

RESEARCH NOTE

Open Access



Polymorphisms of *brain-derived neurotrophic factor* genes are associated with anxiety and body mass index in fibromyalgia syndrome patients

Boya Nugraha^{1*} , Sumadi Lukman Anwar^{2†}, Christoph Gutenbrunner¹ and Christoph Korallus¹

Abstract

Objective: Fibromyalgia syndrome has been associated with familial clusters although the specific genetic predisposition is not clear. Accordingly, studies concerning genetic factors associated with this disease are important. Brain-derived neurotrophic factor (*BDNF*) has been shown to play a role in patients with fibromyalgia syndrome, particularly in mediating manifestations of pain and mood-related symptoms. Research on genetic factors, including genetic variations or single nucleotide polymorphisms, especially related to *BDNF* in fibromyalgia is very limited. Therefore, this study was aiming at determining the association of polymorphisms of *BDNF*, particularly rs2049046 (A>T) and rs7124442 (A>G), with body mass index (BMI) and mood-related symptoms in FMS.

Results: In fibromyalgia syndrome cases, *BDNF* polymorphisms were associated with body mass index and anxiety score, specifically rs7124442 (A>G) (Fisher's exact test χ^2 ; $p < 0.05$; odds ratio (OR): 1.02) and rs2049046 (A>T) (Fisher's exact test χ^2 ; $p < 0.05$; OR: 0.55), respectively. Additionally, patients with fibromyalgia syndrome who have AA (95% CI (8.71, 11.63)) and AT (95% CI (9.32, 11.74)) alleles of rs2049046 showed higher score of anxiety compared to patients with TT (95% CI (3.98, 8.20)) allele (ANOVA test; $p < 0.01$). These results suggest that *BDNF* polymorphisms (rs7124442 and rs2049046) are associated with body mass index and anxiety symptoms in patients with fibromyalgia syndrome.

Keywords: Fibromyalgia, Single nucleotide polymorphism, Brain-derived neurotrophic factor, Mood symptom

Introduction

Etiology and pathogenesis of fibromyalgia syndrome (FMS) are still not clear and need to be elucidated more. In patients with FMS, familial inheritance might have an important role, since FMS is often found in more than one member of a family [1]. Therefore, studies concerning genetic factors associated with this disease are important and relevant. Genetic variations or single nucleotide

polymorphisms (SNPs) have been associated with different types of diseases. SNPs also affect the development of diseases [2], response to drug treatment [3] and pathogens [4]. Therefore studies of SNPs on FMS patients could advance the understanding of the pathogenesis of FMS.

Regarding the mode of inheritance in FMS, no specific genes have been reported. Only a few studies have suggested some underlying genetic polymorphisms in FMS patients, such as catechol-*o*-methyltransferase, serotonergic system of 5HTTA [5], and D4 dopamine receptor exon III repeat polymorphism [6]. Another gene of interest in FMS is brain-derived neurotrophic factor (*BDNF*),

*Correspondence: boya.nugraha@gmail.com

[†]Boya Nugraha and Sumadi Lukman Anwar contributed equally to this work

¹ Department of Rehabilitation Medicine, Hannover Medical School, Hannover, Germany

Full list of author information is available at the end of the article



although the pattern of familial inheritance is not clearly uncovered.

The role of *BDNF* in patients with FMS is already known to be unquestionable, since *BDNF* expression is found to be higher in patients with FMS compared to healthy subjects, both in plasma [7] and serum [8], as well as cerebrospinal fluid [9]. *BDNF* is also known to be related to mental symptoms, such as depression [10] and anxiety [11]. These symptoms are frequently observed in patients with FMS [12]. Additionally, our previous study showed a correlation of *BDNF* and depression in patients with FMS [8].

Therefore, it is important to explore if *BDNF* at the gene level (polymorphism) is also associated with the phenotype manifestations (symptoms) of FMS. This study aimed to examine the association of polymorphisms of *BDNF*, particularly rs2049046 and rs7124442, with several FMS symptoms.

Main text

Materials and methods

Patients

Seventy-two ($n=72$) female FMS patients with age range of 40–70 years were recruited from Rheumatology practices in Hannover, outpatients of the Department of Rehabilitation Medicine of Hannover Medical School and the patient organization “RheumaLiga”, Hannover. Recruitment was also performed by advertising the study in local newspaper. They were screened based on the definition of the American College of Rheumatology (ACR) criteria for fibromyalgia [13] by physicians of the Department of Rehabilitation Medicine, Hannover Medical School, Hannover, Germany. Patients had to understand the German language. Patients were not restricted to have their treatments either pharmacological or non-pharmacological.

Patients with recent or past history of psychiatric disorders, inflammatory, endocrine or other clinically significant chronic diseases (e.g., diabetes, rheumatoid arthritis, inflammatory bowel disease), abnormal liver function, pregnant and breastfeeding women were excluded.

Healthy controls (HCs)

HCs should be in the range of 18–70 years old. Forty-two ($n=42$) female HCs in the age range of 25–68 years old were recruited and selected. Most of them were staffs of Hannover Medical School, Germany. Exclusion criteria: chronic pain, psychiatric disorders, pregnancy and breastfeeding women.

Questionnaires

All patients and HCs completed pain intensity (Visual Analogue Scales; VAS [14]), intensity of fatigue (VAS

[8]), and depression and anxiety questionnaires (Hospital Anxiety and Depression Scale; HADS [15]).

Patients grouping

Subgroups of patients were assessed for body mass index (BMI) (18.5–24.9: low; 25.0–29.9: normal; >30.0: obese) [16], and the HADS-anxiety (HADS-A) and HADS-depression (HADS-D) scores using the classification given by Zigmond and Snaith [15] (HADS-A/HADS-D score < 8: no depression/anxiety; HADS-A/HADS-D score 8–10: mild depression/anxiety; HADS-A/HADS-D score > 10: positive depression/anxiety).

DNA extraction and generation of the polymerase chain reaction (PCR) product

Overnight fasting peripheral venous blood samples were collected in EDTA tubes (Monovette®, Sarstedt, Germany) from all patients and HCs between 08:00 and 10:00 am. Genomic DNA from whole blood containing EDTA was extracted by using DNeasy® Blood & Tissue Kit (Cat No. 69506, Qiagen) and according to the manufacturer’s instructions.

Prior to pyrosequencing analysis, 50 ng DNA from each sample was amplified with PCR using 0.4 μM pair of primers (Sigma-Aldrich, Darmstadt, Germany), 0.2 mM dNTP, 0.02 unit/L Taq polymerase (Invitrogen, Karlsruhe, Germany), 1× PCR buffer (Invitrogen, Karlsruhe, Germany), and purified HPLC water to add the total volume of 25 μL. The PCR process was optimized for each of the primer sets with final concentration of MgCl₂ (1.5 mM) and the annealing temperature (60 °C). The amplification was programmed using the following conditions: 15 min at 95 °C; 45 cycles of (94 °C for 30 s; 60 °C for 30 s; 72 °C for 30 s); and 72 °C for 5 min. PCR products were checked using DNA ladder (1 Kb Plus DNA Ladder Invitrogen) in 4% acrylamide gel and visualized by using UV light after incubation with ethidium bromide for 30 min for amount and specific sizes of 129 bp for rs2049046 and 140 bp for rs7124442, respectively. Sets of primers were designed using Pyromark Assay Design SW 1.0 (Qiagen, Hilden, Germany).

Primers for the two *BDNF* SNPs:

rs2049046

Forward primer 5'- 3' TCACCCAGGTGATTTTTA TGC

Reverse primer 5'- 3' CCAATTTGTGCAGACCTT AAA

rs7124442

Forward primer 5'- 3' TGTCCCTCAAAGGAAGC TG

Reverse primer 5'- 3' TGTAGATTTGTTTTGTGT TGTTTGAA

Pyrosequencing

Pyrosequencing analysis was done as described by Anwar et al. [15] using PyroMark Q96 (Qiagen, Hilden, Germany). Strand separation was done using streptavidin Sepharose® (SigmaAldrich, Darmstadt, Germany) using PyroMark Q96 Vacuum Workstation (Qiagen, Hilden, Germany).

The following pyrosequencing primers were used:

rs2049046: pyrosequencing primer 5'- 3' TGCTCC GAGGAGGTCC

rs7124442: pyrosequencing primer 5'- 3' ATGCTT GGAATATCTGC

Pyrograms were analyzed using PSQ 96MA SNP/Pyro-mark ID Software (Qiagen, Hilden, Germany) to determine the genotypes of each sample (Additional file 1:

Figure s1). We also performed Sanger sequencing for samples with polymorphisms of rs2049046 (A/T) and rs7124442 (A/G) as a validation.

Statistical analysis

T-tests were used to compare demographic and clinical features of HCs and patients with FMS. Chi square test or Fischer’s exact test was used to test (a) genotype and allele distribution, (b) genotype distribution in the sub-groups of BMI, anxiety and depression. ANOVA was used to compare any significance of clinical features among genotype distribution. Results with $p < 0.05$ were considered statistically significant using SPSS 19.0 (IBM Corp., Chicago). p values for Hardy–Weinberg equilibrium were also determined.

Table 1 Demographic of HC and FMS patients

Variables	HCs (n = 42)	FMS patients (n = 72)	$p^{\#}$
Age (years-old)	53.12 ± 0.83	54.19 ± 1.10	0.495
Pain (VAS)	0.95 ± 0.20	6.11 ± 0.21	<0.000
Fatigue (VAS)	1.80 ± 0.36	6.36 ± 0.23	<0.000
Anxiety (HADS-A)	4.62 ± 0.56	9.75 ± 0.44	<0.000
Depression (HADS-D)	2.81 ± 0.50	8.16 ± 0.46	<0.000
BMI (kg/m ²)	24.80 ± 0.57	27.70 ± 0.63	0.001
No. tender points	–	15.39 ± 0.27	–
Disease duration (years)	–	7.29 ± 0.59	–

BMI body mass index, FMS fibromyalgia syndrome, HADS Hospital Anxiety and Depression Scale, HCs healthy controls, VAS Visual Analogue Scales; Data presented as mean ± SEM

[#] t test

Results

Table 1 shows demographic and clinical features of HCs and patients with FMS. FMS patients have significantly higher scores in pain, fatigue, anxiety, depression. The BMI of patients with FMS is also higher as compared to HCs. The tender points of FMS patients in this study were 15. The patients also have had this disease for about 7 years.

The genotype and allele frequency distributions of two different types of *BDNF* SNPs (rs2049046 and rs7124442) are shown in Table 2. The genotype distribution and allele frequency of these *BDNF* SNPs were not significantly different between HCs and patients with FMS (rs2049046: $p > 0.05$; Odds ratio (OR): 0.55;

Table 2 Genotype and allele frequency distribution of BDNF SNPs in HCs and FMS patients

Group		Genotypes			p HWE [#]	Allele	
		rs2049046				rs2049046	
		AA	AT	TT		A	T
HC (n = 42)	n	8	27	7	0.063	43	41
FMS (n = 72)	n	26	33	13	0.656	85	59
χ^2		$p > 0.05^{\S}$				$p > 0.05^{\S}$	
		OR: 0.55					
Group		Genotypes			p HWE [#]	Allele	
		rs7124442				rs7124442	
		AA	GA	GG		A	G
HC (n = 42)	n	21	19	2	0.373	41	23
FMS (n = 72)	n	38	28	6	0.794	104	40
χ^2		$p > 0.05^{\S}$				$p > 0.05^{\S}$	
		OR: 1.02					

HWE Hardy–Weinberg equilibrium, OR odds ratio

^{\S} χ^2 Fisher’s exact test

[#] Chi-square test

rs7124442: $p > 0.05$; OR: 1.02). Additionally, the Hardy–Weinberg equilibrium of rs2049046 and rs7124442 in both patients and HC were not significantly different.

Table 3 shows the genotype distribution of each of the *BDNF* SNPs and clinical scores in patients with FMS. Significant difference was found in rs2049046 in anxiety score, but no differences in other clinical symptoms, such as pain fatigue, number of tender points, BMI and depression. FMS patients with lower anxiety score have TT genotype at rs2049046. In rs7124442, there were no significant differences in all clinical symptoms. Table 3 also shows the genotype distribution of the two *BDNF* SNPs, patients with FMS were sub-grouped according to their BMI, anxiety and depression scores. Significant differences were found in BMI of rs7124442 and anxiety of rs2049046, but not in the subgroup of depression.

Discussion

Pathogenesis of FMS is still not clear and need to be elucidated further. Studying genetic abnormalities in this group of patients are important and relevant. Thus, the purpose of the study was to elucidate the abnormalities of *BDNF* in patients with FMS from a genetic perspective. *BDNF* has been known to play a role in the neuronal system, including neuronal development and synaptic functions. Polymorphisms or variants of *BDNF* are associated with different types of diseases which reflect its involvement in neuronal function. The association of *BDNF* in chronic pain, including patients with FMS has been well-known. In this study, we observed no significant differences of *BDNF* between patients with FMS and healthy subjects at SNPs rs2049046 and rs7124442, which had not been determined previously in FMS. Some association has already been found in

Table 3 Genotype distribution of two *BDNF* SNPs of FMS and its clinical features

Clinical feature scores based on genotype distribution of <i>BDNF</i> SNPs								
	rs2049046			<i>p</i>	rs7124442			
	AA (n = 26)	AT (n = 33)	TT (n = 13)		GG (n = 6)	GA (n = 28)	AA (n = 38)	<i>p</i>
Pain	6.0 ± 0.4	5.4 ± 0.3	5.9 ± 0.6	N.S	6.5 ± 0.6	5.7 ± 0.4	5.6 ± 0.3	N.S
Fatigue	5.8 ± 0.4	6.0 ± 0.4	6.2 ± 0.6	N.S	5.0 ± 1.0	6.0 ± 0.4	6.1 ± 0.3	N.S
No. tender points	14.5 ± 0.6	15.4 ± 0.5	14.6 ± 0.8	N.S	15.5 ± 0.9	15.2 ± 0.5	14.6 ± 0.5	N.S
BMI	27.2 ± 1.1	27.6 ± 0.9	29.1 ± 1.5	N.S	24.7 ± 1.4	29.4 ± 1.1	26.9 ± 0.8	N.S
Anxiety	10.0 ± 0.8	10.4 ± 0.6	7.4 ± 1.1	<0.002 [§]	12.2 ± 1.9	9.6 ± 0.7	9.4 ± 0.6	N.S
Depression	8.3 ± 0.8	8.5 ± 0.7	7.5 ± 1.1	N.S	9.2 ± 1.4	7.8 ± 0.8	8.4 ± 0.6	N.S

Genotype distribution of two <i>BDNF</i> SNPs in different subgroups of clinical phenotypes								
rs2049046	rs7124442							
	BMI	AA	AT	TT	BMI	AA	GA	GG
18.0–24.9	11	12	3	18.0–24.9	19	5	3	
24.9–29.9	9	11	6	24.9–29.9	10	13	3	
>30	6	10	4	>30	9	10	0	
	N.S				<i>p</i> = 0.032 [#]			

rs2049046	rs7124442						
	HADS-A	AA	AT	TT	HADS-A	AA	GA
<8	7	3	6	<8	9	6	1
8–10	8	14	5	8–10	14	11	2
>10	11	16	2	>10	16	10	3
	<i>p</i> = 0.048 [#]				N.S		

rs2049046	rs7124442						
	HADS-D	AA	AT	TT	HADS-D	AA	GA
<8	12	14	8	<8	20	12	2
8–10	5	9	1	8–10	5	9	1
>10	10	9	4	>10	14	5	4
	N.S				N.S		

SNP single nucleotide polymorphisms, BMI body mass index, HADS-A HADS-anxiety, HADS-D HADS-depression, N.S not significant

[§] ANOVA test

[#] χ^2 Fisher's exact test

other patients with chronic pain (migraine) involving the SNP rs2049046 [17]. Interestingly, when we focused only on the FMS population, significant differences were observed in the BMI of rs7124442 and anxiety subgroup of rs2049046.

In FMS group, patients with AA homozygous and AT heterozygous at rs2049046 demonstrated higher anxiety scores compared to TT homozygous at rs2049046. Meanwhile, in a study of migraine populations both genotype and allele frequencies of *BDNF* rs2049046 were not significantly different [17], although the heterozygous AT genotype at this SNP was associated with the increased risk of migraine [18]. Regarding the mood/stress related situation, rs2049046 has been seen to show similar moderating effects on social stress-sensitivity [19].

It has been known that high score of BMI is associated with chronic pain, including FMS [19]. Even, obese subjects have higher chances of having FMS by 56% as compared to normal body weight individuals [20]. Additionally, obesity is also affected the severity of symptoms and disease activity in patients with FMS [19]. Through several studies, it has been shown that *BDNF* is associated with patients' BMI in different types of health conditions [20–23]. Therefore, subgrouping of patients according to their BMI was performed and investigated in this study. This hypothesis was approved in our result that *BDNF* rs712442 is associated with BMI.

The *BDNF* SNP at rs7124442 is located in the 3'-untranslated region (UTR) of the *BDNF* gene. The polymorphism at this site seems to influence the activity-dependent *BDNF* mRNA targeting, translation and/or degradation at active synaptic sites as well as the pro*BDNF* transcript [25, 26]. *BDNF* rs7124442 SNP has been shown to be functionally related to *BDNF* plasma levels in subjects with eating disorders [24]. This association has also been examined previously with respect to Alzheimer's disease [28]. Increased risk for major depression in two- and three-loci gene interactions in a Chinese population for SNPs rs7124442 and rs6265 has been observed [25], although in our FMS population, we could not observe the association of rs7124442 with mood related disorders.

The most studied *BDNF* variant, in general, is rs6265. Reflecting its function, this SNP has been reported in FMS patients with differences reflected in their BMI [27], which may be the only *BDNF* variation study in patients with FMS. Moreover, there are neuroplastic effects of mature *BDNF* that are also affected [28], which are suggested to be associated with several diseases, including major depression [29], anxiety [30], and hypothalamus–pituitary–adrenal-axis activity [31]. Therefore, our results according to our knowledge for both SNPs at rs7124442 and rs2049046 are new in the FMS population.

Conclusions

These results suggest that *BDNF* polymorphisms are associated with body mass index (rs7124442) and anxiety (rs2049046) in patients with FMS.

Limitations

One limitation in this study was the small sample size which may be the cause of our finding no significant differences for both *BDNF* SNPs between patients with FMS and HCs. More studies with larger numbers of samples are still needed to elucidate the role of genetic variations of *BDNF* in patients with FMS with further consideration of other factors, such as sex and the age of the patients. However, our results could observe some interesting findings in the FMS patient subgroups such as significant association of BMI and anxiety score with *BDNF* SNP at rs2049046 and rs7124442, respectively. This report is an exploratory study that could give important insights for further research, e.g. for sample size calculation for larger studies. Therefore, our current findings should be carefully extrapolated to the general population.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13104-020-05226-8>.

Additional file 1: Figure S1. Pyrograms from individuals with polymorphisms of rs712442 and rs2049046. Representative pyrograms from a HC with AT allele and a FMS patient with AT allele of rs2049046 were shown in panel A and B, respectively. Representative pyrograms from a HC with GA allele and a FMS patient with AA allele of rs712442 were shown in panel C and D, respectively.

Abbreviations

SNPs: Single nucleotide polymorphisms; FMS: Fibromyalgia syndrome; *BDNF*: Brain-derived neurotrophic factor; HC: Healthy control; VAS: Visual Analogue Scales; HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS-anxiety; HADS-D: HADS-depression; PCR: Polymerase chain reaction; BMI: Body mass index; N.S.: Not significant; UTR: 3'-untranslated region.

Acknowledgements

Open access funding provided by Projekt DEAL. We would like to thank to Prof. Ulrich Lehmann (Institute of Pathology, Hannover Medical School, Germany) who gave us permission to use pyrosequencing.

Authors' contributions

Conceptualization, BN, CG; methodology, BN, SLA; software, BN, SLA; validation, BN, SLA; formal analysis, BN, SLA; investigation, BN, SLA, CK; resources, BN, CG; data curation, BN, SLA, CK; writing—original draft preparation, BN; writing—review and editing, BN, SLA, CK, CG; visualization, BN; supervision, CG; project administration, BN, CK; funding acquisition, BN, CG. All authors read and approved the final manuscript.

Funding

This research received no external funding.

Availability of data and materials

Raw data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. All procedures were done with written consent of the subjects as approved by the Hannover Medical School Ethics Committee no. 5498. All patients agreed to participate on the basis of informed consent.

Consent for publication

Not applicable (no details, images or videos of individual person in this manuscript).

Conflicts of interest

The authors declare no conflict of interest.

Author details

¹ Department of Rehabilitation Medicine, Hannover Medical School, Hannover, Germany. ² Department of Surgery, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Received: 5 July 2020 Accepted: 5 August 2020

Published online: 28 August 2020

References

- Buskila D, Sarzi-Puttini P. Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome. *Arthritis Res Ther.* 2006;8:218. <https://doi.org/10.1186/ar2005>.
- Melchers I, Blaschke S, Hecker M, Cattaruzza M. The -786C/T single-nucleotide polymorphism in the promoter of the gene for endothelial nitric oxide synthase: insensitivity to physiologic stimuli as a risk factor for rheumatoid arthritis. *Arthritis Rheum.* 2006;54:3144–51. <https://doi.org/10.1002/art.22147>.
- Yang CH, Chuang LY, Cheng YH, Wen CH, Chang HW. Dynamic programming for single nucleotide polymorphism ID identification in systematic association studies. *Kaohsiung J Med Sci.* 2009;25:165–76. [https://doi.org/10.1016/S1607-551X\(09\)70057-9](https://doi.org/10.1016/S1607-551X(09)70057-9).
- Casas E, Garcia MD, Wells JE, Smith TP. Association of single nucleotide polymorphisms in the ANKRA2 and CD180 genes with bovine respiratory disease and presence of *Mycobacterium avium* subsp. *paratuberculosis*(1). *Anim Genet.* 2011;42:571–7. <https://doi.org/10.1111/j.1365-2052.2011.02189.x>.
- Matsuda JB, Barbosa FR, Morel LJ, Franca Sde C, Zingaretti SM, da Silva LM, Pereira AM, Marins M, Fachin AL. Serotonin receptor (5-HT 2A) and catechol-O-methyltransferase (COMT) gene polymorphisms: triggers of fibromyalgia? *Rev Bras Reumatol.* 2010;50:141–9.
- Buskila D, Cohen H, Neumann L, Ebsstein RP. An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. *Mol Psychiatry.* 2004;9:730–1. <https://doi.org/10.1038/sj.mp.4001506>.
- Haas L, Portela LV, Bohmer AE, Oses JP, Lara DR. Increased plasma levels of brain derived neurotrophic factor (BDNF) in patients with fibromyalgia. *Neurochem Res.* 2010;35:830–4. <https://doi.org/10.1007/s11064-010-0129-z>.
- Nugraha B, Korallus C, Gutenbrunner C. Serum level of brain-derived neurotrophic factor in fibromyalgia syndrome correlates with depression but not anxiety. *Neurochem Int.* 2013;62:281–6. <https://doi.org/10.1016/j.neuint.2013.01.001>.
- Sarchielli P, Mancini ML, Floridi A, Coppola F, Rossi C, Nardi K, Acciarresi M, Pini LA, Calabresi P. Increased levels of neurotrophins are not specific for chronic migraine: evidence from primary fibromyalgia syndrome. *J Pain.* 2007;8:737–45. <https://doi.org/10.1016/j.jpain.2007.05.002>.
- Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biol Psychiat.* 2005;57:1068–72. <https://doi.org/10.1016/j.biopsych.2005.01.008>.
- Suliman S, Hemmings SM, Seedat S. Brain-derived neurotrophic factor (BDNF) protein levels in anxiety disorders: systematic review and meta-regression analysis. *Front Integr Neurosci.* 2013;7:55. <https://doi.org/10.3389/fnint.2013.00055>.
- Fietta P, Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. *Acta Bio-medica Atenei Parmensis.* 2007;78:88–95.
- Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160–72.
- Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS Pain), numeric rating scale for pain (NRS Pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res.* 2011;63(Suppl 11):S240–52. <https://doi.org/10.1002/acr.20543>.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361–70.
- WHO. Body mass index—BMI. <https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>. Accessed 23 July.
- Sutherland HG, Maher BH, Rodriguez-Acevedo AJ, Haupt LM, Griffiths LR. Investigation of brain-derived neurotrophic factor (BDNF) gene variants in migraine. *Headache.* 2014;54:1184–93. <https://doi.org/10.1111/head.12351>.
- Lemos C, Mendonca D, Pereira-Monteiro J, Barros J, Sequeiros J, Alonso I, Sousa A. BDNF and CGRP interaction: implications in migraine susceptibility. *Cephalalgia.* 2010;30:1375–82. <https://doi.org/10.1177/0333102410368443>.
- van Winkel M, Peeters F, van Winkel R, Kenis G, Collip D, Geschwind N, Jacobs N, Derom C, Thiery E, van Os J, et al. Impact of variation in the BDNF gene on social stress sensitivity and the buffering impact of positive emotions: replication and extension of a gene-environment interaction. *Eur Neuropsychopharmacol.* 2014;24:930–8. <https://doi.org/10.1016/j.eurpsy.2014.02.005>.
- Akbarian SA, Salehi-Abargouei A, Pourmasoumi M, Kelishadi R, Nikpour P, Heidari-Beni M. Association of brain-derived neurotrophic factor gene polymorphisms with body mass index: a systematic review and meta-analysis. *Adv Med Sci.* 2018;63:43–56. <https://doi.org/10.1016/j.advms.2017.07.002>.
- Gunstad J, Schofield P, Paul RH, Spitznagel MB, Cohen RA, Williams LM, Kohn M, Gordon E. BDNF Val66Met polymorphism is associated with body mass index in healthy adults. *Neuropsychobiology.* 2006;53:153–6. <https://doi.org/10.1159/000093341>.
- Bonaccorso S, Sodhi M, Li J, Bobo WV, Chen Y, Tumuklu M, Theleritis C, Jayathilake K, Meltzer HY. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with increased body mass index and insulin resistance measures in bipolar disorder and schizophrenia. *Bipolar Disord.* 2015;17:528–35. <https://doi.org/10.1111/bdi.12294>.
- Monnereau C, Jansen PW, Tiemeier H, Jaddoe VW, Felix JF. Influence of genetic variants associated with body mass index on eating behavior in childhood. *Obesity.* 2017;25:765–72. <https://doi.org/10.1002/oby.21778>.
- Mercader JM, Fernandez-Aranda F, Gratacos M, Ribases M, Badia A, Villarejo C, Solano R, Gonzalez JR, Vallejo J, Estivill X. Blood levels of brain-derived neurotrophic factor correlate with several psychopathological symptoms in anorexia nervosa patients. *Neuropsychobiology.* 2007;56:185–90. <https://doi.org/10.1159/000120623>.
- Zhang CX, Chen YM, Chen WQ. Association of psychosocial factors with anxiety and depressive symptoms in Chinese patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2008;79:523–30. <https://doi.org/10.1016/j.diabres.2007.10.014>.
- Liu B, He W, Liu D (2019) Functional BDNF rs7124442 variant regulated by miR-922 is associated with better short-term recovery of ischemic stroke. *Ther Clin Risk Manag* 15:1369–1375. <https://doi.org/10.2147/TCRM.S225536>
- Huang R, Huang J, Cathcart H, Smith S, Poduslo SE. Genetic variants in brain-derived neurotrophic factor associated with Alzheimer's disease. *J Med. Genet.* 2007;44(2):e66.
- Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL, et al. Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci.* 2004;24(18):4401–11.
- Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, et al. Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. *Biol. Psychiat.* 2005;58(4):307–14.
- Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, et al. Interactions between BDNF Val66Met polymorphism and early life

stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular psychiatry*. 2009;14(7):681–95.

31. Schule C, Zill P, Baghai TC, Eser D, Zwanzger P, Wenig N et al. Brain-derived neurotrophic factor Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. *Psychoneuroendocrinology*. 2006;31:1019–25. <https://doi.org/10.1016/j.psyneuen.2006.06.002>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

