

The role of *BDNF* gene polymorphism in formation of clinical characteristics of migraine

Abstract

Objective: There is evidence that brain-derived neurotrophic factor (*BDNF*) has a role in migraine pathophysiology. In our research, association of substitutions in *BDNF* gene (rs6265, rs11030107, rs2049046) with clinical parameters of migraine is considered.

Background: Brain-derived neurotrophic factor (*BDNF*) is a neurotrophin presented widely in central nervous system. *BDNF* regulates axonal growth and differentiation; synapse formation; activity of dopaminergic, serotonergic, GABA-ergic, and cholinergic neurons. Apparently, *BDNF* participates in the development of the primary forms of headaches.

Patients and Methods: The research included 155 patients with migraine (according to ICHD-III, 2013). The control group consisted in 203 unexamined individuals. Patients underwent clinical neurological examination and blood sampling. Genotypes were determined using PCR-RFLP method.

Results: We did not find a significant association between studied SNPs and migraine. We showed that the TT-genotype of rs2049046 influences the migraine chronification the episodes transform by regression of prodromal period, and the endurance of episodes themselves shortens. The GG genotype of rs6265 has no significant influence on the formation and manifestation of migraine. Possession of G-allele of rs1030107 influences the formation of drug abuse and higher frequency of photo- and phonophobia during the migraine episode.

Conclusions: Our results suggest that the substitutions rs2049046 and rs1030107 in *BDNF* gene play role in formation of clinical manifestations of migraine.

Keywords: Migraine, Clinical manifestations, Genetic association study, Brain-derived neurotrophic factor, Single nucleotide polymorphism

Volume 4 Issue 2 - 2016

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Received: November 28, 2015 | **Published:** January 20, 2016

Abbreviations: *BDNF*, Brain-Derived Neurotrophic Factor; *CGRP*, Calcitonin Gene-Related Peptide (*CALCA* gene); TrkB, Tyrosine kinase Beta

Introduction

Brain-derived neurotrophic factor (*BDNF*) is a neurotrophin presented widely in central nervous system (CNS). The general function of *BDNF* in CNS is maintaining neuronal viability in ischemic condition, as well as providing neuronal plasticity and modulating behavioral activity. *BDNF* regulates axonal growth and differentiation of neurons; synapse formation; activity of dopaminergic, serotonergic, GABA-ergic, and cholinergic neurons. *BDNF* also supports cognitive processes such as learning and memory. *BDNF* modulates both activating and inhibiting synapses affecting sodium channels and thus regulating neuronal excitability. Human *BDNF* gene is located in 11p14.1 region. It has 9 promoters and 11 exons. The sequence that encodes functional protein resides in the last exon. Alternative promoters provide 9 tissue- and time-specific transcripts that encode various leading peptides of pre-pro-protein *BDNF*.^{1,2} The gene is expressed in nociceptive sensory neurons modulating metabotropic and ionotropic glutamate receptors. *BDNF* mRNA is translated into pre-pro-*BDNF* which is then processed into pro-*BDNF* and delivered to synapse. In the synapse, pro-*BDNF* is processed to form functional *BDNF* molecule. Targets of *BDNF* are tyrosine kinase receptors (TrkB). Activation of TrkB receptors triggers cascades that provide biological effects of *BDNF* (see Figure 1):

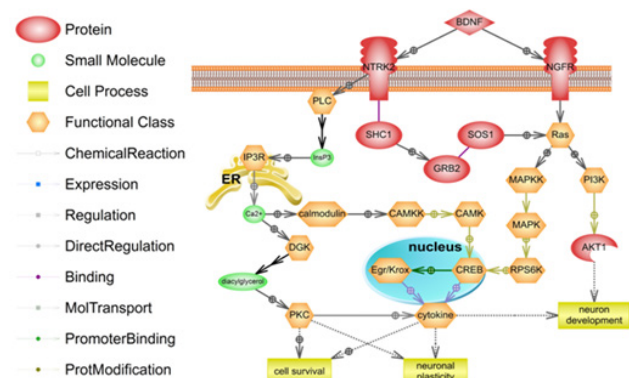


Figure 1 BDNF activated signaling pathways.

BDNF can interact with two receptors: NGFR (nerve growth factor receptor) and NTRK2 (neurotrophic tyrosine kinase, receptor, type 2). Both can activate PI3K (phosphatidylinositol 3-kinase) through activation of Ras (RAS oncogene homolog). PI3K activate AKT1 that play important role in neuron development. Also Ras through MAPKK (mitogen-activated protein kinase kinase or ERK activator kinases) activate MAPK (mitogen-activated protein kinase or ERK MAP kinases). The MAPK regulate activation of RPS6K (ribosomal protein S6 kinase) which phosphorylate CREB. Transcription factor CREB is a positive regulator of *Egr/Krox* (*Egr* transcription factors) transcription. Activation of CREB and *Egr/Krox* lead to expression of cytokines - important players in cell survival

and in neuronal plasticity and neuron development too. NTRK2 also can activate PLC (phospholipase C) which produce InsP3. The last activate IP3R that lead to increase of intracellular calcium (Ca²⁺). Calcium leads to activation of CAMKK-CAMK regulation (calmodulin-dependent protein kinase kinases and calmodulin-dependent kinases, respectively) through interaction with calmodulin. Then CAMK phosphorylate and activate Egr/Krox and expression of cytokines. In another way Ca²⁺ can activate diacylglycerol kinase, which activate PKC (protein kinase C) - regulator of cell survival and neuronal plasticity - through diacylglycerol. InsP3: inositol 1,4,5-trisphosphate; ER: endoplasmic reticulum. Designed in PathwayStudio 10.0 (Elsevier).

- Activation of protein kinases that support neuronal survival;
- Activation of RAS-dependent signaling pathway that supports growth and differentiation of neuronal cells;
- Activation of phospholipase C that indirectly stimulates expression of cytokines and Egr/Krox transcription factors.

The role of *BDNF* in the development of emotional affective disorders is the most studied one. For instance, major depression is accompanied with altered levels of *BDNF* and activity of TrkB receptors in key structures of “neuronal depression fields”: decrease of *BDNF* in prefrontal cortex and hippocampus, and increase of *BDNF* in the nucleus accumbens, amygdaloid complex, and ventral zone of operculum. The activity of TrkB receptors is increased in the prefrontal cortex and hippocampus, while no changes were found in nucleus accumbens. Oppositely, increased level of *BDNF* and high activity of TrkB receptors in the nucleus accumbens were registered in patients with addiction disorders.³ Patients with major depression are characterized with lower level of *BDNF* in blood serum which correlates with severity of depression.⁴ More, successful therapy with antidepressants is accompanied with decrease of *BDNF* level.⁵ Six single-nucleotide polymorphisms were recorded in *BDNF* gene, which correlate with depression.⁶ One of the most precisely studied substitutions is G/A transition in position 196 within exon 8 (rs6265) resulting in Val to Met substitution in codon 66 (5'-region of *proBDNF*).⁷ The substitution itself has no influence on *BDNF* protein but activity of *BDNF*-dependent secretion becomes suppressed. It is followed by abrupt changes in intracellular transfer and folding of *proBDNF*. It is proposed that this alteration may represent marker for resistant depression. However, such correlation was revealed only in Asiatic population during meta-analysis.⁸

The role of brain neurotrophic factors in the development of chronic pain syndromes comorbid with depression is now under active investigation. The *BDNF* is proposed to be key substance which provides transmission of signal from glial cells to neurons. On one hand, *BDNF* activates neurons of I plate of posterior horn of spinal cord; this area is known to participate in pain transmission.⁹ On the other hand, genotype GG of *BDNF* gene (rs6265) decreases the activity of brain neurotrophic factor. Absence of habituation after repeated pain stimuli was recorded in healthy individuals with GG genotype. It is possibly connected with anomalies of *BDNF*-mediated mechanisms of synaptic memory and plasticity or direct neurotransmitter effect of neurotrophin.¹⁰

Studies on role of *BDNF* in development of primary forms of headaches are of special interest. Data on changes of *BDNF* content in serum of patients' blood are controversial. For example, decrease of *BDNF* in blood serum was reported for migraine (both with and without aura) and cluster headache.¹¹ In another case, the significant increase of *BDNF* content was found in plasma during migraine

episode in comparison with period between episodes, and also between patients having tension headaches and healthy people.¹² As Sarchielli with coauthors reported that chronic migraine and other chronic pain syndromes (fibromyalgias) are associated with increase of *BDNF* content in cerebrospinal fluid.¹³ In latest study lower levels of *BDNF* in plasma from patients with chronic migraine was shown.¹⁴ The connection between primary headaches and *BDNF* is not random: the coexpression of brain neurotrophic factor and calcitonin gene-related peptide (*CGRP*, main pain transmitted for migraine) was described in transgeminal ganglion by Buldyrev et al.¹⁵ Is there any relation between *BDNF* gene polymorphism and migraine formation? No differences in frequencies of allele variants of rs6265 between healthy people and patients were found in research of Marziniak et al.¹⁶ No significant influence of genotype on clinical presentation was also recorded. However, Lemos and coauthors¹⁷ studied changes in genes *BDNF* (rs7124442, rs6265, rs11030107, rs2049046) and *CGRP* (rs1553005) and obtained somewhat contradictory results. Patients with migraine were reported to have significantly higher frequency of G-allele in rs6265 and genotype AT in rs2049046, when comparing with healthy people. In addition, correlation was found between genotype TT in rs2049046 of *BDNF* and C-allele in rs1553005 of *CGRP*, which evidences for linkage of these genes. They are localized in contiguous loci (segments 11p14.1 and 11p15.2 for *BDNF* and *CGRP*, respectively). In 2014 Sutherland et al.¹⁸ confirmed previous studies that the functional *BDNF* SNP rs6265 (Val66Met) is not associated with migraine. However, they found that rs2049046, which resides at the 5' end of one the *BDNF* transcripts, may be associated with migraine. The present study was aimed at influence of substitutions in *BDNF* (rs6265, rs11030107, and rs2049046) on development and clinical manifestation of migraine.

Materials and methods

Patients

Totally 155 patients with migraine constituted the experimental group; all those patients applied to University Headache Clinic in 2013-2014 years. The age of patients comprised 41.6±12.5 years. 67.8% had episodic migraine, 32.2%- chronic migraine, 18.5%-migraine with aura. The control group consisted of 203 (healthy volunteers), living in the city of Moscow (without diagnosis of migraine or other type of headache). People of both groups were of similar age (from 18 to 57 years). Diagnosis of headache form was made in accordance with criteria of International Classification of Headache Disorders III-beta (2013).¹⁹ All the patients underwent a neurological interview and examination. Clinical information with regard to migraine characteristics was extracted from our database. Blood samples were collected by a qualified phlebologist. The research has been carried out in accordance with ethical standards laid down in the 1964 declaration of Helsinki and was approved by local ethics committee of Vavilov Institute of General Genetics Russian Academy of Science (Moscow). Written informed consent was obtained from all the participants.

Molecular genetics and statistical analysis

DNA was extracted according to protocol to commercial DNA MagnaTM DNA Prep 200 kit (Isogen Lab Ltd., Moscow, Russia). Genotypes were identified by PCR-RFLP method. The PCR was conducted according to protocol of commercial kit GenePakTM PCR Core (Isogen Lab Ltd., Moscow, Russia). Primers were synthesized by DNA Synthesis, LLC (Moscow, Russia). The restriction endonucleases produced by SibEnzyme Ltd. (Novosibirsk, Russia) were used for digestion; reactions were carried out in conditions

recommended by producer. Primer sequences together with restriction endonucleases are listed in Table 1.

The analysis of allele frequencies and their association with migraine was conducted using χ^2 method (Pearson's chi-square test) and using HaploView 4.2 software. Statistic processing of obtained results was conducted using parametrical (Student's and Fisher's tests) method with assistance of SPSS v17 software package.

Results

The allele and genotype frequencies we acquired are presented in Table 2. The distribution of genotype frequencies for rs6265 in studied groups (control: $\chi^2=0.00$, $p=0.97$; patients: $\chi^2=2.26$, $p=0.13$) and for rs11030107 in control group ($\chi^2=0.01$, $p=0.92$) corresponded to Hardy-Weinberg equilibrium. The deviation from Hardy-Weinberg equilibrium was observed for rs2049046 in distribution of genotype frequencies (control: $\chi^2=11.73$, $p<0.001$; patients: $\chi^2=12.93$, $p<0.001$) and for rs11030107 in patients ($\chi^2=5.28$, $p=0.02$).

Analysis using Pearson's chi-square test showed no association with migraine for all three SNPs (Table 2).

We analyzed our experimental data using HaploView 4.2 software in order to reveal associations between studied SNPs and migraine. The results of this analysis are presented in Table 3.

We did not find any significant difference in frequencies of studied alleles between patients and control group and therefore conclude that generally there is no association between studied SNPs and migraine. Association of allele G in rs6265 substitution in BDNF gene does not pass permutation test. We also analyzed the inheritance of studied SNPs (linkage disequilibrium test). High χ^2 value of 5.365 (the number of degrees of freedom- 1, difference is significant at $p=0.021$, $D'=0.28$, $LOD=0.94$, $R^2=0.04$) was observed only for the pair of

polymorphic loci rs6265 and rs2049046. This allows us to reject the hypothesis of independent inheritance and conclude joint inheritance of the following allele combinations: rs6265-A/ rs2049046-A and rs6265-G/ rs2049046-T.

Meanwhile, the influence of studied substitutions on clinical parameter of the disease is of interest, as well. As distortions in regulation of BDNF content play the important role in development of emotionally-affected disorders, we also conducted the comparative analysis of frequencies of BDNF genotypes in groups with episodic and chronic migraine (Table 4). As seen from this table, GG-variant of rs6265 substitution possibly contributes into development of chronic migraine, also being discussed as factor of depression pathogenesis.

To evaluate influences of substitutions in BDNF gene on manifestation of symptoms, we also performed comparative analysis of different allele variants. As frequencies of AA-genotype of rs2049046, AA-genotype of rs6265 and GG-genotype of rs11030107 were low enough, these genotypes were analyzed together with heterozygotes (Table 5). Our data evidence for fact that the TT-genotype of polymorphism rs2049046 influences the migraine chronification the episodes transform by regression of prodromal period, and the endurance of episodes themselves shortens. Additionally, patients with TT-genotype are significantly more often characterized with sickness which regresses to a lesser degree during migraine transformation. The GG genotype of rs6265 has no significant influence on formation and manifestation of migraine. Possession of G-allele of rs1030107 influences the formation of drug abuse. For example, abuse of analgesics (especially codeine-containing) is more often observed among carriers of G-allele, and the drug abuse is expressed significantly stronger. Except this, patients bearing G-allele in rs11030107 are characterized with higher frequency of photo- and phonophobia during migraine episode.

Table 1 Primer sequences and restriction endonuclease used in the work

Substitution	Location in the gene	Sequence of primers	Restriction enzyme	RFLP product length, bp
rs6265 c.196G>A (p.Val66Met)	Exon 2	F: GAGGACAAGGTGGCTTGGCCTA R: GGCCGAACCTTCTGTGCCTC	PspC I	AA=157; GG=116+41; AG=157+116+41
rs11030107 c.-21-14703T>C	Intron 1	F: CAGGTGGGGCTTGTCTTTCAAG R: GCATGTTCTCCCTTTAGGGACAT	Taq I	AA=118; GG=93+25; AG=118+93+25
rs2049046 c.-22+18416A>T	Intron 3	F: CAAAGTGTGACTTCAGATTGTCTG R: AGAATAAGACAGCAGTACCGTACTT	Hinf I	AA=166+35; TT=198; AT=198+166+35

Table 2 Frequencies of alleles and genotypes for studied genes and results of Pearson's chi-square test

SNP	Genotype frequencies			Allele frequencies	
	AA	AG	GG	A	G
rs6265					
patients	0.01	0.33	0.66	0.18	0.82
controls	0.02	0.24	0.74	0.14	0.86
	$\chi^2=4.29$, $p=0.12$			$\chi^2=2.45$, $p=0.12$	
rs11030107					
patients	0.67	0.33	0	0.83	0.17
controls	0.76	0.23	0.1	0.87	0.13
	$\chi^2=4.18$, $p=0.12$			$\chi^2=0.97$, $p=0.33$	
rs2049046					
patients	0.13	0.64	0.23	0.46	0.56
controls	0.14	0.58	0.28	0.43	0.57
	$\chi^2=1.82$, $p=0.40$			$\chi^2=0.27$, $p=0.60$	

Notes: χ^2 – chi-square value, p -value – significance value. The number of degrees of freedom – 2; difference is not significant at $p > 0.05$.

Table 3 The associations between studied SNPs and migraine

Marker	Associated allele	Allele ratio; case, control	χ^2	p-value	χ^2 after permutation test	p-value after permutation test
rs2049046	A	134:164, 167:241	1.146	0.2843	1.146	0.8700
rs6265	G	239:59, 300:108	4.245	0.0394	4.245	0.1860
rs11030107	G	48:248, 23:127	0.058	0.8097	0.058	1.0000

Notes: χ^2 – chi-square value, p-value – significance value. The number of degrees of freedom – 1; difference is not significant at $p > 0.05$.

Table 4 rs6265, rs11030107 and rs2049046 genotypes of patients with chronic and episodic migraine

Genotype	Episodic migraine %	Chronic migraine %	p-value
rs2049046			
AA	11.1	10.9	0.9
AT	81.1	65.2	0.04
TT	7.8	23.9	0.008
rs6265			
AA	2.3	0	0.2
AG	31.4	32.6	0.8
GG	66.2	67.4	0.9
rs11030107			
AA	70.4	62.2	0.3
AG	29.6	33.3	0.6
GG	0	4.4	0.06

Table 5 The features and specter of migraine symptoms in patients with different genotypes

Symptom	rs2049046			rs6265			rs11030107		
	TT	AA+AT	p	GG	AA+AG	p	AA	AG+GG	p
Representation of chronic migraine, %	70.3	38.8	0.008	36.0	34.1	0.9	32.9	42.9	0.3
Representation of drug abuse, %	44.4	31.1	0.3	36.4	31.1	0.6	29.4	45.3	0.04
Number of single doses of analgesics per month	42.6±65.7	31.3±57.9	0.5	31.5±53.7	38.1±70.6	0.6	30.4±55.8	41.0±70.2	0.04
Abuse of codeine-containing drugs, %	35.7	34.4	0.9	34.3	39.4	0.6	28.6	48.2	0.04
Age of migraine manifestation	17.5±10.2 years	18.1±8.7 years	0.8	18.8±9.7 years	16.6±6.7 years	0.2	18.2±8.6 years	17.4±9.7 years	0.7
Duration of disease	24.8±12.2 years	23.4±12.6 years	0.7	23.3±12.4 years	23.5±13.2 years	0.9	24.0±12.3 years	21.1±12.5 years	0.3
Positive hereditary history for migraine, %	57.2	73.4	0.2	68.0	75.6	0.4	73.1	62.9	0.3
Presence of aura, %	26.7	17.4	0.4	17.9	19.1	0.9	21.7	13.5	0.3
Presence of prodrome, %	13.3	38.3	0.05	36.1	31.6	0.6	36.8	35.7	0.9
Presence of postdrome, %	14.3	31.6	0.1	23.9	39.5	0.09	27.8	37.0	0.4
Number of migraine days per month	12.1±8.1	8.1±9.8	0.1	9.3±10.5	7.7±9.1	0.4	8.3±9.6	9.7±10.9	0.5
Duration of migraine attack	19.3±12.8 hours	37.8±27.6 hours	0.02	35.1±28.4 hours	35.6±25.4 hours	0.9	37.9±28.9 hours	29.0±21.3 hours	0.07
Pain intensity	8.1±1.3 VAS points	8.3±1.5 VAS points	0.5	8.3±1.6 VAS points	8.4±1.3 VAS points	0.9	8.3±1.5 VAS points	8.4±1.6 VAS points	0.2
Throbbing pain, %	78.6	77.7	0.9	75.3	81.0	0.5	79.0	77.8	0.9
Allodynia during episode, %	38.5	47.6	0.5	41.1	56.1	0.2	44.7	50.0	0.6
Time of most intensive pain achievement	76.6±58.3 minutes	98.3±81.1 minutes	0.4	92/5±74.5 minutes	103.3±86.8 minutes	0.5	99.4±84.6 minutes	82.1±48.4 minutes	0.2
Recurrent headache, %	20.0	43.1	0.2	43.1	40.0	0.7	38.3	45.5	0.6
Sickness, %	100	89.3	0.001	90.1	92.9	0.6	91.4	80.1	0.4
Vomiting, %	26.7	50.0	0.09	45.6	52.4	0.5	45.7	50.0	0.7
Photophobia, %	86.7	85.1	0.9	86.4	83.3	0.7	82.7	94.4	0.02
Phonophobia, %	86.7	83.9	0.9	86.4	81.0	0.4	82.7	94.4	0.02
Osmophobia, %	42.9	54.1	0.4	50.6	52.4	0.9	52.5	54.3	0.9

Table Abbreviations: VAS: Visual Analogue Scale.

Discussion

The present investigation demonstrated that the SNPs rs6265, rs2049046 and rs11030107 in *BDNF* gene are not associated with migraine in the sample studied by us. No such correlation was found and in work of Marziniak et al.¹⁶ It is possibly connected with specificity of samples of patients. In our investigation, we used DNA from patients of specialized medical center for headaches; the third part of them had chronic migraine, drug abuse, and depression. However, TT genotype of rs2049046 appeared to be more important for development of chronic migraine. It was also found out that carriers of G-allele of rs11030107 are more predisposed to heavy drug abuse and often consume with codeine-containing drugs.

Polymorphism of *BDNF* gene may underlie comorbidity between migraine and emotionally-affected disorders (especially depression), this phenomenon being demonstrated in large-scale studies.²⁰ It is proposed that succession of stress events leads to decrease of content of brain neurotrophic factor as a result of increase of activity of hypothalamo-pituitary-adrenal axis.²¹ TrkB receptors are widely distributed in serotonergic neurons of raphe nucleus,³ the structure responsible for both depression development and chronic headache. The *BDNF* was proved to move from hippocampus to raphe nucleus via retrograde transport,²² thus activating serotonergic neurons. Moreover, *BDNF* possesses direct antidepressant effect²³ and mediates an action of selective inhibitors of serotonin reuptake.³ It might be that normally pain stimulus leads to secretion of calcitonin gene-related peptide which in its turn causes increase of *BDNF* level. The latter activates central antinociceptive systems, which is a neurogenetic mechanism. The malfunction of *BDNF* in patients with migraine (e.g., in case of mutation in rs6265) defect of central antinociceptive systems arises in response to pain impulsion and *CGRP* secretion, which was confirmed in study of trigeminal induced potentials by Di Lorenzo with colleagues.²⁴

The role of *BDNF* in development of addictions and drug abuse is also of significant interest. For example, use of prohibited psychostimulant agents (cocaine, amphetamines) leads to increase of *BDNF* level. Morphine injection inhibits *BDNF* synthesis in ventral area of operculum, but after cessation of opiates' injections synthesis of *BDNF* reactivates.³ The *BDNF* content is increased also in addictions which do not deal with drugs e.g. in case of gambling.²⁵ The rs6265 substitution is also a risk factor for nicotine addiction and more severe alcoholic addiction.³ The amino acid substitution Val66Met (and subsequent decrease in intensity of *BDNF* synthesis) is also typical for anomalies of food behavior.²⁶ We demonstrated interrelation between substitution in rs11030107 in *BDNF* gene and development of drug abuse (primarily codeine-containing drugs) in patients with migraine.

Conclusion

Hence, brain neurotrophic factor modulates numerous physiological functions in the central neural system and may participate in different stages of migraine pathogenesis. The genetically determined *BDNF* deficiency may lead to malfunction of activation of central analgesic actions in response to nociceptive stimulation as one of the mechanisms underlying migraine chronification. Besides, polymorphisms in *BDNF* gene may serve as common reasons for development of both migraine and associated depression, as well as of drug abuse phenomenon.

Acknowledgements

The authors thank the subjects for their participation in this

research study. We thank Paul Golovatenko-Abramov for help with manuscript preparation and Taisiya Kochetkova for help with genetic analysis. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None.

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