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The genetic influence of the brain-derived neurotrophic factor Val66Met polymorphism in chronic low back pain

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Abstract

Background: The Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene is a potential biomarker of vulnerability to pain. Thus, the present study aimed to investigate the association of this polymorphism with clinical and biopsychosocial factors in patients with chronic low back pain (CLBP).

Methods: A total of 107 individuals with CLBP answered questionnaires that were validated and adapted for the Brazilian population, including the Brief Inventory of Pain, the Central Sensitization Inventory, the Roland Morris Disability Questionnaire, the Tampa Scale for Kinesiophobia, the Pain Catastrophizing Scale, the Survey of Pain Attitude-Brief, and the Hospital Anxiety and Depression Scale. All of the subjects were genotyped for the BDNF Val66Met polymorphism.

Results: The sample showed moderate scores of disability, central sensitization, and kinesiophobia, in addition to mild anxiety, hopelessness, and ruminant thoughts. No significant association was observed between the Val66Met polymorphism and the variables analyzed. Besides, there was no relationship between the BDNF Val66Met polymorphism with CSI, catastrophization, or disabilities that were generated by CLBP.

Conclusion: The results showed that the Val66Met polymorphism of the BDNF gene was not associated with clinical and biopsychosocial characteristics of CLBP in the sample studied.

Keywords: Central sensitization, Catastrophizing, BDNF, Polymorphism, Single nucleotide polymorphism, Val66Met

Background

In the populations suffering from chronic pain, low back pain is one of the most prevalent musculoskeletal disorders, affecting 70 to 85% of adults at some point in their life [1]. Regardless of the primary or secondary pathology, the consequences of persistent pain include the fear of movement, pain catastrophizing, anxiety, and central sensitization. These outcomes appear to be the major contributors of pain and disability under these conditions [2, 3].

It is well known that the experience of pain is influenced by biological, psychological, and behavioral factors. Among the biological factors, there is a growing interest in the genetic aspects, in an attempt to explain some of the differences in the pain responses between individuals [4]. Studies have considered that the genetic factors represent more than a 50% susceptibility to chronic low back pain (CLBP) [5], whereas the variation in the genes that are involved in pain perception and its modulation, transduction, transmission, and conduction by the nervous system can result in variabilities in the experience of pain [6].

The brain-derived neurotrophic factor (BDNF) is a neurotrophin that is involved in neurogenesis and synaptic plasticity in the central nervous system. The

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Val66Met polymorphism (c.196G > A, dbSNP: rs6265) of the BDNF gene represents the replacement of valine (Val) with a methionine (Met) at codon 66. This substitution in the BDNF pro-region changes the intracellular trafficking and packaging of the pro-BDNF, its availability in the synaptic cleft, and the deterioration of synaptic plasticity, thus decreasing the BDNF secretion [7]. The Val66Met polymorphism has been considered as a marker of vulnerability to pain. Individuals with the Met allele were more likely to have chronic pain when associated with the presence and severity of chronic musculoskeletal pain in multiple sites, in studies that investigated individuals with childhood or recent life stress [8], and with an increased risk of chronic postoperative pain [9]. However, the studies on the role of BDNF, both in relation to the genotypes, their expression, and the serum protein levels in chronic pain, still show inconclusive results.

Most treatment strategies for CLBP are still based on the biomedical model, that is, structural-anatomical-mechanical [10]. However, the biopsychosocial model is based on a dynamic relationship between the biological changes, psychological status, and social context, emphasizing that these factors have different roles in chronic pain, disability, and emotional maladjustment [11]. Therefore, the present study aimed to investigate the association of the single nucleotide polymorphism (SNP) Val66Met of the BDNF gene with clinical and biopsychosocial factors in patients with CLBP.

Methods

All of the procedures complied with the requirements of Resolution 466/12 of the National Health Council. The data collection occurred after the approval by the Research Ethics Committee from the Lutheran University of Brazil (ULBRA), under protocol number 2.254.800. All of the patients gave written informed consent before their participation.

Subjects

The study was carried out in Palmas (Tocantins, Brazil), at the Lutheran University Center of Palmas (CEULP/ULBRA), in the community service center, the Clinical School of Physiotherapy (CSP). The eligibility criteria were individuals over 18 years of age of both genders, who had CLBP for over 3 months.

Procedure

The individuals with CLBP answered questionnaires that were validated and adapted for the Brazilian population, such as the Brief Inventory of Pain (BIP) [12]; the Central Sensitization Inventory (CSI) [13]; the Roland Morris Disability Questionnaire (RMDQ) [14]; the Tampa Scale for Kinesiophobia [15]; the Pain Catastrophizing Scale (PCS) [16]; and the Hospital Anxiety and Depression Scale (HADS) [17]. Afterward, 5 ml of peripheral blood was collected using sodium ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, and it was then frozen.

Genetic analyses

The total DNA was purified from the blood samples and the Val66Met SNP (rs6265) was genotyped through the real-time polymerase chain reaction (PCR) when using TaqMan® SNP Genotyping assays (Thermo Fisher Scientific; catalog 4,351,379, assay ID: C__11592758_10). All of the assays were run on a StepOnePlus™ system (Biosystems Inc., Foster City, USA).

Statistical analyses

The data was analyzed using descriptive statistics, and by employing mean, standard deviations, and percentages through the SAS version 9.4 program. A bivariate analysis was performed to compare the variables under study in relation to the genotypes of Val66Met. For the qualitative variables, the Chi-square test was applied, and for the quantitative variables, the Mann-Whitney non-parametric test was applied. The allele frequencies were determined by direct counting of the alleles. The departures from the Hardy-Weinberg equilibrium were evaluated by the Chi-square test. $p < 0.05$ was considered statistically significant.

Results

The sample was composed of 107 patients (56.5% women) with CLBP. The clinical and demographic characteristics of the sample are shown in Table 1. Briefly, the mean age was 46.2 ± 14.3 years, the BMI was 26.8 ± 5.1 kg/m^2 (26.7% with obesity), with a score of 49.6 ± 14.4 in the CSI assessment, presuming central sensitization, and a score of 15.7 ± 5.3 in the RMDQ, presuming disabilities. The analysis of the BIP showed that the patients had pain in at least roughly nine body regions, summing the low back. The Tampa scores were considered moderate (45.6 ± 7.8). The PCS scores evidenced rumination thoughts. In addition, mild anxiety was observed according to the HADS scores.

In the present study, it was observed that 26 (24.3%) patients were carriers of the Met allele of SNP Val66Met in the BDNF gene. There were no significant associations between the Val66Met genotypes and either the quantitative (Table 2) or the qualitative variables studied (Table 3).

Discussion

The present study found no associations between the BDNF Val66Met genotypes and the biopsychosocial phenotypes in patients with CLBP. The Val66Met

Table 1 Characteristics of the sample studied

Variable	Mean	SD
Age	46.24	14.27
Subjective assessment of stress	5.84	2.39
BMI	26.82	5.14
Total CSI score	49.6	14.39
Total RMDQ score	15.7	5.3
BIP pain intensity		
Worst	6.49	2.59
Least	3.16	2.45
Average	5.37	2.26
Now	4.56	3.02
BIP interference		
General activity	5.83	3.34
Mood	5.5	3.52
Walking	5.41	3.32
Normal work	5.97	3.7
Relations	3.58	3.34
Sleep	5.44	3.46
Enjoyment of life	4.48	3.63
Σ pain-body regions	8.95	6.04
Total Tampa score	45.61	7.82
Total PCS score	2.17	1.2
PCS rumination	2.68	1.33
PCS helplessness	1.53	1.31
HADS-anxiety	9.04	3.47
HADS-depression	6.91	3.98

BMI body mass index, *BPI* the brief inventory of pain, *CSI* central sensitization inventory, *HADS* hospital anxiety and depression scale, *PCS* pain catastrophizing scale, *RMDQ* Rolland-Morris disability questionnaire, *SD* standard deviation

polymorphism is the most studied in the BNDF gene and it has been investigated in several pathological conditions in humans [18–20]. The Val66Met polymorphism has also been associated with the methylation patterns, and it is being related to the epigenetic regulation of the BDNF gene [21]. From a biological perspective, it is known that the responses of an organism's experience to the external environment can be reflected in the epigenetic changes. Thus, the gene expression could also be regulated by the epigenetic modifications to the chromatin structure and the patterns of DNA methylation. These adaptations can modify, among others, neuronal morphology and the activity to produce changes in behavior [22, 23]. Alterations in the chromatin structure represent mechanisms by which pain can be converted gradually and progressively into the pathological processes of neuroinflammation, central sensitization, and ultimately, chronic pain syndromes [24].

The averages of the disabilities of the patients in the present study due to CLBP were classified as moderate from the RMDQ. It is recommended to consider an assessment of the multidimensional nature of CLBP in the management of pain [25]. This could be physical (for example, disability and body composition), psychological (for example, kinesiophobia, fear-avoidance, pain catastrophizing, pain self-efficacy, depression, anxiety, and sleep quality), and/or social (social functioning and work absenteeism) factors.

Most of the evaluated patients presented overweight/obesity conditions. Adiposity may modulate pain through peripheral sensitization from increased systemic inflammation [26]. In addition, it was observed that the increased fat infiltration of the paraspinal musculature could be associated with a compromised function of the muscles that control and support the low back [27, 28]. The findings from the BIP data also showed that the worst pain affected the normal work of the patients, restricting the performance of the activities of daily living.

The individuals in the present study reported being physically inactive. The relationship between a cluster of unhealthy lifestyle behaviors (smoking, alcohol drinking, physical activity, weight control, breakfast, snacking, and sleep) and low back pain (LBP) was investigated in a cross-sectional study of over 400,000 Japanese adults showing an association of this cluster with an increased risk of LBP, regardless of age and BMI [29]. Moreover, chronic pain is at least partly attributed to a sedentary and inactive lifestyle and it could be recognized as a lifestyle-related disease. Physical activity/inactivity may also determine the genetic/epigenetic and neural factors encoded in the brain [30]. A single session of exercise and regular physical activity induce changes in the genes that regulate the nociceptive processes, the learning of fear, and the stress responses, as well as those that are involved in the pathophysiology of chronic diseases [31].

In the current study, the mean of the total scores in Tampa was moderate. Fear can be learned through associative learning. Previous study reported that conditioning to fear was able of inducing a rapid increase in methylation of the BDNF gene in the hippocampus, and it occurred during the consolidation of fear [32]. It is well known that the fear and the avoidance of particular movements could add to a disability, but the assessment and removal of these barriers to movement might, therefore, reduce the disability [33]. A psychological factor that distinctly predicts changeability in the perception of pain and the development of moderate kinesiophobia is pain catastrophizing [34]. In the present study, the CLBP patients presented scores that suggested rumination and helplessness thoughts, besides mild anxiety and central sensitization. Anxiety and stress predict chronic pain in

Table 2 Comparison of the quantitative variables according to the BDNF Val66Met genotypes

Variable	Val/ Val (*n* = 81)	Val/Met (*n* = 26)	*P*-value
Age	46.2 ± 14.3	46.5 ± 14.6	0.73
Subjective assessment of stress	5.9 ± 2.5	5.8 ± 2.1	0.62
BMI	27.1 ± 5.2	26.4 ± 4.9	0.47
Total CSI score	50.3 ± 14.6	48.0 ± 13.9	0.50
Total RMDQ score	15.6 ± 5.5	15.8 ± 4.8	0.99
BIP pain intensity			
Worst	6.5 ± 2.5	6.4 ± 2.9	0.97
Least	3.2 ± 2.4	2.8 ± 2.4	0.42
Average	5.4 ± 2.1	5.2 ± 2.8	0.52
Now	4.6 ± 3.0	4.2 ± 3.0	0.45
BIP interference			
General activity	5.9 ± 3.4	5.4 ± 3.2	0.44
Mood	5.7 ± 3.5	4.9 ± 3.7	0.36
Walking	5.4 ± 3.2	5.3 ± 3.5	0.96
Normal work	6.1 ± 3.8	5.3 ± 3.4	0.16
Relation	3.6 ± 3.4	3.5 ± 3.2	0.92
Sleep	5.4 ± 3.6	5.3 ± 3.2	0.76
Enjoyment of life	4.3 ± 3.7	5.1 ± 3.5	0.34
Summation of pain body regions	9.0 ± 5.0	8.7 ± 8.8	0.07
Total Tampa score	45.6 ± 8.1	45.9 ± 7.2	0.87
Total PCS score	2.2 ± 1.2	1.9 ± 1.1	0.32
PCS rumination	2.8 ± 1.4	2.3 ± 1.1	0.18
PCS helplessness	1.5 ± 1.3	1.4 ± 1.4	0.51
HADS anxiety	9.3 ± 3.5	8.4 ± 3.5	0.52
HADS depression	7.1 ± 3.8	6.6 ± 4.4	0.35

Values are shown as mean ± standard deviation
BMI body mass index, *BPI* the brief inventory of pain, *CSI* central sensitization inventory, *HADS* hospital anxiety and depression scale, *PCS* pain catastrophizing scale, *RMDQ* Rolland-Morris disability questionnaire
P-value for the Mann-Whitney test

the long term and they might mediate the vulnerability to pain [35]. Thus, there is plausibility that the extent of central sensitization symptoms in people with non-specific LBP might be associated with the pre-morbid trait anxiety sub-types and the abnormal trait sensory processing profiles [36, 37]. Moreover, depression and anxiety are barriers to treatment adherence in various chronic pain conditions, such as low back pain [38].

Although 74% of the patients in the present study reported themselves to be active/employed, they described the pain during a month at an intense level and with chronicity for up to 13 months. This is important since CLBP is also considered responsible for absenteeism at work, and with high rates of disability, generating high costs for the health system, social security, and society in general [39]. Moreover, non-opioids were the main medication used, and most of the patients reported a modest relief of the pain with the medication.

The importance of behavioral approaches to back pain management does not preclude the continuing need to investigate mechanisms and the potential biological determinants of non-specific low back pain [40]. The relative importance of the genetic factors in human musculoskeletal pain conditions, such as CLBP, painful temporomandibular joint disorders, fibromyalgia, and chronic widespread pain, is becoming clearer. Several polymorphisms in the genes are contributing to serotonergic and adrenergic pathways that are associated with musculoskeletal pain [41]. Despite studies demonstrating evidence that the BDNF Val66Met polymorphism influences the cortical processing of experimental electrical pain stimuli in an indirect manner [4], or in pain catastrophizing [42], the findings in the present study did not show the influence of this polymorphism in chronic pain complaints.

Certain limitations must be considered in the interpretation of the current study's findings. First, the

Table 3 Comparison of the qualitative variables according to the BDNF Val66Met genotypes

	Genotype		
	Val/ Val N (%)	Val/Met N (%)	*P*-value
Gender			
Female	45 (55.6)	16 (61.5)	0.59
Male	36 (44.4)	10 (38.6)	
Civil status			
Living alone	42 (51.8)	11 (42.3)	0.40
Living with partner	39 (48.2)	15 (57.7)	
Ethnicity			
White	14 (18.2)	8 (34.8)	
Brown	46 (59.7)	13 (56.5)	0.14
Black	17 (22.1)	2 (8.7)	
Schooling			
Until high school	63 (77.8)	16 (64.0)	0.17
Complete high school	18 (22.2)	9 (36.0)	
Have children			
No	19 (23.5)	6 (23.1)	0.97
Yes	62 (76.5)	20 (76.9)	
Healthy			
Good, very good, or great	35 (44.3)	12 (46.1)	0.87
Regular, bad, or lousy	44 (55.7)	14 (53.9)	
Chronicity pain			
3–12 months	21 (25.9)	5 (19.2)	
13–60 months	27 (33.3)	13 (50.0)	0.31
> 60 months	33 (40.8)	8 (30.8)	
Pain intensity			
Least	8 (9.9)	4 (15.4)	
Moderate	14 (17.3)	3 (11.5)	0.62
Intense	59 (72.8)	19 (73.1)	
Pain duration in the month			
Intermittent	37 (46.2)	15 (65.2)	0.11
Constant	43 (53.8)	8 (34.8)	
Comorbidities			
No	46 (56.8)	16 (61.5)	0.67
Yes	35 (43.2)	10 (38.5)	
Physical activity			
Inactive	55 (67.9)	18 (69.2)	
Insufficiently active	8 (9.9)	4 (15.4)	0.80
Moderately active	13 (16.0)	3 (11.5)	
Vigorously active	5 (6.2)	1 (3.9)	
Smoking			
No	68 (91.9)	21 (91.3)	0.93
Yes	6 (8.1)	2 (8.7)	
Alcoholism			
No	66 (89.2)	22 (95.7)	0.35
Yes	8 (10.8)	1 (4.3)	

Table 3 Comparison of the qualitative variables according to the BDNF Val66Met genotypes *(Continued)*

	Genotype		
	Val/ Val N (%)	Val/Met N (%)	*P*-value
Satisfaction			
Unsatisfied or a little satisfied	33 (51.6)	9 (40.9)	0.39
Satisfied or much satisfied	31 (48.4)	13 (59.1)	
Occupational situation			
Active/employed	62 (76.5)	18 (69.2)	0.45
Unemployed	19 (23.5)	8 (30.8)	
Low back pain in family history			
No	36 (44.4)	12 (46.2)	0.88
Yes	45 (55.6)	14 (53.8)	
Overweight/obesity			
No	32 (41.0)	11 (42.3)	0.91
Yes	46 (59.0)	15 (57.7)	
CSI			
No	14 (17.3)	4 (15.4)	0.82
Yes	67 (82.7)	22 (84.6)	
RMDQ			
No	28 (34.6)	9 (34.6)	0.97
Yes	53 (65.4)	17 (65.4)	
Medication			
Non opioid	33 (62.3)	12 (80.0)	0.20
Weak opioid	20 (37.7)	3 (20.0)	
Medication frequency			
Every 6 h	35 (66.0)	7 (50.0)	0.27
If there is pain	18 (34.0)	7 (50.0)	
Start of medication			
12 months ago	32 (68.1)	8 (80.0)	
13–60 months	7 (14.9)	1 (10.0)	0.75
More than 60 months	8 (17.0)	1 (10.0)	
Relief of pain with medication			
50% relief	32 (62.8)	5 (45.5)	0.29
More than 50% relief	19 (37.2)	6 (54.5)	
Tampa score			
Light	7 (8.6)	2 (7.7)	
Moderate	47 (58.1)	14 (53.8)	0.89
Critical	27 (33.3)	10 (38.5)	
HADS-anxiety			
No	34 (42.0)	11 (42.3)	0.98
Yes	47 (58.0)	15 (57.7)	
HADS-depression			
No	53 (65.4)	20 (76.9)	0.27
Yes	28 (34.6)	6 (23.1)	

CSI central sensitization inventory, *HADS* hospital anxiety and depression scale, *RMDQ* Rolland-Morris disability questionnaire
P-value for the Chi-square test

statistical power of the sample size that was analyzed was limited. Second, this was a cross-sectional study, which might limit the causality identification of the demographic and clinical variables that were investigated. Third, to have a better understanding of the role of BDNF in CLBP, it would be important to investigate the correlation between the genotypes and the serum levels.

Conclusion

The present study showed no association between the Val66Met BDNF polymorphism with the clinical and biopsychosocial characteristics in patients with CLBP. However, further studies are still needed to elucidate if the BDNF Val66Met polymorphism could influence other distinct subjective pain experience outcomes in different samples with CLBP.

Abbreviations

BDNF: Brain-derived neurotrophic factor; BIP: Brief inventory of pain; BMI: Body mass index; CLBP: Chronic low back pain; CSI: Central Sensitization Inventory; CEULP/ULBRA: Lutheran University Center of Palmas; HADS: Hospital anxiety and depression scale; LBP: Low back pain; Met: Methionine; NAC: Community service center; PCR: Polymerase chain reaction; PCS: Pain catastrophizing scale; RMDQ: Roland Morris disability questionnaire; SD: Standard deviation; SNP: Single nucleotide polymorphism; ULBRA: Lutheran University of Brazil; Val: Valine

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Authors' contributions

A.S. Yamada, A.H. de Souza, and D. Simon designed the study. A.S. Yamada and C. Ferraz collected the data. A.S. Yamada and D. Simon performed the statistical analyses. A.S. Yamada, A.H. de Souza, and D. Simon interpreted and discussed the results. A.S. Yamada and D. Simon wrote the paper. A.S. Yamada, F.T.T. Antunes, C. Ferraz, A.H. de Souza, and D. Simon contributed to the final version of the manuscript. All of the authors have reviewed and approved the final version of the article, including the authorship list.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Lutheran University of Brazil (ULBRA), under protocol number 2.254.800. All subjects signed the informed consent form. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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