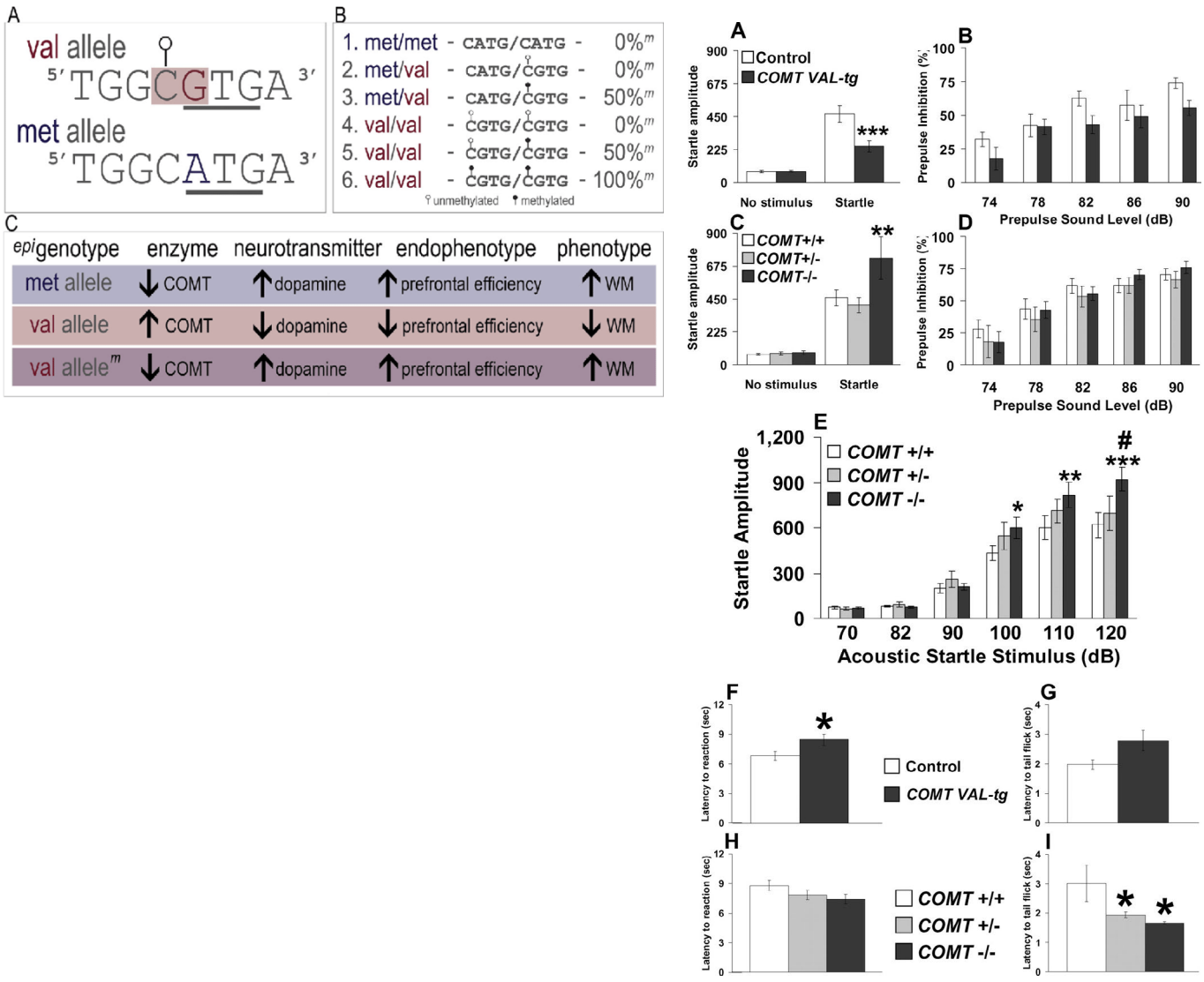

Figure 2: Schematic of the sample of nucleotide mutation in COMT gene along with the bonding pattern in women with PMDD.

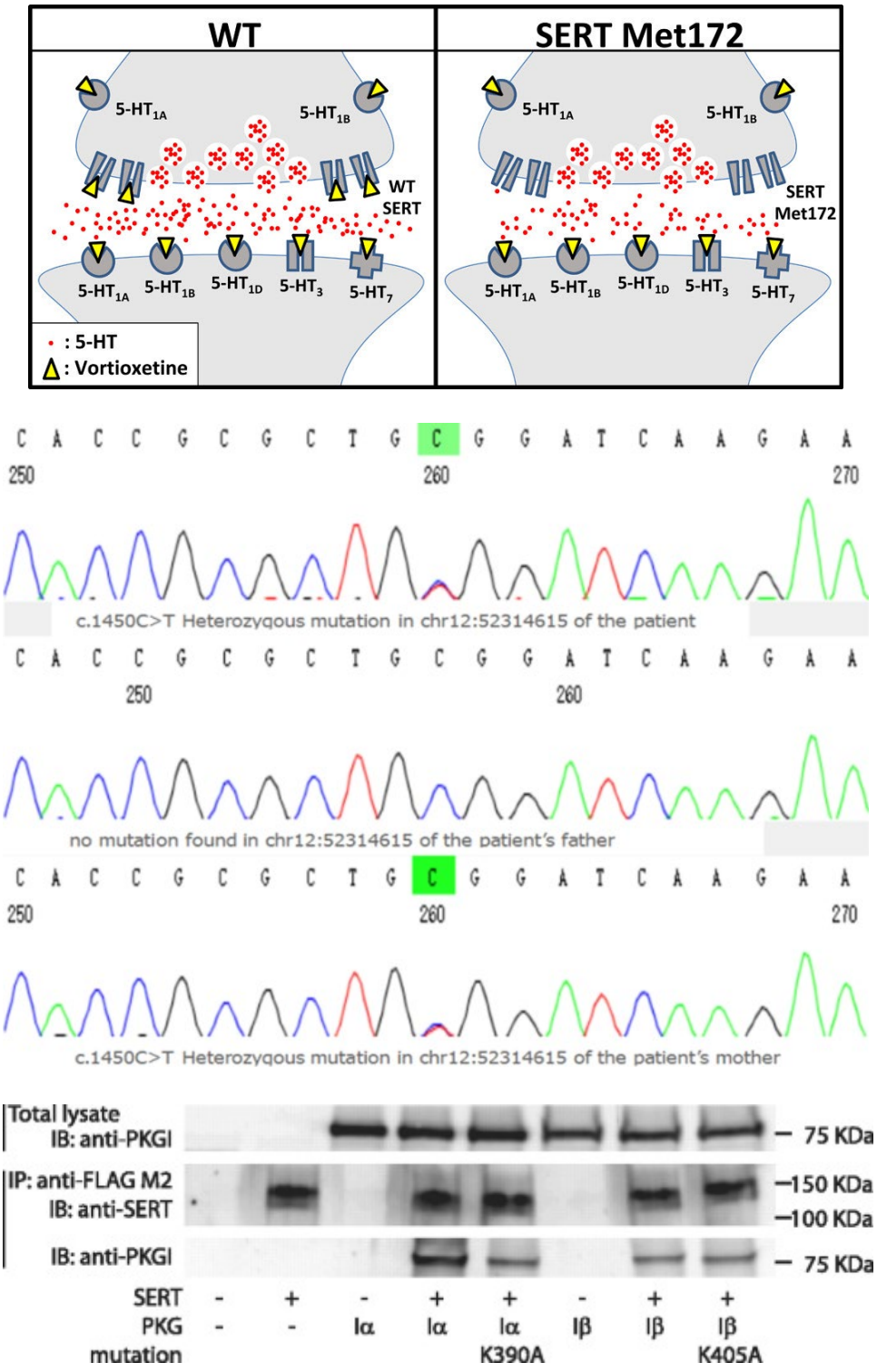

Figure 3: Schematic of the sample of nucleotide mutation in SERT gene along with the bonding pattern in women with PMDD.

4. Discussion

Premenstrual dysphoria is a mood disorder that occurs before the menstrual cycle. While the symptoms of PMDD are similar to premenstrual syndrome (PMS), it is much more severe and can lead to extreme mood swings that can interfere with daily life and functioning. Research shows that women with PMS may have changes in genes that affect how the body processes stress and sex hormones. These differences mean that women with PMDD are more sensitive to hormones that affect both mood and general health. While PMS can affect a woman's life and performance, it is not classified as a disorder and symptoms can usually be managed by the person themselves. Treatment for PMDD focuses on reducing and managing the symptoms of the disease. Some treatment options include: Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are effective in treating PMDD symptoms. According to the results obtained

from this study, it can be seen that genetics plays a significant role in causing women's PMD disorder and these genes can be responsible for other types of women's disorders as well [1-5].

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