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Polymorphisms of iodothyronine deiodinases (DIO1, DIO3) genes are not associated with recurrent depressive disorder

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ABSTRACT

Background: Depressive disorder is characterized by disturbances in the hypothalamic-pituitary-thyroid (HPT) axis and in the metabolism of thyroid hormones (TH). The evidence for changes in TH levels is observed in human sera and cerebrospinal fluid as well as in animal model studies. Iodothyronine deiodinases (DIOs) type 1, 2 and 3 (DIO1, DIO2, DIO3) are important enzymes for the synthesis and determination of TH concentration. This study aims to examine the link between recurrent depressive disorders (rDD) and two functionally known polymorphisms *DIO1*a-C/T (rs11206244) and *DIO1*b-A/G (rs12095080) within the *DIO1* gene encoding DIO1 and two polymorphisms *DIO3*-C/T (rs17716499), *DIO3*-A/C (rs7150269) within the *DIO3* gene encoding DIO3.
Methods: Both variants were genotyped in 254 rDD patients and 197 healthy subjects using polymerase chain reaction. Basic methods and statistical analyses were used to estimate genetic variants in the risk of the disease.
Results: No significant associations were found between the polymorphisms examined here and rDD. There were no significant associations between genotypes distribution and demographic/medical variables. Odds ratios (OR_{dis}) and corresponding 95% confidence interval (95% CI) were calculated, for example: for CC genotype of *DIO1*a C/T (OR_{dis} = 0.86, 95% CI: 0.59, 1.25).
Conclusion: Functional variants within the *DIO1* gene, which affect TH levels and polymorphisms in *DIO3*, are not confirmed to be associated with rDD. Nevertheless, considering previous data which indicate that the *DIO1* gene is related to the depression, further studies on a larger sample size are recommended.

Introduction

Depressive disorder is a thoroughly investigated disease, the etiology of which has not been fully explained so far.

Disturbances in the hypothalamic-pituitary-thyroid (HPT) axis and changes in thyroid hormone (TH) concentrations are often found in depressive patients [1–3]. For example, sera thyroxine (T4) levels and cerebrospinal fluid reverse triiodothyronine (rT3) concentration [4,5] are found to be increased, while basal thyroid secreting hormone (TSH) levels are decreased and associated with increased free T4 (FT4) levels [3–5]. In a large-scaled study, both increases in FT4 and lowered TSH levels were associated with severity of depression [3]. Studies in animal models revealed that antidepressants may increase triiodothyronine [T3] brain levels [6]. In addition, hypothyroidism is reported to be linked with depression development, risk and management [7].

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Inflammatory processes play an important role in depressive disorders and are also subject to thorough examinations. The disturbances between pro- and anti-inflammatory markers, elevated pro-inflammatory cytokine levels, and a higher number and increased activity of immune cells are observed in patients diagnosed with depression [8]. Alterations in TH metabolism without changes in the HPT axis and thyroid function during various pathologies have been described and are referred to as the non-thyroidal illness syndrome [9]. Moreover, there are reports linking thyroid function, thyroid hormones and proper brain activity [2,10]. In depression, HPT axis dysfunction is associated with activated inflammatory pathways, suggesting that disorders in the HPT-axis, e.g. lowered TSH levels, are at least partly related to the immune-inflammatory response as detected in the non-thyroidal illness syndrome [11].

The metabolism and levels of TH are under an influence of different factors, including type 1, 2 and 3 iodothyronine deiodinases (DIO1, DIO2, DIO3), which participate in the conversion of T4 to T3 and rT3 [12]. DIO1 is responsible for 80% of circulating T3 levels, but also generates an inactive form of T3, known as rT3. The expression of DIO1 is observed in the thyroid, kidney and liver, and additionally in lymphocytes; the regulation of its synthesis and secretion by pro-inflammatory cytokines has been indicated and described [12]. Synthesized by DIO1, circulating T3 may access directly from blood and cerebrospinal fluids and is a source of the hormone in neurons – the main cellular site of T3 action [12,13]. The DIO3 enzyme is involved in the reductive deiodination from the inner ring of T4 and T3. DIO3 eliminates T4 by transformation to rT3 and synthesizes of diiodothyronine (T2) from T3. Under normal conditions, DIO3 is expressed in most organs, including the brain – mainly neurons of the hippocampus and the cerebral cortex [12,14].

Genetic variants within the genes involved in TH metabolism – including DIOs – may influence expression, protein levels and activity, and affect the endpoint of different mechanisms. If the functionality of the variant is not well known it may be in linkage disequilibrium (LD) with the one located within the same gene or the gene nearby. Polymorphisms can also impact the risk and development of many diseases, including mental retardation, bipolar disorder, hypertension, osteoarthritis [15]. The polymorphism within *DIO1* is associated with the efficacy of T3 supplementation to antidepressant treatment [16]; *DIO2* variants are related to the risk of bipolar disorders [17] and according to our recent study to recurrent depressive disorders (rDD) [18]. Research results obtained by Panicker et al. [19] suggest a relationship between *DIO2* psychological well-being and a combined T4/T3 therapy.

Specific reports provide information that polymorphisms within the genes encoding for deiodinase may affect TH concentration in healthy subjects. For example, single nucleotide polymorphisms (SNPs) *DIO1*a-C/T and *DIO1*b-A/G within the *DIO1* gene encoding for DIO1 are associated with the levels of TH [20]. Allele T of the *DIO1*a-C/T variant is correlated to higher serum rT3 levels and lower T3/rT3 ratio, suggesting lower enzymatic activity for T allele carriers; on the other hand, allele G of the second polymorphism is related to higher T3/rT3 ratio and suggests higher enzyme activity for carriers of this allele.

The biology of depression has been extensively investigated. The hypotheses of the disease etiology are among others based on the changes in TH concentration, including low levels of T3 and high levels of rT3 [21]. A possible explanation could assume that changes in TH metabolism in patients with depression result from the deiodination processes. The regulatory cascade through which TH are metabolized may be related to *DIO1*, *DIO2* and *DIO3* gene variants or to the expression of the respective genes.

To the best of our knowledge there is no study investigating *DIO1* and *DIO3* genes and the risk of depression. We have chosen *DIO1* and *DIO3* to examine whether in particular respectively encoding enzymes (DIO1, DIO3) govern TH metabolism and serve as an important determinant of tissue and peripheral levels [12]. In addition, besides genes, enzymes and consequently TH are able to influence the immune system by decreasing or increasing the immune response [22]. The relationship between the status of TH and the immune system is very important in depressive disorders. It is widely known and described that immune disturbances and inflammation are involved in the background and pathomechanism of depression [23]. One may hypothesize that *DIO1* and *DIO3* are a denominator of the complex etiology of rDD.

The main aim of this study was to investigate functional polymorphisms within the *DIO1* rs11206244 (C/T), rs12095080 (A/G) and *DIO3* rs17716499 (C/T), rs7150269 (A/C) genes in patients suffering from recurrent depressive disorders (rDD) and the risk of the diseases in question.

Materials and methods

Subjects

The study was carried out in a group of 451 subjects, including 254 patients diagnosed with rDD and 197 healthy subjects. The patients were diagnosed according to ICD-10 [24] criteria (F33.0–F33.8). A medical history was assessed with the use of the standardized Composite International Diagnostic Interview (CIDI) form [25]. The Hamilton Depression Rating Scale (HDRS) served to estimate the level of depressive symptoms. Depression severity was estimated with the use of the 17-item Hamilton Depression Rating Scale (HDRS) [26]. All the subjects were examined during the course of their hospitalization. The study group included subjects hospitalized for the first time due to a depressive episode and depression treatment-naïve, as well as those treated for many years earlier and with multiple hospitalization episodes in the past; the latter were admitted for various degrees of health deterioration. The number of depression episodes and disease duration periods were recorded for each patient. HDRS was administered at admission during the symptomatic phase, which would generally be either before or shortly after a modification of the previous antidepressant drug regimen. Reassessment of the mental condition was conducted 8 weeks after the pharmacological treatment, also with the use of the HDRS scale. The patients were subject to an antidepressant therapy with drugs from the SSRI group (Selective Serotonin Reuptake Inhibitors): fluoxetine, sertarline, citalopram, paroxetine. Patient examinations were conducted by the same person in each case.

The control subjects consisted of selected healthy community individuals with a negative family history for psychiatric disorders, enrolled to the study on the basis of the criteria of the psychiatric CIDI interview. Control subjects were interviewed to obtain and collect data about their health after informed contest. We obtained detailed demographic and clinical data from 139 rDD patients and 69 controls; the data are presented in Table 1. Patients and control subjects with other psychiatric diagnoses, including axis I and II disorders, were not recruited and could not participate in the study. Severe or chronic diseases with confirmed inflammatory or autoimmune etiology as well as thyroid diseases were considered additional exclusion criteria. All the patients were native inhabitants of central Poland and were unrelated to one another. To avoid a population stratification effect, the genotypes were determined only in the individuals of Polish origin, i.e. all four grandparents identified themselves to be of Polish origin. Selection of individuals for the tested group was performed randomly, without replacement sampling.