Peregud *et al. Egyptian Liver Journal* (2023) 13:59
https://doi.org/10.1186/s43066-023-00296-2

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Relationship between BDNF gene polymorphisms and alcohol-related liver cirrhosis

Danil I. Peregud[1,2*], Valeria Yu. Baronets[1], Anna S. Lobacheva[1], Alexandr S. Ivanov[3], Irina V. Garmash[3], Olga S. Arisheva[3], Zhanna D. Kobalava[3], Sergey V. Pirozhkov[4] and Natalia N. Terebilina[1]

Abstract

Background and aim Brain-derived neurotrophic factor (BDNF) functions not only in the brain but also in peripheral tissues such as the liver. Genetic factors determine the development of alcohol dependence and somatic consequences of chronic intoxication, especially liver cirrhosis. The BDNF gene polymorphisms are associated with alcohol dependence; however, their relationship with the development of alcohol-related liver cirrhosis (ALC) has not yet been established. This study evaluated the association between single-nucleotide polymorphisms (SNPs) within the BDNF gene and liver cirrhosis in heavy drinkers.

Methods BDNF-related SNPs rs925946, rs6265, rs10835210, rs7103411, and rs75945125 were determined using real-time PCR in heavy drinkers with and without liver cirrhosis. Single SNPs and defined haplotypes within the BDNF gene were tested for association with ALC.

Results According to both codominant and recessive genetic models, carriers of the rs925946 TT genotype have an elevated risk of liver cirrhosis development with odds ratios (confidence intervals) 6.287 (1.286–30.738) and 6.321 (1.317–30.348), respectively. BDNF SNPs rs6265, rs10835210, rs7103411, and rs75945125 do not associate with risk of ALC. One block of haplotypes consisting of rs10835210 and rs7103411 demonstrated linkage disequilibrium (D' = 1 and r^2 = 0.228). The revealed haplotypes do not associate with the development of liver cirrhosis in alcohol heavy drinkers.

Conclusion Thus, the BDNF rs925946 SNP is associated with the risk of ALC in heavy drinkers. Future investigations of the BDNF gene-related genetic markers of ALC will help to objectively assess the risk and severity of liver damage and correct the corresponding therapy.

Keywords Alcohol use disorder, Alcohol-related liver cirrhosis, Genetic polymorphisms, BDNF

*Correspondence:
Danil I. Peregud
peregud_d@yahoo.com
Full list of author information is available at the end of the article

Introduction

Excessive alcohol consumption may induce the development of alcohol-related liver disease (ALD) gradually progressing from fatty liver to steatohepatitis, which can eventually lead to alcohol-related liver cirrhosis (ALC) in 8–20% of heavy drinkers [1]. Both alcohol dependence and somatic consequences of chronic intoxication, such as liver cirrhosis, are genetically determined. Genetic background is the main risk factor of ALC with heritability ranging from 21 to 67% [2]. Finding and validation of the genetic markers of ALC will supplement the battery of clinical tools assessing the severity of alcohol-induced liver damage and help to correct the corresponding therapy [3].

Clinical data demonstrate that polymorphisms within the gene encoding the brain-derived neurotrophic factor (BDNF) and circulating BDNF concentration may be biomarkers of drinking behavior in alcohol dependence and recovery during the abstinence period [4–6]. BDNF gene polymorphisms are associated with alcohol dependence; however, their relationship with the development of ALC has not yet been established.

BDNF is a secreted protein possessing neuroregulatory properties. It modulates neurogenesis, differentiation, and survival of neurons and is involved in activity-dependent synaptic plasticity, linking synaptic activity with long-term functional and structural modification of synaptic connections [7, 8]. Physiological activity of BDNF is not limited to the brain. BDNF also functions in peripheral tissues such as the liver where it is implicated in direct or indirect regulation of basic hepatic metabolic processes [9]. BDNF is believed to be a key neurotrophin contributing to molecular, structural, and functional disturbances in the brain accompanying alcohol use disorder (AUD) [10, 11]. However, little is known about BDNF involvement in alcohol-related liver damage.

Meanwhile, few investigations have shown the relationship between circulating BDNF levels and ALD. Serum levels of BDNF are associated with liver stiffness in individuals with AUD [12]. In particular, both elastometry measurements and serum GGT (γ-glutamyl transferase) activity predicted BDNF levels during 2 months of abstinence in a regression model [12]. On the contrary, serum BDNF was poorly correlated with the liver function tests, as shown by the absence of its relationship with bilirubin, prothrombin activity, and Child–Pugh score in patients with AUD [13].

Few studies focus on the role of BDNF in liver cirrhosis. One work described the association of BDNF gene single nucleotide polymorphisms (SNPs) with hepatitis B virus (HBV)-induced cirrhosis, implying the possibility that ALC may also be influenced by the BDNF gene [14]. Additionally, cirrhotic patients have higher serum BDNF levels than healthy individuals independently on the presence of depression or anxiety symptoms [15]. Moreover, patients with lower Child–Pugh score have higher serum BDNF levels [15].

To date, there are no data demonstrating associations between genetic markers within the BDNF gene and the development of ALC. Meanwhile, BDNF-related SNPs may interact with ALC. We made an analysis of the existing literature and chose BDNF polymorphisms that matched the following criteria: SNP associates with cirrhosis of etiology non-related to alcohol consumption and/or associates with alcohol dependence or affects circulating BDNF levels or associates with cirrhosis-provoking factors. Parameters of investigated BDNF SNPs (namely rs6265, rs10835210, rs7103411, rs75945125, and rs925946) are listed in Table 1. BDNF SNP rs6265 and rs6265-rs10835210 haplotypes are associated with viral-induced cirrhosis [14]. Additionally, both rs6265 [16, 17] and rs10835210 [18] have been shown to associate with alcohol dependence. BDNF SNP rs7103411 associates with comorbid AUD [19, 20]. Additionally, we studied two polymorphic loci rs925946 and rs75945125, which are not directly related to cirrhosis or alcohol dependence. rs75945125 is a SNP associated with circulating

Table 1 Studied BDNF polymorphisms

SNP (major/minor alleles)	Position (GRCh38.p13)	Hardy–Weinberg equilibrium χ^2 (p)		Reported MAF (1000 Genomes Project)	Observed MAF
		AUD, $n = 71$	ALC, $n = 110$		
rs925946 (G/T)	chr11:27645655, 3′-UTR (reverse strand)	0.325 (0.850)	3.369 (0.186)	0.253	0.243
rs6265 (G/A)	chr11:27658369, Exon – missense	1.380 (0.502)	0.870 (0.647)	0.201	0.146
rs10835210 (C/A)	chr11:27674363, Intron	0.077 (0.963)	1.750 (0.417)	0.245	0.450
rs7103411 (T/C)	chr11:27678578, Intron	2.386 (0.303)	3.937 (0.140)	0.247	0.157
rs75945125 (T/C)	chr11:27757378, 5′-UTR (reverse strand)	0.138 (0.933)	0.366 (0.833)	0.104	0.050

Abbreviations: *BDNF* brain-derived neurotrophic factor, *SNP* single nucleotide polymorphism, *UTR* untranslated region, *AUD* alcohol use disorder, *ALC* alcohol-related liver cirrhosis, *MAF* minor allele frequency

BDNF levels, which maps near the BDNF gene [21]. rs925946 is located in the intergenic region downstream of the BDNF gene (or intronic in BDNF-AS gene) and is strongly associated with obesity [22, 23], which is considered to be a risk factor for cirrhosis. Based on the literature data, we came up with the hypothesis that BDNF SNPs or haplotypes presented in the table may be associated with ALC. Thus, this study investigated a possible link between BDNF gene polymorphisms and ALC.

Methods

Subjects

Individuals of Caucasian ancestry with excessive alcohol consumption were recruited from Vinogradov Moscow City Clinical Hospital No.64 and Clinic affiliated with Serbsky National Medical Research Center for Psychiatry and Drug Addiction, Moscow, Russia. During the period from 2016 to 2020, one hundred eighty-one eligible patients were enrolled into the study. Subjects with verified cancer or positive for hepatitis B or C viruses were excluded from the study. Patients were divided into AUD without clinically significant signs of liver cirrhosis (AUD, $n = 71$) and alcohol-related liver cirrhosis (ALC, $n = 110$) groups. All patients were considered heavy alcohol drinkers as they had a history of alcohol consumption of more than 14 standard drinks per week for several years. The studied subjects have been consuming more than 100 g of alcohol per day for at least 10 years, taking the amounts acknowledged to provoke ALD [24]. Problems related to alcohol drinking were screened by self-reported interviews using the CAGE (Cut down, Annoyed, Guilty, Eye-opener) and AUDIT (alcohol use disorders identification test) questionnaires. The diagnosis of liver cirrhosis was based on the clinical presentation of hepatic encephalopathy and jaundice, presence of portal hypertension, ascites, and hepatomegaly as determined by ultrasonography, presence of esophageal varices according to upper gastrointestinal endoscopy, and METAVIR equivalent stage F4 according to ultrasound elastography. Liver cirrhosis was staged by calculation Child–Pugh score. Clinical and laboratory characteristics of patients (Table 2) included in this study were described previously [25]. The study protocol followed the Declaration of Helsinki and was approved by the Institutional Ethics Committee. All subjects provided written informed consent for research studies.

Biochemistry

The serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, alkaline phosphatase (ALP), and total bilirubin were measured on a SAPPHIRE 400 biochemical analyzer (Hirose Electronic System Co., Ltd., Japan) with compatible kits of reagents (Randox Laboratories Ltd., UK).

Table 2 Clinical and laboratory characteristics

Parameter	AUD, $n = 71$	ALC, $n = 110$	p value
Platelet count, $\times 10^9$/L	216.5 (169.0; 251)	164.5 (113.5; 243.5)	$p = 0.003$
ALT, U/L	27.9 (21.7; 43.3)	24.1 (15.8; 39.0)	$p = 0.012$
AST, U/L	46.1 (28.1; 62.6)	56.1 (33.2; 108.7)	$p = 0.017$
AST/ALT ratio	1.4 (1.1; 1.7)	2.8 (2.6; 1.5)	$p = 8.613 \times 10^{-12}$
GGT, U/L	46.6 (36.1; 71.3)	197.5 (80.0; 302.0)	$p = 6.879 \times 10^{-10}$
ALP, U/L	178.0 (144.0; 213.5)	137.0 (95.0; 197.0)	$p = 3.556 \times 10^{-4}$
Total bilirubin, μmol/L	13.3 (10.7; 19.2)	50.8 (26.4; 152.1)	$p = 2.559 \times 10^{-17}$
Child–Pugh class			
A	0	17	–
B	0	24	
C	0	69	
Encephalopathy:			
Yes	7	53	$\chi^2 = 26.893$; $p <$
No	64	57	0.001
Type II diabetes mellitus:			
Yes	1	21	$\chi^2 = 11.034$; $p =$
No	70	89	0.001

Continuous variables are shown as median (lower quartile; upper quartile). Mann–Whitney *U* test was performed for pairwise comparisons of continuous variables between the AUD and ALC groups. Chi-square test was used to compare categorical variables between the groups

Abbreviations: *AUD* alcohol use disorder, *ALC* alcohol-related liver cirrhosis, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* γ-glutamyl transferase

Genotyping

Genomic DNA was isolated from whole blood using the spin column-based DNA purification kit "K-sorb" (#EX-514; Syntol, Russia) according to the manufacturer's instructions and stored at − 80 °C before use. The genotyping of BDNF SNPs was conducted by using predesigned and validated kits of reagents "SNP-Screen" based on TaqMan chemistry (Syntol, Russia). Real-time PCR was performed on an ANK-48 thermocycler (Institute for Analytical Instrumentation RAS and Bauman Moscow State Technical University, Russia) according to the manufacturer's instructions. Positive synthetic controls of each possible genotype and negative (no-template) controls for each PCR run were included. Genotype discrimination was performed using ANK_Expert Software ver. 1.0.5.100 (Syntol, Russia).

Statistics

Statistical analysis was performed using Prism 6 for Windows (GraphPad Software Inc., USA) and IBM SPSS Statistics version 23.0 (IBM Corp., USA). The Kolmogorov-Smirnov and Lilliefors tests were used to check whether variables follow a normal distribution. Variables are shown as median with lower and upper quartiles. The Hardy-Weinberg equilibrium of the expected and observed genotype distribution was analyzed by χ^2 test. The genotypes and allele frequencies were evaluated using the χ^2 test. The association between single SNPs and risk of liver cirrhosis in heavy drinkers was estimated by computing odds ratios (ORs) and confidence intervals (CIs). Contingency tables were used to calculate of χ^2 and ORs. Adjusted ORs were estimated using logistic regression analysis with the presence of encephalopathy and diabetes as covariates. The Mann–Whitney *U* test was performed for pairwise comparisons of continuous variables between the AUD and ALC groups. Linkage disequilibrium calculation and visualization were performed using Haploview software, version 4.2 [26]. Inferred haplotype blocks were constructed using the Gabriel confidence interval method [27]. Statistical significance was assumed at two-sided p values at < 0.05 level.

Results

The distribution of genotypes of the studied BDNF polymorphisms in the experimental groups was in accordance with the Hardy–Weinberg equilibrium (Table 1). There were no differences in the frequencies of the allele and genotype distributions between heavy drinkers with and without liver cirrhosis for each of the studied BDNF SNPs (Table 3). Analysis of ORs revealed an association between the rs925946 locus and ALC (Table 3). In particular, according to both codominant and recessive genetic models, carriers of the rs925946 TT genotype had an elevated risk of liver cirrhosis (Table 3). According to ORs, BDNF SNPs rs6265, rs10835210, rs7103411, and rs75945125 do not affect risk of ALC (Table 3).

The analysis revealed one block of haplotypes (Fig. 1A). Linkage disequilibrium was observed between rs10835210 and rs7103411 polymorphisms, indicating that the two SNPs are commonly inherited together. The results demonstrated that $D' = 1$ and $r^2 = 0.228$ between rs10835210 and rs7103411 (Fig. 1B). Next, the distribution of each haplotype in heavy drinkers with and without liver cirrhosis was analyzed. Two-locus haplotype analysis showed that frequencies of rs10835210 and rs7103411 haplotypes were not significantly different in ALC patients compared to heavy drinkers without cirrhosis (Table 4). Haplotype-based association analysis was performed for rs10835210 and rs7103411 SNPs combinations. No significant association was found between haplotypes and the development of liver cirrhosis in alcohol heavy drinkers (Table 4).

Discussion

Using the same sample set studied here, we previously demonstrated that the development of ALC in heavy drinkers has a genetic background highly specific for liver cirrhosis [25]. In particular, patients carrying the PNPLA3 (patatin-like phospholipase domain-containing 3) rs738409 CG or CG+GG genotypes as compared with CC genotype carriers or G allele as compared with C allele carriers have a significant risk of ALC [25]. Moreover, PNPLA3 rs738409 CC carriers had a lower stage of cirrhosis as compared with CG+GG carriers [25]. In this study, we attempted to extend the range of genetic markers of ALC and tested the candidate SNPs rs925946, rs6265, rs10835210, rs7103411, and rs75945125 related to the BDNF gene. The relationship between BDNF gene polymorphisms and ALC has not yet been studied. According to this study, rs925946 is the only SNP associated with an elevated risk of liver cirrhosis in heavy alcohol drinkers. In particular, according to both codominant and recessive genetic models, carriers of the rs925946 TT genotype have an elevated risk of liver cirrhosis development. We could not confirm the association of BDNF SNP rs6265 with cirrhosis established by Shu and co-authors for cirrhosis of viral etiology [14], presumably due to specific nature of pathology—viral-induced vs. alcohol-induced cirrhosis or variability between ethnic groups—Chinese Han vs. Caucasian.

As reviewed by Marcos-Pasero and co-authors rs925946 polymorphism is associated with obesity, body weight, and body mass index (BMI) in European, European-American, and African-American cohorts [22]. According to the meta-analysis performed by Akbarian and co-authors, rs925946 is associated with

Table 3 Distribution of genotype and allele frequencies and association of single SNPs within the BDNF gene with liver cirrhosis in heavy drinkers

SNP	Genotypes	AUD, $n = 71$	ALC, $n = 110$	χ^2 (p value)	OR (95% CI), p value
rs925946	GG, *n* (%)	45 (63.4)	62 (56.4)	0.009 (0.924)	1
	GT, *n* (%)	24 (33.8)	36 (32.7)	2.935 (0.087)	0.984 (0.480–2.019), 0.966
	TT, *n* (%)	2 (2.8)	12 (10.9)	0.613 (0.434)	***6.287 (1.286–30.738), 0.023***
	Dominant model	45 (63.4)	62 (56.4)	2.907 (0.088)	1
	GG, *n* (%)	26 (36.6)	48 (43.6)	2.282 (0.131)	1.366 (0.700–2.665), 0.360
	GT+TT, *n* (%)	69 (97.2)	98 (89.1)		1
	Recessive model	2 (2.8)	12 (10.9)		***6.321 (1.317–30.348), 0.021***
	GG+GT, *n* (%)	114 (80.3)	160 (72.7)		
	TT, *n* (%)	28 (19.7)	60 (27.3)		
	G allele, *n* (%)				
	T allele, *n* (%)				
rs6265	GG, *n* (%)	52 (73.2)	80 (72.7)	0.078 (0.780)	1
	GA, *n* (%)	16 (22.5)	29 (26.4)	0.833 (0.361)	0.182 (0.014–2.354), 0.192
	AA, *n* (%)	3 (4.2)	1 (0.9)	0.009 (0.924)	0.947 (0.435–2.063), 0.891
	Dominant model	52 (73.2)	80 (72.7)	0.929 (0.335)	1
	GG, *n* (%)	19 (26.8)	30 (27.3)	0.047 (0.829)	0.828 (0.392–1.750), 0.620
	GA+AA, *n* (%)	68 (95.8)	109 (99.1)		1
	Recessive model	3 (4.2)	1 (0.9)		0.184 (0.014–2.365), 0.194
	GG+GA	120 (84.5)	189 (85.9)		
	AA, *n* (%)	22 (15.5)	31 (14.1)		
	G allele, *n* (%)				
	A allele, *n* (%)				
rs10835210	CC, *n* (%)	12 (16.9)	29 (26.4)	1.086 (0.297)	10.595 (0.249–1.421), 0.243
	CA, *n* (%)	33 (46.5)	48 (43.6)	1.665 (0.197)	0.570 (0.202–1.269), 0.147
	AA, *n* (%)	26 (36.6)	33 (30.0)	1.698 (0.193)	1
	Dominant model	12 (16.9)	29 (26.4)	0.586 (0.444)	0.556 (0.247–1.251), 0.156
	CC, *n* (%)	59 (83.1)	81 (73.6)	1.941 (0.164)	1
	CA+AA, *n* (%)	45 (63.4)	77 (70.0)		0.721 (0.360–1.442), 0.355
	Recessive model	26 (36.6)	33 (30.0)		
	CC+CA	57 (40.1)	106 (48.2)		
	AA, *n* (%)	85 (59.9)	114 (51.8)		
	C allele, *n* (%)				
	A allele, *n* (%)				
rs7103411	TT, *n* (%)	49 (69.0)	75 (68.2)	0.002 (0.963)	1
	TC, *n* (%)	22 (31.0)	35 (31.8)	–––	0.892 (0.439–1.814), 0.752
	CC, *n* (%)	0 (0.0)	0 (0.0)	0.002 (0.963)	–––
	Dominant model	49 (69.0)	75 (68.2)	–––	1
	TT, *n* (%)	22 (31.0)	35 (31.8)	0.002 (0.967)	0.892 (0.439–1.814), 0.752
	TC+CC, *n* (%)	71 (100.0)	110 (100.0)		–––
	Recessive model	0 (0.0)	0 (0.0)		
	TT+TC	120 (84.5)	185 (84.1)		
	CC, *n* (%)	22 (15.5)	35 (15.9)		
	T allele, *n* (%)				
	C allele, *n* (%)				
rs75945125	TT, *n* (%)	65 (91.5)	98 (89.1)	0.081 (0.775)	1
	TC, *n* (%)	6 (8.5)	12 (10.9)	–––	1.368 (0.451–4.151), 0.581
	CC, *n* (%)	0 (0.0)	0 (0.0)	0.081 (0.775)	1
	Dominant model	65 (91.5)	98 (89.1)	–––	1.368 (0.451–4.151), 0.581
	TT, *n* (%)	6 (8.5)	12 (10.9)	0.077 (0.781)	–––
	TC+CC, *n* (%)	71 (100.0)	110 (100.0)		
	Recessive model	0 (0.0)	0 (0.0)		
	TT+TC	136 (95.8)	208 (94.5)		
	CC, *n* (%)	6 (4.2)	12 (5.5)		
	T allele, *n* (%)				
	C allele, *n* (%)				

χ^2 values were established by using contingency tables. Logistic regression analysis with the presence of encephalopathy and diabetes as covariates was used to calculate ORs. Statistically significant values are in bold italic

Abbreviations: *BDNF* brain-derived neurotrophic factor, *SNP* single nucleotide polymorphism, *AUD* alcohol use disorder, *ALC* alcohol-related liver cirrhosis, *OR* odds ratio, *CI* confidence interval

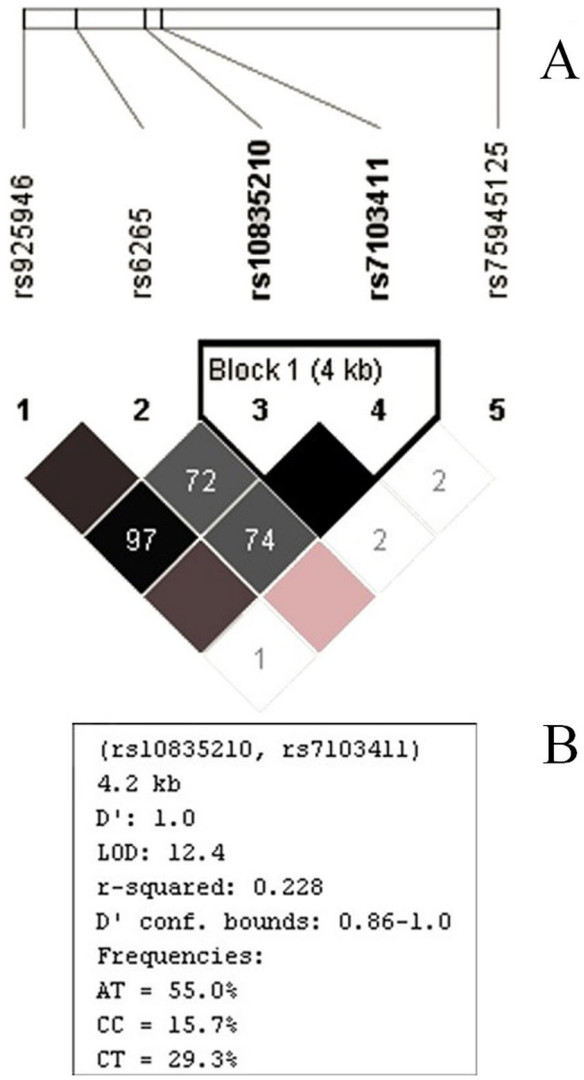

Fig. 1 Relative positions and linkage disequilibrium estimates between the BDNF polymorphisms. **A** Linkage equilibrium plot of pairwise SNPs within the BDNF gene in pooled sample. Colored squares correspond to *D*′ values for each pair of SNPs with numerical estimates given within squares (*D*′ × 100). Regions of high linkage disequilibrium are shown in black. Markers with lower linkage disequilibrium are shown in tints of gray, with the color intensity decreasing with decreased *D*′ value. Regions of low linkage disequilibrium are shown in white. Haplotype blocks were defined by the Haploview software with the option of using the haplotype block definition proposed by Gabriel et al. [26, 27]. **B** Linkage disequilibrium estimates for the revealed block of haplotype. Abbreviations: BDNF, brain-derived neurotrophic factor; SNP, single nucleotide polymorphism

BMI [23]. There was a link between rs925946 (GG vs TG/TT polymorphism) and BMI (OR = 1.12, 95% CI = 1.08–1.17) [23]. A significantly greater BMI was observed in those with the TG/TT genotype than in carriers of the GG genotype across studies [23]. Obesity

Table 4 Association analysis of rs10835210 and rs7103411 haplotypes with liver cirrhosis in heavy drinkers

Haplotype	AUD, $n = 71$	ALC, $n = 110$	χ^2 (p value)	OR (95% CI)
AT, *n* (%)	85 (59.9)	114 (51.8)	2.254 (0.133)	0.721 (0.467–1.101)
CT, *n* (%)	35 (24.6)	71 (32.3)	2.423 (0.120)	1.457 (0.899–2.309)
CC, *n* (%)	22 (15.5)	35 (15.9)	0.011 (0.916)	1.032 (0.569–1.807)

χ^2 and ORs values were established by using contingency tables

Abbreviations: *AUD* alcohol use disorder, *ALC* alcohol-related liver cirrhosis *OR* odds ratio, *CI* confidence interval

is considered an independent risk factor for the development of severe liver fibrosis, fibrosis progression, and cirrhosis. Moreover, several population-based studies identified obesity as an independent risk factor for alcohol-induced liver damage [28]. However, it is still unclear whether the hepatotoxic consequences of obesity and ethanol abuse are additive or synergistic.

In addition to the brain, expression of BDNF has been reported in peripheral tissues including the liver [29, 30], although the functional role of BDNF signaling in the liver is not fully understood. BDNF is involved in liver homeostasis, playing a role in metabolic processes such as fatty acid oxidation and synthesis, glycogenesis and gluconeogenesis [9]. BDNF may exert a hepatoprotective effect in rodents. As demonstrated by Xiong and co-author, BDNF can protect mice from a diet that induces steatohepatitis [31]. On the other hand, BDNF may provoke liver damage in rodents. Hepatic BDNF facilitates the emergence of insulin resistance, dyslipidemia, and liver disease following high-fat diet [32]. BDNF mRNA is significantly increased in both human and animal liver fibrosis [33]. Moreover, BDNF stimulation increased pro-inflammatory cytokines and fibrogenic markers in hepatic stellate cells [33]. BDNF values significantly increase following progression of the fibrosis stages as measured by the liver stiffness in subjects with AUD [12]. On the contrary, circulating BDNF levels are lower in AUD patients with impaired liver function [34]. Ceccanti and co-authors obtained similar results in rodents. They demonstrated that perinatal exposure to 11% ethanol solution or to red wine with same ethanol concentration caused depletion of BDNF in the liver of 18-month-old male mice [35]. At the basal conditions, BDNF deficiency in mice did not affect hepatic cell death or lipid accumulation [36]. However, during endoplasmic reticulum stress, BDNF deficiency enhanced apoptosis and steatosis in the wild-type animals [36]. Yang and co-authors showed a negative correlation between the mature BDNF levels

in the parietal cortex and those in the liver of patients with major depressive disorder, schizophrenia, and bipolar disorder, thereby implying that production of mature BDNF and BDNF pro-peptide in the brain and liver might have a role in the pathophysiology of psychiatric disorders [30]. These results may suggest the existence of the brain-liver axis [30].

The BDNF polymorphism rs925946 that, according to this study, is associated with the risk of ALC locates within the intronic region of the BDNF-AS gene. BDNF-AS is a natural non-coding antisense transcript that is transcribed from the human BDNF locus in the opposite direction and may have an important role in the regulation of BDNF expression in humans [37]. BDNF association with ALC has not yet been established. However, some investigations have shown the interaction of BDNF with ALD. Girard and co-authors reported that BDNF values increase significantly in accordance with the liver fibrosis stages in AUD subjects, and linear regression analysis demonstrated a relationship between BDNF levels as the dependent variables and liver elasticity as the predictor [12]. Moreover, serum BDNF levels increase after alcohol withdrawal and negatively correlate with GGT levels as a measure of liver functionality [38]. Based on the literature data, we suppose that carriage of the BDNF rs925946 TT genotype may affect hepatic BDNF expression and function, thereby providing a link between BDNF and liver cirrhosis associated with chronic alcohol intoxication.

Meanwhile, this study has some limitations: (i) BMI data and circulating BDNF levels were not collected, (ii) the sample size is relatively small. Confirmation of the relationship between BDNF and ALC is a subject of great demand.

Conclusion

BDNF rs925946 SNP is associated with the risk of ALC in heavy drinkers; according to both codominant and recessive genetic models, carriers of the rs925946 TT genotype have an elevated risk of liver cirrhosis development. Further search for genetic markers of ALC within the BDNF gene and their validation will help to objectively assess the risk and severity of liver damage and correct the corresponding therapy.

Abbreviations

ALC Alcohol-related liver cirrhosis
ALD Alcohol-related liver disease
ALP Alkaline phosphatase
ALT Alanine aminotransferase
AST Aspartate aminotransferase
AUD Alcohol use disorder
BDNF Brain-derived neurotrophic factor
CI Confidential interval
GGT γ-Glutamyl transferase
OR Odds ratio
SNP Single nucleotide polymorphism

Authors' contributions

AL, AI, and IG collected and interpreted clinical data. VB carried out the cytokine analyses. DP performed genotyping. DP, VB, and AI collected and assembled the data. DP contributed to the statistical analysis of the results and prepared the first draft of the manuscript. SP reviewed the manuscript critically and wrote the final manuscript. NT and ZK conceived, designed, and supervised the study. DP is responsible for the integrity of the work as a whole. All authors contributed to and have approved the final manuscript.

Funding

None. The study was carried out within the state assignment of Federal State Budgetary Institution "V. Serbsky National Medical Research Center for Psychiatry and Drug Addiction" of the Ministry of Health of the Russian Federation.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Federal State Budgetary Institution "V. Serbsky National Medical Research Center for Psychiatry and Drug Addiction" of the Ministry of Health of the Russian Federation, 3 Mal. Mogiltsevsky In, Moscow 119002, Russia. [2]Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Butlerova st. 5A, Moscow 117485, Russia. [3]Peoples' Friendship University of Russia, 6 Miklukho-Maklaya str, Moscow 117198, Russia. [4]Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University (Sechenov University) of the Ministry of Health of Russia, 8 Trubetskaya Str., bldg. 2, Moscow 119991, Russia.

Received: 7 July 2023 Accepted: 17 October 2023
Published online: 25 October 2023

References

1. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H (2018) Alcoholic liver disease. Nat Rev Dis Primers. https://doi.org/10.1038/s41572-018-0014-7
2. Stickel F, Moreno C, Hampe J, Morgan MY (2017) The genetics of alcohol dependence and alcohol-related liver disease. J Hepatol 66:195–211
3. Balakrishnan R, Mohammed V, Veerabathiran R (2022) The role of genetic mutation in alcoholic liver disease. Egypt Liver Journal. https://doi.org/10.1186/s43066-022-00175-2
4. Ceballos N, Sharma S (2016) Risk and resilience: the role of brain-derived neurotrophic factor in alcohol use disorder. AIMS Neuroscience 3:398–432
5. Nubukpo P, Ramoz N, Girard M, Malauzat D, Gorwood P (2017) Determinants of blood brain-derived neurotrophic factor blood levels in patients with alcohol use disorder. Alcohol Clin Exp Res 41:1280–1287
6. Kethawath SM, Jain R, Dhawan A, Sarkar S (2020) A review of peripheral brain-derived neurotrophic factor levels in alcohol-dependent patients: current understanding. Indian J Psychiatry 62:15–20

7. Lipsky RH (2007) Marini AM (2007) Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. Ann NY Acad Sci 1122:130–143
8. Poo MM (2001) Neurotrophins as synaptic modulators. Nat Rev Neurosci 2:24–32
9. Iu ECY, Chan CB (2022) Is brain-derived neurotrophic factor a metabolic hormone in peripheral tissues? Biology (Basel). https://doi.org/10.3390/biology11071063
10. Logrip ML, Barak S, Warnault V, Ron D (2015) Corticostriatal BDNF and alcohol addiction. Brain Res 1628:60–67
11. Ron D, Berger A (2018) Targeting the intracellular signaling "STOP" and "GO" pathways for the treatment of alcohol use disorders. Psychopharmacology (Berl) 235:1727–1743
12. Girard M, Carrier P, Loustaud-Ratti V, Nubukpo P (2021) BDNF levels and liver stiffness in subjects with alcohol use disorder: evaluation after alcohol withdrawal. Am J Drug Alcohol Abuse 47:191–198
13. Martín-González C, Romero-Acevedo L, Fernández-Rodríguez CM, Medina-Vega L, García-Rodríguez A, Ortega-Toledo P, González-Navarrete L, Vera-Delgado VE, González-Reimers E (2021) Brain-derived neurotrophic factor among patients with alcoholism. CNS Spectr 26:400–405
14. Shu HC, Hu J, Jiang XB, Deng HQ, Zhang KH (2019) BDNF gene polymorphism and serum level correlate with liver function in patients with hepatitis B-induced cirrhosis. Int J Clin Exp Pathol 12:2368–2380
15. Xu H, Zhou Y, Ko F, Ping J, Zhang J, Zhao C, Xu L (2017) Female gender and gastrointestinal symptoms, not brain-derived neurotrophic factor, are associated with depression and anxiety in cirrhosis. Hepatol Res 47:E64–E73
16. Su N, Zhang L, Fei F, Hu H, Wang K, Hui H, Jiang XF, Li X, Zhen HN, Li J, Cao BP, Dang W, Qu Y, Zhou F (2011) The brain-derived neurotrophic factor is associated with alcohol dependence-related depression and antidepressant response. Brain Res 1415:119–126
17. Mon A, Durazzo TC, Gazdzinski S, Hutchison KE, Pennington D, Meyerhoff DJ (2013) Brain-derived neurotrophic factor genotype is associated with brain gray and white matter tissue volumes recovery in abstinent alcohol-dependent individuals. Genes Brain Behav 12:98–107
18. Narita S, Nagahori K, Yoshihara E, Nishizawa D, Ikeda K, Kawai A, Iwahashi K (2013) The relationship between BDNF gene polymorphisms and alcoholics in Japan. Nihon Arukoru Yakubutsu Igakkai Zasshi 48:407–414
19. Cheah SY, Lawford BR, Young RM, Connor JP, Phillip Morris C, Voisey J (2014) BDNF SNPs are implicated in comorbid alcohol dependence in schizophrenia but not in alcohol-dependent patients without schizophrenia. Alcohol Alcohol 49:491–497
20. Neves FS, Malloy-Diniz L, Romano-Silva MA, Campos SB, Miranda DM, De Marco L, Figueira PG, Krebs MO, Correa H (2011) The role of BDNF genetic polymorphisms in bipolar disorder with psychiatric comorbidities. J Affect Disord 131:307–311
21. Li S, Weinstein G, Zare H, Teumer A, Völker U, Friedrich N, Knol MJ, Satizabal CL, Petyuk VA, Adams HHH, Launer LJ, Bennett DA, De Jager PL, Grabe HJ, Ikram MA, Gudnason V, Yang Q, Seshadri S (2020) The genetics of circulating BDNF: towards understanding the role of BDNF in brain structure and function in middle and old ages. Brain Commun. https://doi.org/10.1093/braincomms/fcaa176
22. Marcos-Pasero H, Aguilar-Aguilar E, Ikonomopoulou MP, Loria-Kohen V (2021) BDNF gene as a precision skill of obesity management. Adv Exp Med Biol 1331:233–248
23. Akbarian SA, Salehi-Abargouei A, Pourmasoumi M, Kelishadi R, Nikpour P, Heidari-Beni M (2018) Association of brain-derived neurotrophic factor gene polymorphisms with body mass index: a systematic review and meta-analysis. Adv Med Sci 63:43–56
24. Aslam A, Kwo PY (2023) Epidemiology and disease burden of alcohol associated liver disease. J Clin Exp Hepatol 13:88–102
25. Peregud DI, Baronets VY, Lobacheva AS, Ivanov AS, Arisheva OS, Garmash IV, Kobalava ZD, Pirozhkov SV, Terebilina NN (2021) PNPLA3 rs738409 associates with alcoholic liver cirrhosis but not with serum levels of IL6, IL10, IL8 or CCL2 in the Russian population. Ann Hepatol. https://doi.org/10.1016/j.aohep.2020.08.065
26. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 21:263–265
27. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, Higgins J, DeFelice M, Lochner A, Faggart M, Liu-Cordero SN, Rotimi C, Adeyemo A, Cooper R, Ward R, Lander ES, Daly MJ, Altshuler D (2002) The structure of haplotype blocks in the human genome. Science 296:2225–2229
28. Schiavo L, Busetto L, Cesaretti M, Zelber-Sagi S, Deutsch L, Iannelli A (2018) Nutritional issues in patients with obesity and cirrhosis. World J Gastroenterol 24:3330–3346
29. Cassiman D, Denef C, Desmet VJ, Roskams T (2001) Human and rat hepatic stellate cells express neurotrophins and neurotrophin receptors. Hepatology 33:148–158
30. Yang B, Ren Q, Zhang JC, Chen QX, Hashimoto K (2017) Altered expression of BDNF, BDNF pro-peptide and their precursor proBDNF in brain and liver tissues from psychiatric disorders: rethinking the brain-liver axis. Transl. Psychiatry. https://doi.org/10.1038/tp.2017.95
31. Xiong J, Liu T, Mi L, Kuang H, Xiong X, Chen Z, Li S, Lin JD (2020) hnRNPU/TrkB defines a chromatin accessibility checkpoint for liver injury and nonalcoholic steatohepatitis pathogenesis. Hepatology 71:1228–1246
32. Teillon S, Calderon GA, Rios M (2010) Diminished diet-induced hyperglycemia and dyslipidemia and enhanced expression of PPARalpha and FGF21 in mice with hepatic ablation of brain-derived neurotropic factor. J Endocrinol 205:37–47
33. Sun TT, Liu XL, Yang GY, Zhang W, Tao L, Ma WT, Wu L, Li Q, Liu C (2022) Neurotrophic factors stimulate the activation of hepatic stellate cells in liver fibrosis. Biochem Biophys Res Commun 630:167–174
34. García-Marchena N, Silva-Peña D, Martín-Velasco AI, Villanúa MÁ, Araos P, Pedraz M, Maza-Quiroga R, Romero-Sanchiz P, Rubio G, Castilla-Ortega E, Suárez J, Rodríguez de Fonseca F, Serrano A, Pavón FJ (2017) Decreased plasma concentrations of BDNF and IGF-1 in abstinent patients with alcohol use disorders. PLoS One. https://doi.org/10.1371/journal.pone.0187634
35. Ceccanti M, Mancinelli R, Tirassa P, Laviola G, Rossi S, Romeo M, Fiore M (2012) Early exposure to ethanol or red wine and long-lasting effects in aged mice. a study on nerve growth factor, brain-derived neurotrophic factor, hepatocyte growth factor, and vascular endothelial growth factor. Neurobiol Aging 33:359–367
36. Cırrık S, Hacioglu G, Abidin İ, Aydın-Abidin S, Noyan T (2019) Endoplasmic reticulum stress in the livers of BDNF heterozygous knockout mice. Arch Physiol Biochem 125:378–386
37. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T (2007) Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics 90:397–406
38. Girard M, Labrunie A, Malauzat D, Nubukpo P (2020) Evolution of BDNF serum levels during the first six months after alcohol withdrawal. World J Biol Psychiatry 21:739–747

Publisher's Note