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Vascular endothelial growth factor gene (*VEGFA*) polymorphisms may serve as prognostic factors for recurrent depressive disorder development

Piotr Gałecki [a,f,*,1], Elżbieta Gałecka [b,1], Michael Maes [e], Agata Orzechowska [a,f], Dominika Berent [a,f], Monika Talarowska [a,f], Kinga Bobińska [a,f], Andrzej Lewiński [b,c], Małgorzata Bieńkiewicz [d], Janusz Szemraj [g]

[a] *Department of Adult Psychiatry, Medical University of Łódź, Poland*
[b] *Department of Endocrinology and Metabolic Diseases, Medical University of Łódź, Poland*
[c] *Polish Mother's Memorial Hospital-Research Institute, Łódź, Poland*
[d] *Department of Quality Control and Radiological Protection, Medical University of Łódź, Poland*
[e] *Maes Clinic @ TRIA, Piyavate Hospital, Bangkok, Thailand*
[f] *Babiński Memorial Hospital, Łódź, Poland*
[g] *Department of Medical Biochemistry, Medical University of Łódź, Poland*

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ABSTRACT

Recurrent depressive disorder (rDD) is a multifactorial disease. Vascular endothelial growth factor (VEGF) is one of the factors that have been suggested to play a role in the etiology and/or development of this disease. Limited information related to the role of *VEGFA* gene polymorphism in depressive disorder is available. The aim of the study was to analyze the association between *VEGFA* gene polymorphisms (+405G/C; rs2010963, +936C/T; rs 3025039), *VEGFA* gene expression, and its serum protein levels in rDD in the Caucasian population.

In the current study, 268 patients and 200 healthy controls of the Caucasian origin were involved. Genotyping and gene expression were performed using polymerase chain reaction (PCR)-based methods. Enzyme-linked immunosorbent assay (ELISA) was used for detection of circulating serum VEGF levels.

The distribution of *VEGFA* polymorphism +405G/C differed significantly between rDD patients and healthy subjects. The results of this study indicated that the C allele and CC genotype of *VEGFA* are risk factors for rDD. Haplotypes CC and TG are the important factors for depression development. Further, *VEGFA* mRNA expression and VEGF levels were higher in rDD patients than in controls.

The *VEGFA* gene polymorphism may serve as a prognostic factor for rDD development. Our study showed higher levels of both *VEGFA* mRNA in the peripheral blood cells and serum VEGF in patients diagnosed with rDD than in healthy controls. The obtained results suggest VEGF and the gene encoding the molecule play a role in the etiology of the disease and should be further investigated.

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1. Introduction

Depressive disorder is one of the most common psychiatric diseases in the modern world. The etiology of this disease and the contributing factors are not fully understood. Many studies have pointed to the heterogenic pathomechanism of the disease in question (Ustün et al., 2004).

Imaging studies demonstrated a reduction in hippocampal volume and lowered expression of neurotrophin in depressed patients (Cole et al., 2011; Molteni et al., 2010). The frequency of memory disturbances, one of the features of depression, directly correlates with reduced hippocampal volume (von Gunten and Ron, 2004). Chronic stress that has been described as an often causative factor in the development of depressive symptoms (Uliaszek et al., 2012), negatively regulates hippocampal function and reduces neurotrophic factor

Abbreviations: rDD, recurrent depressive disorder; VEGF, Vascular endothelial growth factor; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; COX-2, cyclooxygenase-2; VEGFA, Vascular Endothelial Growth Factor gene; rDD, recurrent depressive disorder; WHO, World Health Organization; CIDI, Composite International Diagnostic Interview; HDRS, Hamilton Depression Rating Scale; PCR-RFLP, polymerase chain reaction/restriction fragment length polymorphism; qRT-PCR, quantitative real-time polymerase chain reaction; *ACTB*, beta actin gene; *M2B*, Beta-2-microglobulin gene; *RPL13A*, Ribosomal protein L13a gene; *GADPH*, Glyceraldehyde-3- phosphate dehydrogenase gene; ELISA, enzyme – linked immunosorbent assay; TMB, tetramethylbenzidine; SD, standard deviations; LD, linkage disequilibrium; CI, confidence interval; ORdis, disease odds ratio.

* Corresponding author. Medical University of Łódź, Poland.
E-mail addresses: galeckipiotr@wp.pl (P. Gałecki), galeckipiotr@wp.pl (J. Szemraj).

[1] Both authors contributed equally to this manuscript.

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expression (Mirescu and Gould, 2006; Warner-Schmidt and Duman, 2006). There is evidence that neurogenesis is lowered in depression, while chronic treatment with antidepressants increases the process and prevents the reduction in hippocampal volume (Hviid et al., 2010; Warner-Schmidt and Duman, 2006). The above findings formed the basis of the neurotrophic/neurogenesis hypothesis of depressive disorder (Fournier and Duman, 2012).

The alternative hypothesis regarding the etiology of depression focuses on inflammation processes. Patients diagnosed with a depressive disorder have an increased level of immune cells (i.e., monocyte/macrophage), an increased expression of pro-inflammatory cytokines and other molecules (Anisman, 2011; Maes et al., 2011), including inflammatory-related enzymes such as inducible nitric oxide synthase (iNOS), myeloperoxidase (MPO), and cyclooxygenase-2 (COX-2) (Gałecki et al., 2012, 2013).

Neurogenesis is directly related to the process of angiogenesis and vascular endothelial growth factor (VEGF) is considered to provide a linkage between these two processes (Xiong et al., 2010). VEGF plays an important role in the induction and enhancement of angiogenesis. The molecule is expressed in neurons and glial cells and is also known as the neuroprotective and neurotrophic factor affecting the mechanism of neurogenesis (Takahashi and Shibuya, 2005).

VEGF is also expressed in immune cells (monocytes, macrophages, neutrophils) and is one of the important inflammatory mediators induced by proinflammatory cytokines, prostaglandin E2, nitric oxide and reactive oxygen species — molecules released during inflammation (Ben-Av et al., 1995; Kajdaniuk et al., 2011) and as mentioned before in depressive disorder.

Results of the study using an animal model of depression showed that chronic fluoxetine administration increases the expression of the gene encoding VEGF (Warner-Schmidt and Duman, 2007), while, treatment with other antidepressants increases VEGF protein levels in animal hippocampus (Greene et al., 2009). Infusion of VEGF into the brain area replaces the effect of antidepressants (Warner-Schmidt and Duman, 2007). Study by Minelli et al. (2011) has observed a significant correlation between serum VEGF levels and the reduction of depressive symptoms after electroconvulsive therapy. Interestingly, an increase in *VEGFA* expression is a characteristic finding in inflammatory disease i.e., in rheumatoid arthritis (RA) (Kasama et al., 2001) and asthma (Nomura et al., 2005), both diseases often co-existing with a depressive disorder (Covic et al., 2012; Trzcińska et al., 2012). In addition, brain inflammatory factors could be a result of systemic infection (Anisman and Hayley, 2012).

Some recent studies argue that VEGF may be related to the development and management of depressive disorders (Iga et al., 2007; Lee and Kim, 2012).

The gene encoding VEGF is localized on chromosome 6p21.3. (Lutty et al., 1996). The *VEGFA* gene includes two polymorphisms that are relatively common and may influence *VEGFA* expression. The +405G/C (rs 2010963) variant is located within the 5′ untranslated region of the *VEGFA* gene. Watson et al. (2000) found correlation between VEGF protein levels and genotype for +405G/C in peripheral blood mononuclear cells. The second polymorphism +936C/T (rs3025039) is located in the 3′ untranslated region. Plasma VEGF levels are significantly lower in carriers of the T allele than in non-carriers (Krippl et al., 2003; Renner et al., 2000).

It is acknowledged that genetic factors can significantly modify the risk for depressive disorder and the total contribution of genetic factors in the etiology of depression is estimated at approximately 40% (Sullivan et al., 2000). Therefore, the relevant DNA sequence variations of genes that are proposed to determine the susceptibility of an individual to the development of a depressive disorder should be further investigated.

The *VEGFA* gene, mRNA expression and protein levels were studied in major depression, mostly in the Asian population, by several authors (Iga et al., 2007; Lee and Kim, 2012; Tsai et al., 2009). Limited information regarding the relation between gene variants, gene and protein expression as well as the risk and the course of recurrent depressive disorder (rDD) in a homogenic Caucasian group is available.

As the *VEGFA* gene expression and protein levels vary in patients diagnosed with a depressive disorder, the objective of this study was to investigate the role of two functionally known *VEGFA* polymorphisms, +405G/C and +936C/T, as risk factors determining the susceptibility of an individual to rDD. Furthermore, the relationship between the *VEGFA* genotypes, haplotypes, mRNA expression and VEGF levels, was also evaluated in the studied cohort of patients and corresponding healthy controls.

2. Materials and methods

2.1. Subjects

A group of 268 patients, was recruited (152 females; 56.7%), and enrolled in the current study. The mean age in that group was 45.5 ± 9.98 years (mean ± SD), number of depressive episodes was 3.8 ± 1.49 (mean ± SD), and duration of disease was 8.5 ± 5.6 (mean ± SD). The diagnosis was established according to ICD-10 criteria (F33.0–F33.8) (World Health Organization, 1992). In all qualified cases, medical history was obtained, using the standardized Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992). Hamilton Depression Rating Scale (HDRS) was performed to assess the level of depressive symptoms. Additionally, the number of depressive episodes, duration of the disease, and the age of onset were assessed in each patient. The control group consisted of 200 healthy subjects (121 females; 60.5%) with a family history negative for psychiatric disorders. The mean age in that group was 37.1 ± 7.84 years (mean ±SD). The control subjects included community volunteers, enrolled to the study following the criteria of the psychiatric CIDI interview (World Health Organization, 1992). Both patients and controls with other psychiatric diagnoses, concerning axis I and II disorders, as well as inflammatory, atherosclerosis-related cardiovascular diseases were excluded from the study. All the patients and control subjects were native, unrelated inhabitants of the central Poland. To avoid the population stratification effect we chose to examine the genotypes in Polish patients only, i.e., all four grandparents identified themselves to be of Polish origin.

A written informed consent was obtained from all the participants of the study. The study protocol had been approved by the Local Bioethics Committee No. RNN/883/11/KB.

Genotyping of *VEGFA* gene polymorphisms using polymerase chain reaction/restriction fragment length polymorphism PCR–RFLP assay.

Peripheral blood samples were drawn from analyzed subjects in the morning, between 7.00 and 9.00 AM after an all night fast.

The isolation of genomic DNA from the peripheral blood lymphocytes was performed using the proteinase K digestion and phenol/chloroform extraction. The *VEGFA* gene +405G/C, and 936C/T variants were determined by PCR–RFLP assay. The primers for amplifying the *VEGFA* fragments were 5-CGACGGCTTGGGGAGATTGC-3 (forward) and 5-GGGC GGTGTCTGTCTGTCTG-3 (reverse) for +405G/C variant and 5-AGGGTT CGGGAACCAGATC-3 (forward) and 5-CTCGGTGATTTAGCAGCAAG-3 (reverse) for +936C/T variant.

The PCR reactions were performed on 25 μl volume containing 200 ng genomic DNA, 1 μM of each primer (+936C/T polymorphism) or 0.4 μM of each primer (+405G/C polymorphism), 0.2 mM deoxynucleotide triphosphates, 2.5 μl buffer DyNAzyme™ II 10× and 1 unit of DyNAzyme™ II DNA polymerase (Finnzymes). The PCR cycle conditions consisted of an initial denaturation step at 94 °C for 3 min, followed by 35 cycles for 30 s at 94 °C, 30 s at 62 °C, 30 s at 72 °C, and a final elongation at 72 °C for 10 min.

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