GENETICS OF PREMENSTRUAL DYSPHORIC DISORDER

Thesis

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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً
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Maged Mahmoud Elshourbagy

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Glossary of Terms

Allele..... One of the variant forms of a gene at a particular locus.

Exon..... A nucleotide sequence in DNA that carries the code for the final messenger RNA molecule and thus defines a protein's amino acid sequence.

Gene..... The functional and physical unit of heredity passed from parent to offspring.

Genotype..... The genetic identity of an individual that does not show as outward characteristics.

Intron ..... A non-coding region of DNA that is originally copied into RNA but is cut out of the final RNA transcript.

Linkage ..... The association of genes and/or markers that lie near each other on a chromosome. Linked genes and markers tend to be inherited together.

Locus ..... The place on a chromosome where a specific gene is located (plural: loci).

Nucleotide ... One of the structural components of DNA and RNA, consisting of a base (guanine, thymine, adenine or cytosine) plus a molecule of sugar and one of phosphoric acid.

PCR ..... Polymerase chain reaction) A fast, inexpensive technique for making an unlimited number of copies of any piece of DNA.

Glossary of Terms(Cont…)

Phenotype ... The observable traits or characteristics of an organism, such as hair colour, weight, presence or absence of disease.

Polymorphism A common variant in the sequence of DNA among individuals.

Promoter..... The part of a gene that contains the information to turn the gene on or off. The process of transcription is initiated at the promoter.

RFLP..... Restriction fragment length polymorphisms) genetic variations at a site where a restriction enzyme cuts a piece of DNA. Such variations affect the size of the resulting fragments.

SNP..... single nucleotide polymorphism) common, single nucleotide variations that occur in human DNA at a frequency of one every 1,000 bases

List of Abbreviations

CI	Confidence interval
CNS	Central nervous system
COPE	Calendar of premenstrual experience
CRH	Corticotrophin-releasing hormone
DNA	Dexoribonucleic acid
DRSP	Daily Record of Severity of Problems
FBC	Full blood count
FSH	Follicle-stimulating hormone
GABA	Gamma amino butyric acid
GnRHa	Gonadotrophic releasing hormone analogues
HRT	Hormone replacement therapy
LD	Linkage disequilibrium
LH	Luteinising hormone
MAOA	Monoamine oxidase A
PMDD	Premenstrual Dysphoric Disordrer
PMS	Premenstrual Syndrome
RCT	Randomised controlled trial
RFLP	Restriction fragment length polymorphism
SNP	Single-nucleotide polymorphism
SSRIs	Selective serotonin reuptake inhibitors
STR	Short tandem repeat
Taq	Thermus aquaticus
5-HT	Serotonin`

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INTRODUCTION

Premenstrual syndrome (PMS) is characterized by recurrent psychologic and/or somatic symptoms that occur specifically during the luteal phase of the menstrual cycle, and resolve by menstruation. Premenstrual dysphoric disorder (PMDD) is the extreme, predominantly psychologic end of the PMS spectrum, and is estimated to occur in 3% to 8% of women with PMS. Premenstrual syndrome (PMS) can be a source of real distress and discomfort to menstruating women ***(Angst et al., 2001).***

The definitive aetiology of PMS remains obscure. The current predominant theory proposes that women who develop PMDD have an underlying dysregulation of the serotonergic system and that the normal hormonal changes occurring during the luteal phase seem to amplify this condition, precipitating the occurrence of PMDD in susceptible individuals. Suppressionof the normal hormonal changes occurring during the luteal phase by GnRH analogues or prolonging serotonin activity at the synapseby selective serotonin reuptake inhibitors (SSRIs) havetherapeutic effectiveness in the treatment of severe PMS and PMDD. SSRIs have comparable effectiveness to GnRH analogues; they are effective in up to 70% of women suffering with these disorders ***(Eriksson et al., 2008).***

Evidence from family and twin studies suggests that genetic factors contribute to PMDD ***(Kendler et al., 1992).*** These findings made the researchers hypothesized that PMS/PMDD is at least in part genetically determined, and furthermore, that the serotonergic system is involved and it is essential to determine whether specific polymorphic genotypes are associated with the occurrence of PMDD ***(Magnay et al., 2006).***

The most thoroughly studied serotonin-related gene is the one encoding the serotonin transporter (5-HTT) which is also called SLC6A4. The Serotonin-transporter-linked polymorphic region (5-HTTLPR) is an insertion/deletion polymorphism in the promoter region of the SLC6A4, resulting in one short allele (S allele) and one long allele (L allele). The S allele of the 5-HTTLPR gives rise to a lower invitro transcriptional activity of the 5-HTT. The S allele has also been associated with low serotonergic function as measured by a reduced prolactin response to serotonin-releasing agents, as well as with reduced platelet serotonin uptake. The same allele has also been associated with increased the catabolism of serotonin ***(Bellivier, Roy and Leboyer, 2002; Bah et al, 2008).***

Single nucleotide polymorphism (SNP) in the region rs25531 (A and G alleles) was detected in repeat 6 of the 5-HTTLPR of long allele (L allele), also the S allele carries this

polymorphism. Because of their close proximity, 5-HTTLPR and rs25531 are strongly linked. The SNP can be found in the context of both L and S alleles. However, the combination SG is rare, thus many studies currently consider 5-HTTLPR as a triallelic marker: LA, LG and S (A or G). Functionally, the allelic composites LG and S (A or G) are associated with low, nearly equivalent expression of the transporter protein relative to LA allele ***(Hu et al., 2006).*** Out of those carrying the long 5-HTTLPR allele, 10% carry a G allele on the rs25531 locus, resulting in altered affinity for the transcription factor, and thus lower promoter activity, rendering the serotonin transporter availability similar to that of carriers of the S allele ***(Nakamura et al, 2000; Wendland et al 2006).***

Previous studies failed to demonstrate significant 5-HTTLPR genotype and allele differences between women with PMDD and control subjects ***(Melke et al, 2003 and Magnay et al, 2006).*** However, these studies did not take into consideration the effect the SNP rs2553 in the women carring the long allele. It becomes esstional first to investigate whether rs25531 per se is a risk factor for premenstrual dysphoric disorder. Second, to determine whether reclassification of the 5-HTTLPR L allele into the high-activity LA and low-activity LG variants results in a significant association of genotype or haplotype with PMDD.

AIM OF THE WORK

The aim of the current study is to investigate whether rs25531 per se is a risk factor for premenstrual dysphoric disorder. Second, to determine whether reclassification of the 5-HTTLPR L allele into the high-activity LA and low-activity LG variants results in a significant association of genotype or haplotype with PMDD.

PREMENSTRUAL DYSPHORIC DISORDER

History of PMDD:

Premenstrual syndrome first appeared in the medical literature in 1931 in two papers, one by German psychoanalyst Karen Horney and another more influential paper by American gynecologist Robert Frank***(Horney 1931;Frank, 1931).***Research on this condition was pursued on a small scale. However, intensified public awareness emerged out of controversies in the 1980s. First, in three widely publicized criminal trials held in the UK in 1980, women defendants successfully pleaded diminished responsibility or mitigation due to premenstrual syndrome in crimes of manslaughter, arson and assault. These trials received wide attention in the popular press***(Dalton, 1980)***.

Premenstrual dysphoric disorderhas not been widely accepted as a condition distinct from PMS by most doctors and regulatory agencies or by those producing disease classification systems like the International Classification of Diseases (ICD) ***(Knaapen et al., 2008)***.

Premenstrual dysphoric disorder was first defined in 1987 in the Diagnostic and Statistical Manual of Mental