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Research article

PREDICTING THE RISK OF DEVELOPING VIBRATION DISEASE AND VEGETATIVE-SENSORY POLYNEUROPATHY UNDER VIBRATION EXPOSURE USING ANALYSIS OF CANDIDATE GENE POLYMORPHISM

G.F. Mukhammadiyeva[1], E.R. Shaikhlislamova[1,2], D.D. Karimov[1], D.O. Karimov[1], E.F. Repina[1], T.G. Yakupova[1], E.R. Kudoyarov[1]

[1]Ufa Research Institute of Occupational Health and Human Ecology, 94 Stepana Kuvykina St., Ufa, 450106, Russian Federation
[2]Bashkir State Medical University, 3 Lenina St., Ufa, 450008, Russian Federation

In this study, we investigated the association of IL-6 (rs1800795), TNF-α (rs361525), IL-1β (rs16944), MMP-1 (rs1799750) and SOD2 (rs4880) gene polymorphisms with the risk of developing vibration disease (VD) and autonomic sensory polyneuropathy (ASPN).

We examined 45 patients with VB, 10 patients with ASPN and 76 people who were not exposed to vibration in their professional activities. Polymorphic gene variants were determined using a real-time polymerase chain reaction.

The polymorphic variant rs16944 of the IL-1β gene was established to carry both the G allele (p = 0.027) and the homozygous G/G genotype (p = 0.015) with elevated frequency in the group of patients with VD relative to the control group. Allele A of the rs361525 polymorphic variant of the TNF-α gene was more common in patients with ASPN as compared to controls, (p = 0.047). Statistically significant differences in polymorphic variants rs1800795 of the IL-6 gene, rs1799750 of the MMP-1 gene and rs4880 of the SOD2 gene were not found in both groups of patients as compared to the control group. However, when comparing groups of patients with each other, we established that the G allele of the polymorphic variant rs1800795 of the IL-6 gene was more often recorded in patients with ASPN (p = 0.032).

The results obtained by examining the patients with VD and ASPN made it possible to establish that the rs361525 polymorphic variant of the TNF-α gene is associated with an elevated risk of developing ASPN, while carriers of the homozygous genotype G/G of the rs16944 polymorphic variant of the IL-1β gene have a high prognostic risk of developing VD. Polymorphic variants of the IL-1β and TNF-α genes can be considered probable molecular genetic predictors of VD and ASPN.

Keywords: *vibration disease, autonomic-sensory polyneuropathy, gene polymorphism, IL-6, TNF-α, IL-1β, MMP-1, SOD2, risk.*

Long vibration exposure can be found in various industries. It is a well-known risk factor able to cause occupational diseases. Apart from vibration disease, occupational vibration induces some complex changes in the body typical for disorders of the nervous system and

Guzel F. Mukhammadiyeva – Candidate of Biological Sciences, Senior Researcher at the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: ufniimt@mail.ru; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0002-7456-4787).

Elmira R. Shaikhlislamova – Candidate of Medical Sciences, director; Associate Professor of the Department of Therapy and Occupational Diseases with the course of Institute of Additional Professional Education (e-mail: fbun@uniimtech.ru; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0002-6127-7703).

Denis D. Karimov – Candidate of Biological Sciences, Senior Researcher at the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: lich-tsar@mail.ru; ORCID: https://orcid.org/0000-0002-1962-2323).

Denis O. Karimov – Candidate of Medical Sciences, Head of the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: karimovdo@gmail.com; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0003-0039-6757).

Elvira F. Repina – Candidate of Medical Sciences, Senior Researcher at the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: e.f.repina@bk.ru; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0001-8798-0846).

Tatyana G. Yakupova – Junior Researcher at the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: tanya.kutlina.92@mail.ru; ORCID: https://orcid.org/0000-0002-1236-8246).

Eldar R. Kudoyarov – Junior Researcher at the Department of Toxicology and Genetics with the Experimental Clinics for Laboratory Animals (e-mail: ekudoyarov@gmail.com; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0002-2092-1021).

cardiovascular diseases as well as diseases of the musculoskeletal system and gastrointestinal tract. Occupational polyneuropathy holds a significant place among them. It develops due to exposure to both local and whole body vibration. Occupational polyneuropathy caused by local vibration exposure is often accompanied with peripheral angiodystonia. In such cases, regional cerebral angiodystonia is a usual concomitant disease that occurs in patients with autonomic sensory polyneuropathy (ASPN) of the limbs caused by whole body vibration exposure [1–3].

Heredity is known to play a significant role in adaptation and responses to occupational exposures. Variability of workers' individual sensitivity to occupational factors can be explained relying on genetic variability. Gene polymorphisms can be considered as risk predictors regarding many diseases. Identification of individual disease risks at the molecular level facilitates more accurate diagnostics as well as effective selection of preventive and therapeutic measures. Rapid development of genetic studies over recent years has made it possible to get a better insight into the role that belongs to genetic factors in the development of occupational diseases [4–6]. However, molecular-genetic aspects of many occupational diseases still remain poorly explored.

The aim of this study was to investigate the association of the *IL-6* (rs1800795), *TNF-α* (rs361525), *IL-1β* (rs16944), *MMP-1* (rs1799750) and *SOD2* (rs4880) gene polymorphisms with the risk of developing vibration disease (VD) and autonomic sensory polyneuropathy (ASPN).

Materials and methods. Forty-five patients with VD and ten patients with ASPN were examined in the Department for Neurology and Occupational Pathology of the Ufa Research Institute of Occupational Health and Human Ecology. Vibration exposure was an etiological factor of both diseases. The control group was made of 76 people who were not occupationally exposed to vibration. All the examined people lived in Bashkortostan. After a participant gave the informed written consent to take part in the study, venous blood was taken into a vacutainer with K_3EDTA.

DNA was extracted from blood samples using Magno-Sorb kits manufactured by the Rospotrebnadzor Central Scientific Research Institute for Epidemiology. Polymorphisms were analyzed by the real-time polymerase chain reaction accomplished using the Rotor-Gene Q device (Qiagen, Germany). Specific oligonucleotide primers and locus-specific stained oligonucleotide DNA probes were used in the analysis.

Data were analyzed in IBM SPSS Statistica v.21 and Microsoft Excel. The χ^2 or the exact Fisher's test was used to describe frequencies of genotypes and alleles of the examined genes. Influence of polymorphisms on a risk of disease was estimated by using odds ratio (*OR*) with 95 % confidence interval (95 % CI). *OR* value below 1 was considered evidence of a negative association between disease and an analyzed genotype or allele (a factor of a lower risk); *OR* value above 1 meant a positive association (a factor of an elevated risk). The statistical significance in the null hypothesis testing was taken as equal to 0.05.

Results and discussion. Frequencies of the genotypes and alleles of the *IL-6* gene rs1800795 polymorphism for the VD and ASPN patients are given in Tables 1 and 2. We did not find any statistically significant differences when comparing both groups with the control. At the same time, the VD patients had the C/C genotype more than 2 times as often but the statistical significance was not reached ($\chi^2 = 3.82$, $p = 0.051$).

We did not find any statistically significant differences between the VD patients and the control either, either per frequencies of the genotypes or alleles of the *TNF-α* gene rs361525 polymorphism ($p > 0.05$) (Table 3).

Data provided in Table 4 clearly show that the ASPN patients predominantly had the allele A of the *TNF-α* gene rs361525 polymorphism (25.0 %) against the control (8.0 %; $\chi^2 = 3.94$, $p = 0.047$). The *OR* value equaled 3.83 (95 % CI: 1.19–12.37) for the allele A, which probably indicates it is a risk factor as regards hereditary predisposition to ASPN development.

Table 1

Frequencies of genotypes and alleles of the *IL-6* gene rs1800795 polymorphism in the VD patients and the control

Genotypes and alleles	VD		Control		χ^2	*p*
	n	%	*n*	%		
C/C	12	28.6	9	12.2	3.82	0.051
C/G	13	30.9	29	39.2	0.47	0.493
G/G	17	40.5	36	48.6	0.43	0.513
C	37	44.1	47	31.8	2.99	0.084
G	47	55.9	101	68.2	2.99	0.084

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 2

Frequencies of genotypes and alleles of the *IL-6* gene rs1800795 polymorphism in the ASPN patients and the control

Genotypes and alleles	ASPN		Control		χ^2	*p*
	n	%	*n*	%		
C/C	0	0.0	9	12.2	0.39	0.534
C/G	3	30.0	29	39.2	0.05	0.831
G/G	7	70.0	36	48.6	0.87	0.353
C	3	15.0	47	31.8	1.63	0.202
G	17	85.0	101	68.2	1.63	0.202

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 3

Frequencies of genotypes and alleles of the *TNF-α* gene rs361525 polymorphism in the VD patients and the control

Genotypes and alleles	VD		Control		χ^2	*p*
	n	%	*n*	%		
GG	39	86.7	63	84.0	0.02	0.896
GA	5	11.1	12	16.0	0.22	0.636
AA	1	2.2	0	0.0	0.07	0.796
G	83	92.2	138	92.0	0.03	0.854
A	7	7.8	12	8.0	0.03	0.854

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 4

Frequencies of genotypes and alleles of the *TNF-α* gene rs361525 polymorphism in the ASPN patients and the control

Genotypes and alleles	ASPN		Control		χ^2	*p*
	n	%	*n*	%		
GG	6	60.0	63	84.0	1.94	0.164
GA	3	30.0	12	16.0	0.42	0.516
AA	1	10.0	0	0.0	1.43	0.233
G	15	75.0	138	92.0	3.94	0.047
A	5	25.0	12	8.0	3.94	0.047

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

The same results were obtained for the allele G of the *IL-1β* gene rs16944 polymorphism in the VD patients (Table 5). Frequency of the allele G was significantly higher in the VD patients (54.9 %) against the control (38.4 %; $\chi^2 = 5.16$, $p = 0.027$; *OR* = 1.96; 95 % CI: 1.13–3.38). The comparison of genotype frequencies established that the G/G genotype was significantly more frequent in the VD patients ($\chi^2 = 6.06$, $p = 0.015$). Carriers of the homozygous G/G genotype of *IL-1β* gene rs16944 polymorphism had thrice as high VD risk (*OR* = 3.25; 95 % CI: 1.35–7.86).

We did not establish any significant differences between the ASPN patients and the control when estimating frequencies of genotypes and alleles of the *IL-1β* gene rs16944 polymorphism ($p > 0.05$) (Table 6).

Tables 7 and 8 provide data on frequencies of the genotypes and alleles of the *MMP-1* gene rs1799750 polymorphism in the VD patients, ASPN patients and the control. We did not establish any significant differences in frequencies of the genotypes and alleles of this polymorphism in the analyzed groups ($p > 0.05$).

We did not find any significant differences in the analyzed groups when estimating possible associations between the alleles and genotypes of the *SOD2* gene rs4880 polymorphism and VD and ASPN risks ($p > 0.05$) (Tables 9 and 10).

Table 5

Frequencies of genotypes and alleles of the *IL-1β* gene rs16944 polymorphism in the VD patients and the control

Genotypes and alleles	VD		Control		χ^2	*p*
	n	%	*n*	%		
A/A	12	29.3	29	39.7	0.83	0.362
A/G	13	31.7	32	43.8	1.15	0.285
G/G	16	39.0	12	16.5	6.06	0.015
A	37	45.1	90	61.6	5.16	0.024
G	45	54.9	56	38.4	5.16	0.024

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 6

Frequencies of genotypes and alleles of the *IL-1β* gene rs16944 polymorphism in the ASPN patients and the control

Genotypes and alleles	ASPN		Control		χ^2	*p*
	n	%	*n*	%		
A/A	3	30.0	29	39.7	0.06	0.806
A/G	4	40.0	32	43.8	0.01	0.913
G/G	3	30.0	12	16.5	0.37	0.544
A	10	50.0	90	61.6	0.57	0.451
G	10	50.0	56	38.4	0.57	0.451

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 7

Frequencies of genotypes and alleles of the *MMP-1* gene rs1799750 polymorphism in the VD patients and the control

Genotypes and alleles	VD		Control		χ^2	*p*
	n	%	*n*	%		
1G/1G	16	41.03	27	35.5	0.14	0.709
1G/2G	14	35.90	34	44.8	0.50	0.478
2G/2G	9	23.08	15	19.7	0.03	0.862
1G	46	58.97	88	57.9	0.00	0.988
2G	32	41.03	64	42.1	0.00	0.988

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 8

Frequencies of genotypes and alleles of the *MMP-1* gene rs1799750 polymorphism in the ASPN patients and the control

Genotypes and alleles	ASPN		Control		χ^2	*p*
	n	%	*n*	%		
1G/1G	2	25.0	27	35.5	0.04	0.839
1G/2G	4	50.0	34	44.8	0.01	0.930
2G/2G	2	25.0	15	19.7	0.01	0.913
1G	8	50.0	88	57.9	0.12	0.733
2G	8	50.0	64	42.1	0.12	0.733

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 9

Frequencies of genotypes and alleles of the *SOD2* gene rs4880 polymorphism in the VD patients and the control

Genotypes and alleles	VD		Control		χ^2	*p*
	n	%	*n*	%		
T/T	20	46.5	22	29.7	2.64	0.104
T/C	17	39.5	34	40.0	0.23	0.631
C/C	6	14.0	18	24.3	1.21	0.271
T	57	66.3	78	52.7	3.57	0.059
C	29	33.7	70	47.3	3.57	0.059

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Table 10

Frequencies of genotypes and alleles of the *SOD2* gene rs4880 polymorphism in the ASPN patients and the control

Genotypes and alleles	ASPN		Control		χ^2	*p*
	n	%	*n*	%		
T/T	3	30.0	22	29.7	0.12	0.726
T/C	6	60.0	34	46.0	0.25	0.619
C/C	1	10.0	18	24.3	0.38	0.540
T	12	60.0	78	52.7	0.14	0.708
C	8	40.00 %	70	47.3	0.14	0.708

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

We compared frequencies of the alleles and genotypes for the following polymorphisms: rs361525 of the *TNF-α* gene, rs16944 of the *IL-1β* gene, rs1799750 of the *MMP-1* gene and rs4880 of the *SOD2* gene. As a result, we did not find any significant differences between the VD patients and the ASPN patients ($p > 0.05$) (Table 11). A significantly more frequent allele G of the *IL-6* gene rs1800795 polymorphism was identified in the ASPN patients (85.0 %) against the VD patients (55.9 %; $\chi^2 = 4.60$, $p = 0.032$; $OR = 4.46$; 95 % CI: 1.22–16.38). Therefore, we can assume that carriers of the allele G of the said polymorphism have higher risks of ASPN development.

When we discuss how the genotypes of the studied polymorphisms are distributed in the analyzed groups, we should first note that we have not managed to find any data on similar research focusing on VD or ASPN patients in the available literature. However, we have compared our findings with those reported by other authors in their works concentrating on diseases able to influence VD and ASPN manifestations.

Table 11

Frequencies of alleles and genotypes of the examined gene polymorphisms in the VD and ASPN patients

Polymorphism	Genotypes, alleles	VD		ASPN		χ^2	*p*
		n	%	*n*	%		
rs1800795 (*IL-6* gene)	C/C	12	28.6	0	0.0	2.28	0.131
	C/G	13	30.9	3	30.0	0.10	0.747
	G/G	17	40.5	7	70.0	1.77	0.184
	C	37	44.1	3	15.0	4.60	0.032
	G	47	55.9	17	85.0	4.60	0.032
rs361525 (*TNF-α* gene)	G/G	39	86.7	6	60.0	2.32	0.128
	G/A	5	11.1	3	30.0	1.07	0.301
	A/A	1	2.2	1	10.0	0.06	0.800
	G	83	92.2	15	75.0	3.38	0.066
	A	7	7.8	5	25.0	3.38	0.066
rs16944 (*IL-1β* gene)	A/A	12	29.3	3	30.0	0.12	0.733
	A/G	13	31.7	4	40.0	0.02	0.902
	G/G	16	39.0	3	30.0	0.03	0.870
	A	37	45.1	10	50.0	0.02	0.888
	G	45	54.9	10	50.0	0.02	0.888
rs1799750 (*MMP-1* gene)	1G/1G	16	41.0	2	25.0	0.20	0.653
	1G/2G	14	35.9	4	50.0	0.12	0.728
	2G/2G	9	23.1	2	25.0	0.12	0.733
	1G	46	59.0	8	50.0	0.15	0.701
	2G	32	41.0	8	50.0	0.15	0.701
rs4880 (*SOD2* gene)	T/T	20	46.5	3	30.0	0.35	0.552
	T/C	17	39.5	6	60.0	0.68	0.412
	C/C	6	14.0	1	10.0	0.03	0.853
	T	57	66.3	12	60.0	0.07	0.787
	C	29	33.7	8	40.0	0.07	0.787

Note: *n* is the number, χ^2 is the chi-square test, *p* is statistical significance.

Interleukin-6 (IL-6) is a multifunctional cytokine able to mediate inflammation and regulate endocrine and metabolic functions. It participates in tissue regeneration and induces various innate and adaptive immune responses [7]. The rs1800795 functional polymorphism is located in the promoter section of the *IL-6* gene in the -174 position. Its allele G is associated with higher production of the said cytokine. This polymorphism has been shown to influence *IL-6* transcription and secretion and these changes are considered significant disease-inducing risk factors [8, 9]. A meta-analysis has provided strong evidence for the association between *IL-6* gene rs1800795 polymorphism and multiple disease risks. The *IL-6* gene could be a useful prognostic biomarker for CAD, inflammatory disease, ischemic stroke, and rheumatoid arthritis [10]. Some previous studies have also established the *IL-6* gene rs1800795 polymorphism to be associated with chronic inflammatory demyelinating polyneuropathy predisposition [11], which is consistent with our study findings.

The tumor necrosis factor alpha (*TNF-α*) gene is located in the main histocompatibility complex. It encodes the TNF-α protein, a significant inflammatory and immune-modulating cytokine. A study has established that TNF-α levels are elevated in synovial fluid, synovial membrane, subchondral bone and

cartilage [12]. The *TNF-α* gene rs361525 polymorphism is among the most examined ones. It participates in regulation of cytokine production. This polymorphism can have its impact on the *TNFα* gene transcription and an elevated *TNF-α* level can promote higher risks of many diseases [13]. A TNF-α level in serum has been reported to correlate with a first developing cardiovascular disease; it is also considered a marker of repeated coronary events in patients after myocardial infarction [14, 15]. In the Chinese Han population, the minor allele T of rs1799724 could increase the risk of AS, while the minor allele A of rs361525 protects individuals from ankylosing spondylitis [16]. Another study has established a correlation between the said polymorphism and a risk of psoriatic arthritis [17]. According to our findings, carriage of the allele A of the *TNF-α* gene rs361525 polymorphism is a significant factor as regards hereditary ASPN predisposition.

Cytokines from the interleukin-1 (IL-1) family are known to participate in inflammation and immune regulation. They also have an important role in the innate and adaptive immunity. Some recent studies have established that IL-1 can have direct influence on bone homeostasis, and improper regulation of IL-1 is associated with bone disease [18]. The cytokine IL-1β, which is encoded by the *IL-1β* gene, is mostly secreted by stimulated macrophages and monocytes and to a lesser extent by some other cells including neutrophils, lymphocytes, endothelial cells and fibroblasts. Apart from immune cells, intervertebral disk cells can secret IL-1β on their own. One of the most widespread polymorphisms of the *IL-1β* gene (rs16944) has been shown to be associated with lumbar intervertebral disk disease [19]. This polymorphism may associate with increased susceptibility to extremity chronic osteomyelitis in Chinese Han population [20]. A meta-analysis has shown an association between the *IL-1β* gene rs16944 polymorphism and an elevated risk of rheumatoid arthritis in Caucasians [21]. In general, our findings that report an association between the *IL-1β* gene rs16944 polymorphism and VD do not contradict these previously published data.

Metalloproteinase-1 (MMP-1) is the most widely expressed proteolytic enzyme of the matrix metalloproteinase family. It plays the key role in degradation and destruction of joint cartilage and bone. MMP-1 is expressed in different cells such as chondrocytes, fibroblasts, epithelial and endothelial cells as well as tumor cells. MMP-1 levels grow considerably in case of pathology and cause connective tissue degradation [22]. Increased MMP-1 expression in chondrocytes stimulates degradation of cartilage collagen and proteoglycane and this leads to pathological damage to cartilage in patients with osteoarthritis [23]. The promoter section of the *MMP-1* gene has been shown to contain rs1799750 single nucleotide polymorphism, which is able to induce elevated transcriptional activity of the gene [24]. There are available data in literature on a reported association between this polymorphism and osteoarthritis [25, 26], systemic sclerosis [27], coronary artery disease [28], increased low back pains, sciatica and disability after lumbar disc herniation [29]. Nevertheless, we did not identify any associations between this polymorphism and VD and ASPN.

Superoxide dismutase-2 (SOD2) is a tetramer enzyme with manganese in its active center. It is the core system of the body antioxidant protection, which is activated by reactive oxygen species and distributed in mitochondria, peroxisomes and cytoplasm [30]. The *SOD2* gene has binding sites for various transcription factors, which act as ligands to activate transcription and participate in protecting cells from agents able to induce an oxidative stress [31]. The *SOD2* gene expression is induced by various cytokines, growth factors, reactive oxygen species, lipopolysaccharides, and heavy metals. Recently, more

and more new data have been reported about the key role the oxidative stress plays in the development of osteoarthritis; high levels of reactive oxygen species can stimulate higher lipid peroxidation, damage mitochondrial DNA and activate signal pathways [32]. All these changes can promote cartilage destruction and collagen and hyaluronan degradation [33]. Several single nucleotide polymorphisms have been identified in the *SOD2* gene including the rs4880 functional polymorphism. Some studies have reported that the *SOD2* gene rs4880 polymorphism is associated with an elevated risk of cardiomyopathy, stroke and coronary artery disease [34–36]. However, we did not obtain similar results when analyzing frequencies of the alleles and genotypes of the said polymorphism in the VD and ASPN patients.

Conclusion. The results obtained by examining the VD and ASPN patients have made it possible to establish that the *TNF-α* gene rs361525 polymorphism is associated with an elevated ASPN risk; carriers of the homozygous G/G genotype of the *IL-1β* gene rs16944 polymorphism have a high predicted VD risk. The *IL-1β* and *TNF-α* gene polymorphisms can be considered probable molecular-genetic predictors of VD and ASPN; however, small samples of patients with the diseases make additional research quite necessary. Our study findings can provide grounds for developing relevant screening programs aimed at detecting people with elevated VD and ASPN risks. Data on associations between gene polymorphisms and disease can be considered within preventive activities.

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