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Do IL-1B and IL-1RN Modulate Chronic Low Back Pain in Patients with Post-Traumatic Stress Disorder?

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A B S T R A C T

The aim of this study was to analyze the association between single nucleotide polymorphism (SNP) in IL1B (rs1143 634) and IL1RN (rs2234677) with chronic low back pain (LBP) in chronic post-traumatic stress disorder (PTSD). A total of 406 war veterans from 1991–1995 war in Croatia participated in this study. They were divided into four groups, according to psychiatric interview, psychometric testing and the presence of LBP, verified by the imaging of lumbar area, into: (i) war veterans suffering from PTSD and LBP (N=102), (ii) war veterans suffering from PTSD only (N=108), (iii) war veterans suffering from LBP only (N=99) and (iv) healthy controls (N=97). Each subject provided a blood sample for IL1B and IL1RN polymorphism testing. We found no association of rs1143634 in IL1-B with LBP. Permutation test showed significant association of rs1143634 in IL1-RN with LBP group and presence of wild type allele A was protective in LBP group. The same SNP (rs1143634) in IL1-B was associated with the intensity of pain. No other associations were observed between these two markers and self-reported measures evaluating PTSD and pain symptoms. These results suggest the potential role of cytokine network in the pathogenesis of chronic PTSD and LBP, although the direct causative pathway remains unclear. The alteration of cytokine network on the level of the brain, spinal medulla and the spine may be responsible for modulation of pain and the occurrence of LBP.

***Key words**: PTSD, chronic pain, single nucleotide polymorphism, IL-1B, IL-1RN*

Introduction

The chronic post-traumatic stress disorder (PTSD) is defined as a psychiatric disorder occurring after experiencing the extreme traumatic stress and manifesting with three clusters of symptoms lasting more than 3 months: persistent re-experiencing of the traumatic event, persistent avoidance of various stimuli or numbing of general responsiveness and increased arousal lasting more than 3 months[1]. Although the majority of patients suffering from chronic PTSD achieve certain remission across period of several years, nearly 40% of them suffer from life-long PTSD[2].

Chronic PTSD is associated with various somatic comorbidities, ranging from autoimmune disorders to cardiovascular and pain disorders[3]. Although some previous reports have implied a link between chronic pain and PTSD, a recent epidemiological study (National Comorbidity Survey-Replication, NCS-R) has strengthen these findings and established plausible association between PTSD and chronic pain disorders[4]. In a sample of 5366 subjects higher risk has been shown for chronic pain condition in PTSD patients in contrast to subject who have not met the criterion of traumatic event for PTSD. In the same study, subjects that have experienced traumatic event, but do not suffer from PTSD, had lower but still significant risk for chronic pain condition in contrast to subject who have not met the criterion of traumatic

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event. Although the association between chronic pain and chronic PTSD is thus well established, few attempts were made to provide the biological insight in the role of pain mechanisms in chronic combat-related PTSD.

One of the possible pathways of revealing pain mechanisms in the chronic PTSD is by investigating cytokines known to be involved in the pain modulation. The activity of cytokine network has role in the pathogenesis of LBP, mainly in the lumbar disc degeneration and other phases such as protrusion, extrusion etc. Akyol et al. have shown higher expression of several cytokines; IL-1B, IL-2, IL-4, IL-10 in degenerated lumbar disc[5]. Astrocytes are believed to be the main source of inflammatory cytokines by activating various signalling pathways in the model of LBP[6]. IL-1 receptor antagonist (IL-1RN), derived from the same precursor peptide as IL-1B, is found to have protective role in LBP pathogenesis, mainly by down-regulating the expression of various matrix metalloproteinases[7], so one can conclude that the antagonistic relationship between these two cytokines is associated with LBP. Furthermore, IL-1RN has been linked with a severity of knee osteoarthritis according to a recent meta-analysis[8]. So far there was only one attempt to link acute LBP and genetic markers of IL-1B (rs1143 634), located on 5th exon (CS –›T), and IL-1RN (rs2234 677), located in 5' untranslated region (G –›A), which were found to be associated with the intensity and duration of pain[9].

The aim of this study was to investigate the association of genetic polymorphism in IL-1B and IL-1RN with chronic LBP in war veterans with or without chronic PTSD.

Methods

Subjects

A total of 536 subjects were initially involved in this study. They were selected to represent a population of Croatian Homeland war veterans, aged 35–54 years, who were exposed to the direct combat conditions as frontline soldiers for at least 3 consecutive months. The subjects were included in the present study by the means of consecutive enrolment from the Clinic for Psychological Medicine in Zagreb and various by direct contact with some of the veterans' nongovernmental organizations in Croatia. We aimed to create four study groups of approximately same size of 100 subjects:

1. War veterans suffering from chronic PTSD and low back pain (LBP)
2. War veterans suffering from chronic PTSD only
3. War veterans suffering from chronic LBP only
4. Healthy controls (war veterans who were at the time of study showing none of these disorders (healthy controls)

In order to classify the subjects into these four groups, we undertook a number of diagnostic procedures. Firstly, all subjects were interviewed by an experienced psychiatrist at the Clinic for Psychological Medicine, University Hospital Centre, Zagreb to assess the presence of PTSD according to DSM-IV-TR criterion[1]. Additional psychometric testing was also performed, aiming to provide a more detailed overview (detailed explanation provided in the next section). Subjects with positive anamnesis of head and spinal injury, acute psychosis, alcohol or illegal substance abuse or those who were diagnosed with any form of the psycho-organic syndrome were excluded from the study. After establishing a PTSD status, we proceeded to classify them according to the LBP status. Initial criterion was the presence of LBP was defined as pain with a minimal duration of 12 months. Subjects who reported suffering from LBP were then directed to a specialist surgeon at the Clinic for Traumatology Zagreb, for further clinical and radiographic testing by means of magnetic resonance imaging. Those who were found to have any form of the organic cause for LBP (to exclude those suffering from lumbar disc protrusion, extrusion, herniation and spinal stenosis) were excluded from subsequent analyses. By doing this, we were able to classify all subjects into positive or negative PTSD and LBP group. Subjects who had no indication of PTSD nor reported LBP were considered to be healthy controls.

Each subject has given an informed consent and the study was conducted by ethical principles set by WMA Declaration of Helsinki, and the entire study was approved by the Ethical Board of the Clinic for Traumatology, University Hospital Centre »Sestre Milosrdnice« Zagreb, Croatia.

Questionnaires

General questionnaire was developed to assess basic demographics, LBP status and psychiatric data. Items assessing LBP included various risk factors such as weight, height, body mass index, vocational and avocational activity, various LBP descriptors such as duration of symptoms, intensity, and potential use of analgesic medications. Items analyzing PTSD included duration PTSD, onset of symptoms, other comorbid psychiatric disorders, psychotropic medication, war exposure, short description of traumatic events, medications.

Trauma Symptom Inventory-A

Trauma Symptom Inventory-A (TSI-A) is a specific self-reported measure developed to evaluate the acute and chronic symptomatology of PTSD, regardless of the traumatic event, which may include combat experience, rape, childhood abuse, natural disaster, physical assault etc[10]. TSI-A is a shorter version of the original Trauma Symptom Inventory. TSI-A consists of 86 items in the form of a four-point scale with symptoms rated retrospectively within the preceding six months through answers varying from »0«, denoting »never«, to »3«, denoting »often«. On the basis of this questionnaire, the following clinical scale evaluating specific symptoms was obtained: Anxious Arousal, Depression, Anger/Irritability, Intrusive Experiences, Defensive Avoidance, Dissociation, Impaired Self-Reference and Tension Reduction Behaviour.

An adequate internal validity was found on a sample of war veterans suffering from PTSD with Cronbach α varying from 0.73 to 0.91, depending on the scale[11]. This measure was reported to correctly classify 85.5% of PTSD cases and has shown similar results for other measures evaluating PTSD in a community sample[12].

Short Form McGill Pain Questionnaire

The Short Form McGill Pain Questionnaire (SFMPQ) was used to assess specific characteristics of LBP[13]. It is based on two factor model of pain which distinguish the pain perception as sensory or affective. This inventory consists of 16 items; 11 items assessing sensory pain and 4 items assessing affective pain. Each item consists of a word or phrase depicting the pain experience with answer ranging from »0«, denoting »absence of particular pain«, to »3«, denoting »severe pain«. Separate item measures overall intensity of pain, ranging from »0« to »5«. Internal consistency of this scale varied from 0.705 to 0.82, depending on the sample[14,15], although most of the studies do not measure Cronbach's α while using this inventory[16]. The authors of this study have not found specific cut off values of SFMPQ used in PTSD patients in literature review.

Radiographic methods

In order to exclude subjects with detectable organic causes of LBP, magnetic resonance imaging by 1.5 T Magnetom Symphony (Siemens Medical System) was used. T1 weighted scans were used to assess anatomic relations and T2 weighted scans were used to assess pathologic change of signal. Repetition time totalled 510–810 ms; echo time 14–17 ms. The slice thickness was 2–3 mm. Field of view was 120–180 mm, with matrix of 512x256. In order to suppress possible bias, radiologists were unaware of the patient's conditions and were asked to report the presence of lumbar disc degeneration, protrusion, herniation and spinal stenosis.

Genotyping SNPs in IL-1B (rs1143634) and IL-1RN (rs2234677)

Each subject has given a blood sample (3 mL) that was collected in labelled test tube and kept on –20 °C. DNA extraction was carried out by G-spin Genomic DNA Extraction Kit (iNtRON Biotechnology). SNP genotyping was performed using real-time PCR, TaqMan probes and technology (Applied Biosystems). Specific probes for each SNP were obtained; C_9546517_10 for SNP in IL-1β (rs1143634) and C_11948096_10 for SNP in IL-1RN (rs2234677). A probe for wild type allele was labeled by VIC® color and a probe for mutant allele was labeled by FAM™ color. The genotypes were determined by TaqMan® assay (Applied Biosystems), according to manufacturer's recommendations, but scaled to final PCR volume of 12.5 μL. The real-time PCR and discrimination of alleles was performed on ABI PRISM® 7000 Sequence Detection System (Applied Biosystems). The reaction conditions were following; 95 °C for 10 min, 45 cycles at 92 °C for 15 sec and at 62 °C for 10 min. A laboratory analysis was performed as a double blind experiment with a negative and positive control on the reaction plate. For each sample same procedure was used.

Statistical analysis

After collecting the data, various descriptive methods were used; means, standard deviations, frequencies and percents. Before parametric analysis, Kolmorogov-Smirnov test was used distribution of data. T-test for independent sample and analysis of variance followed by *post hoc* Tukey HSD were used for parametric data. χ^2-test and Pearson correlation factors were used for categorical data.

TSI-A and SFMPQ scales were transformed into binary variables. Transformation was obtained by taking 25 upper percentiles of participants with highest intensity of subjects' symptoms as cases, while other 75% of subjects served as controls. Logistic regression analysis was performed with age and group as independent variables as controls.

In the analysis of genetic data usual approach to pair analysis was used, followed by permutation test. Hardy-Weinberg equilibrium was assessed by χ^2-test.

A priori statistical power analysis was performed before the study conduction in order to estimate the sample size. Based on these assumptions, the total size of each group was calculated with statistical power of 80% and statistical significance of 0.05. Each group had to contain minimum of 92 subjects, with total sample size being 364.

Following programs were used for statistical analysis: Statistical Package for Social Science 14.00 (SPSS) and PLINK 1.00[17].

Results

A total 541 participants initially responded to participate in this study. After application of exclusion criteria, withdrawal for personal reasons and due to unsuccessful genotyping, the final sample consisted of 406 participants. These participants were subsequently classified in four groups, according to the presence of post-traumatic stress disorder and lower back pain: war veterans suffering from chronic PTSD and LBP (N=102), war veterans suffering from chronic PTSD only (N=108), war veterans suffering from chronic LBP only (N=99) and healthy controls (war veterans who were at the time of study showing none of these disorders; N=97). The comparison of the basic characteristics of these samples indicated strong differentiation in most cases (Table 1). Furthermore, these groups differed strongly in the number of children in the family ($\chi^{2=}$80.93, $p<0.001$), employment status ($\chi^{2=}$90.44, $p<0.001$), smoking ($\chi^{2=}$17.03, $p<0.001$), wine consummation ($\chi^{2=}$72.11, $p<0.001$), and spirits consummation ($\chi^{2=}$39.10, $p<0.001$).

Self-perceived chronic pain and PTSD symptoms

The comparison of the four domains of pain also indicated the existence of strong group differences, with

TABLE 1
THE ANALYSIS OF SOCIAL AND DEMOGRAPHIC NUMERICAL VARIABLES

Attribute	Group	$\bar{X}$	SD	MIN	MAX	ANOVA p	Tukey HSD *post hoc* significant pair-wise differences
Age (years)	PTSD+LBP	44.84	5.25	35.00	54.00	<0.001	1–2, 1–3, 1–4, 2–3, 3–4
	PTSD	41.56	4.25	35.00	54.00		
	LBP	48.35	5.14	35.00	54.00		
	Controls	41.44	5.20	35.00	54.00		
Height (cm)	PTSD+LBP	178.12	7.22	158.00	191.00	<0.001	1–2, 2–3
	PTSD	182.81	5.36	170.00	192.00		
	LBP	178.25	8.13	160.00	200.00		
	Controls	180.53	5.85	168.00	192.00		
Mass (kg)	PTSD+LBP	85.79	13.53	46.00	130.00	0.423	–
	PTSD	84.74	10.89	45.00	130.00		
	LBP	87.60	13.35	55.00	130.00		
	Controls	86.07	11.47	64.00	120.00		
BMI (kg/m^2)	PTSD+LBP	27.04	4.03	18.43	40.12	<0.001	1–2, 2–3
	PTSD	25.37	3.31	14.53	43.94		
	LBP	27.60	4.17	17.96	46.06		
	Controls	26.67	3.13	20.45	34.68		

LBP – low back pain, BMI – body mass index, groups 1 – PTSD+LBP, 2 – PTSD, 3 – LBP, 4 – controls, statistical significance cut off $p<0.001$

TABLE 2
THE DIFFERENCE BETWEEN THE GROUPS ACCORDING TO SFMPQ FACTORS

Attribute	Group	$\bar{X}$	SD	MIN	MAX	ANOVA p	Tukey HSD *post-hoc**
Sensory pain	PTSD + LBP	21.57	6.44	2	33	<0.001	1–2, 1–3, 1–4, 2–3, 3–4
	PTSD	1.92	1.94	0	12		
	LBP	13.74	9.11	0	33		
	Controls	2.31	2.42	0	9		
Affective pain	PTSD + LBP	8.10	2.62	1	12	<0.001	1–2, 1–3, 1–4, 2–3, 3–4
	PTSD	0.69	0.82	0	3		
	LBP	2.63	3.44	0	12		
	Controls	0.30	0.62	0	3		
Total pain	PTSD + LBP	29.77	8.38	3	54	<0.001	1–2, 1–3, 1–4, 2–3, 3–4
	PTSP	2.59	2.30	0	15		
	LBP	16.36	11.08	0	45		
	Controls	2.32	2.15	0	9		
Evaluation of pain	PTSP + LBP	3.50	0.89	0	5	<0.001	1–2, 1–3, 1–4, 2–3, 3–4
	PTSP	0.28	0.50	0	2		
	LBP	3.14	0.98	0	5		
	Controls	0.34	0.50	0	5		

SFMPQ – Short Form McGill Pain Questionnaire, LBP – low back pain, groups 1 – PTSD+LBP, 2 – PTSD, 3 – LBP, 4 – controls, statistical significance cut off $p<0.001$

TABLE 3
THE FREQUENCIES OF IL-1B (RS1143634) AND IL-1RN (RS2234677)

		IL-1B (rs1143634)		
Group	N / %	CC	CT	TT
PTSD + LBP	N	57	39	4
	%	57.0	39.0	4.0
PTSD	N	67	32	6
	%	63.8	30.5	5.7
LBP	N	55	35	3
	%	59.1	37.6	3.2
Controls	N	55	37	4
	%	57.3	38.5	4.2
Total	N	234	143	17
	%	59.4	36.3	4.3

		IL-1RN (rs2234677)		
		GG	GA	AA
PTSD + LBP	N	63	31	5
	%	63.6	31.3	5.1
PTSD	N	51	37	13
	%	50.5	36.6	12.9
LBP	N	47	42	10
	%	47.5	42.4	10.1
Controls	N	61	29	4
	%	64.9	30.9	4.3
Total	N	222	139	32
	%	56.5	35.4	8.1

pair-wise insignificant differences recorded between patients with PTSD and controls, while those with physical symptoms reported much higher levels of pain sensation (Table 2).

PTSD groups have not varied in factors obtained from TSI-A questionnaire. The linear regression analysis predicting the factors obtained from SFMPQ by TSI-A, age and group variables in groups suffering from chronic LBP showed the statistical significance ($p<0.001$) for all four factors; »sensory pain« ($R^2=67.9$), »affective pain« ($R^2=63.0$) and »evaluation of pain« ($R^2=64.5$). The age and most of TSI-A variables were not significant as predictors, except »depression« ($F=5.16$, $p=0.024$) and »intrusive experience« ($F=5.09$, $p=0.025$) in prediction of »affective pain«, while belonging to the particular group was significant at $p<0.001$ for »sensory pain« ($F=197.21$), »affective pain« ($F=92.77$) and »evaluation of pain« ($F=108.22$).

The frequencies of IL-1β (rs1143634) and IL-1RN (rs2234677) genotypes showed no difference among the four study groups for IL-1β ($\chi^{2=}1.35$, $P=0.853$), while that for IL-1RN was marginally significant ($\chi^{2=}9.61$, $p=0.048$; Table 3).

The comparison of the participants suffering from LBP with the controls by using permutation test has shown borderline significance for IL-1RN (rs2234677) ($p=0.049$), unlike for IL-1β (rs1143634) ($p=0.573$). While comparing the LBP group to allele differences the association was found with for IL-1RN (rs2234677) ($p=0.041$, OR=0.63 95%CI [0.40–0.98]).

The use of logistic regression for the final analytic step indicated the lack of significant association of IL-1β SNP with pain intensity (adjusted for age and gender effects), with the exception of evaluation of pain, which seemed to be significantly associated with this genetic marker (Table 4).

Discussion

The association of SNP IL-1RN (rs2234677) with LBP in war veterans without PTSD

We demonstrated the possible association of SNP in *IL-1RN* (rs1143634) with a group of war veterans suffering from chronic LBP without comorbid PTSD. The reasons of our finding may be multiple, varying from unrecognised confounding factors to different pathogenesis of chronic pain in PTSD.

Our findings may be in accordance with the pathogenesis of chronic LBP uncomplicated with psychiatric disorders with distinct pain features. One of the main paradigms concerning this disorder is central senzitation on the level of spinal cord. One of the possible mechanisms is through modulated N-Methyl-D-aspartate (NMDA) excitatory pathways, resulting in neurotoxicity, changes in neuroplasticity and prolonged hyperalgesia of dorsal horns[18]. Numerous data, varying from using NMDA antagonist in animal models evoke algesia (although the data of their usage in human subjects is scarce) to measuring mRNA levels in the neuropathic pain, have confirmed this hypothesis as the most plausible[19,20]. Recent studies have shown the association of hyperactivity of NMDA activity and overexpression of IL-1B in spinal cord[21]. Second possible mechanism of

TABLE 4
THE ASSOCIATION OF IL-1B (RS1143634) WITH PAIN INTENSITY

IL-1ß	Sensory pain		Affective pain		Total pain		Evaluation of pain	
CC*	0.406	1.00	0.419	1,00	0.639	1.00	0.006	1.00
CT	0.299	0.71 [0.37–1.36]	0.448	0.72 [0.31–1.68]	0.564	0.82 [0.42–1.61]	0.001	0.20 [0.07–0.54]
TT	0.488	1.89 [0.31–11.46]	0.342	2.82 [0.33–23.99]	0.511	1.86 [0.29–11.89]	0.392	0.36 [0.03–3.80]

IL-1B hyperactivity is induction through toll-like receptors expressed on astrocytes and microglia stimulated by noxious stimuli, resulting in positive feedback loop[22]. Further evidence of IL-1 cytokines family involvement in the mechanisms of spinal cord central senzitation lies in animal studies, where applying IL-1RN was used to attenuate hyperalgesia[23]. This data indirectly support our hypothesis of IL-1 gene locus involvement in chronic LBP.

The issue arising in interpretation of our findings lies in the lack of association of SNP in IL-1RN (rs2234677) with a group of war veterans suffering from PTSD and LBP contrary to the war veterans suffering from only LBP. This could be explained by altered pain processing in PTSD. Geuze et al. have first published preliminary results of hyperactivation of anterior cingulated cortex (ACC), right putamen and bilateral insula accompanied with decreased activation of right precentral gyrus and the right amygdala by fMRI imaging of pain processing in war veterans suffering from PTSD[24,25]. Interestingly, they found reduced sensitivity to standard pain stimulus, but increased reactivity above the pain threshold. These findings of distinct pain sensitivity were replicated by Defrin et al.[26]. PET study using (11C) cartefanil in PTSD war veterans has found reduced μ-opioid levels in amygdala, nucleus accumbens, and dorsal frontal and insular cortex[27].

These imaging data suggest altered pain processing in PTSD, although our literature search through relevant databases have not found imaging studies in veterans suffering from both PTSD and chronic pain in order to compare with the pain processing in patients suffering from chronic pain only. We hypothesize that there is a likely possibility that LBP in patients suffering from PTSD is, somewhat, distinct syndrome, different than LBP in war veterans without PTSD. Based on both epidemiological and imaging studies of chronic pain in PTSD, it seems that the main pathogenic moment lies in the alteration of brain circuits involved in sensory, cognitive and affective pain processing, while in LBP without comorbid PTSD pathogenesis lies in the central senzitation of spinal cord, therefore cytokine network. This could explain our findings, perhaps contradictory at first glance, but more studies are needed to confirm this suggestion.

The of association between SNP in IL-1B (rs1143634) and self- reported pain questionnaire

SNP in IL1B (rs1143634) was associated with »pain evaluation« – pain intensity on scale from 1 to 5, while both SNPs were not associated with »affective pain« nor »sensory pain« factors derived from Melzack's SFMPQ.

The issue in the interpretation of our results is the lack of association of SNP in *IL*-1RN (rs2234677) and self-reported scale of SFMPQ. To explain this one must consider the definition of pain provided by International Association for Study of Pain (IASP), which focuses on pain as a primarily subjective feeling[28]. We have tried to divide LBP, perhaps semi-successfully, into two entities; the first being objective clinical diagnosis made by psychiatrist, radiologist and surgeon, and the second being subjective perception of pain, measured by SFMPQ. As stressed out by Kerkof et al. in IL-1 locus meta-analyis of knee and hip arthritis, the genetic studies in chronic pain are often tricky, leading to perhaps doubtful conclusions due to diverse phenomenology of chronic pain[8]. They have shown the association of IL-1 region with the intensity of knee arthritis without the association to radiographic findings, showing the discrepancy of objective and subjective state. Although objective measurement of chronic pain[29], especially functional imaging, has advanced our understanding of pain processing, it's utility in genetic research remains questionable, mainly because small samples and expensiveness. Use of algometry might have enhanced our study, the authors question if its usage would bring different results, especially in context of chronic LBP. Because of the reasons explained above, we argue for plausibility of our results suggesting the involvement of IL-1 genetic region in LBP, especially the association of SNP in IL1B (rs1143634) with the subjective evaluation of pain. It is important to note that in this association both LBP groups have been used in analysis.

Merits and limitations of the study

To the authors' knowledge, this is a first study associating IL-1B and IL-RN SNPs with chronic LBP. Furthermore, this is a first association study exploring cytokine network genetics of LBP in context of psychiatric disorder, such as PTSD, adding more clinical relevance to research. The design of the study used more strict criteria than usually used in chronic pain studies. While we defined the duration of chronic pain as a pain lasting for more than one year, chronic pain is usually defined as a pain lasting for more than three months. We have used the narrower definition in order to filtrate a possible confounding factor of the subjects' pain reporting due to different perception of pain and recall error. In the analysis of self-reported questionnaires only upper 25 percentiles as cases and other 75 percentiles as controls have been used in order to clarify results. By using two additional groups: war veterans suffering from PTSD and healthy war veterans, we were able to control for possible confounding factors such as traumatic experience, which is currently hypothesised as being influential on the genome via epigenetic modulation[30,31], although up to date no study has investigated actual epigenetic modulation in PTSD.

One of the possible limitation of this study was omittance to use the semi-structured interview Clinician Administered PTSD Scale[32] in the diagnosis of PTSD, but psychiatric interview at the time of the entrance to the study according to DSM-IV-TR and TSI-A in order to acquire in-depth information about association between self-reported PTSD symptoms and chronic LBP (data not currently published) because of the discrepancy between clinicians' and patients' view of the PTSD symptoms[33]. Second possible limitation is unknown Croatian genetic

homogeneity, although because of European relative genetic homogeneity and low migration rates, one might assume that Croatian population is homogenous. Third limitation was inability to achieve small effect size due to low sample size, although most of psychiatric association studies at molecular level had similar sample size. Another limitation is unknown function of SNPs used in this study.

Conclusion

This study has offered preliminary evidence for role of IL-1 locus in pathogenesis in LBP and indirect evidence of altered brain circuits in pain processing in PTSD. However, as most genetic association studies involving several SNPs, based on specific hypothesis, it suffers from usual pitfalls. Future research is needed in order to replicate these findings and possibly expand knowledge about genetic background of LBP in genome-wide association studies in order to find possible new pathogenic events and enhance our understanding of chronic pain in psychiatric disorders.

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DA LI IL-1B I IL-1 MODULIRAJU DOŽIVLJAJ BOLI KOD KRONIČNE KRIŽOBOLJE U PACIJENATA SA DIJAGNOSTICIRANIM POSTTRAUMATSKIM STRESNIM POREMEĆAJEM?

SAŽETAK

Cilj ovog istraživanja je bio analizirati vezu između pojedinog nukleotidnog polimorfizma (SNP) kod IL1B (rs1143 634) i IL1RN (rs2234677) s doživljajem boli kod kronične križobolje (LBP) u veterana dijagnosticiranih sa posttraumatskim stresnim poremećajem (PTSP). Sudionici su bili podijeljeni u četiri grupe temeljem psihijatrijskog intervjua, psihometrijskog tesitranja i prisutnosti boli u križima. Prvu skupinu su sačinjavali ratni veterani kojima je dijagnosticiran

PTSP i kronična križobolja (N=102), drugu skupinu su sačinjavali ratni veterani kojima je dijagnosticiran samo PTSP (N=108), treću skupinu su sačinjavali ratni veterani kojima je dijagnosticirana samo krnoična križobolja (N=99), a četvrtu skupinu su sačinjavale zdrave kontrole (N=97). Svaki sudionik je bio prodvrgnut testiranju na IL1B i IL1RN polimorfizme iz krvi. Provedenim analizama nije pronađena veza između rs1143634 u IL1-B sa kroničnom križoboljom. Test permutacija je pokazao značajnu vezu rs1143634 u IL1-RN sa kroničnom križoboljom, s time da se prisutnost divljeg tipa alela A pokazala protektivnim faktorom kod kronične križobolje. Pojedini nukleotidni polimorfizam (rs1143634) kod IL1-B je pokazao vezu sa intenzitetom boli. Ovim istraživanjem nisu dokazane nikakve druge veze između navedenih markera i samoiskaza o mjerama PTSP-a ili bolnih simptoma. Rezultati ukazuju na potencijalnu ulogu mreže citokina u patogenezi kroničnog PTSP-a i kronične križobolje, iako direktan uzročni put za sada nije jasan. Promjene u citokinskoj mreži na razini mozga, leđne moždine i kralježnice mogu biti odgovorne za modulaciju boli i pojavnost kronične križobolje.