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Research article

ANALYSIS OF ASSOCIATIONS BETWEEN POLYMORPHIC VARIANTS OF SOME GENES ENCODING TRANSCRIPTION FACTORS AND THE RISK OF DEVELOPING VIBRATION DISEASE

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This work assesses possible associations between polymorphisms of the IRX1, SMAD3, TEAD1 genes and the risk of developing vibration disease (VD), an occupational disease that occurs under prolonged exposure to industrial vibration.

The study involved 80 patients with VB and 105 people in the control group living in the Republic of Bashkortostan. Real-time polymerase chain reaction was used to genotype polymorphic variants of rs12653958 of the IRX1 gene, rs7163797 of the SMAD3 gene, and rs3993110 of the TEAD1 gene. Statistical data analysis was performed using the χ^2 criterion and calculation of the odds ratio (OR) with a 95 % confidence interval.

No significant associations were found between polymorphic variants rs12653958 of the IRX1 gene, rs7163797 of the SMAD3 gene, rs3993110 of the TEAD1 gene and the risk of developing VD. Although certain trends were observed in the distribution of genotype and allele frequencies, no statistically significant differences were found between the patient group and the control group. The most pronounced trend was noted for the polymorphic variant rs3993110 of the TEAD1 gene: the frequency of the A/A genotype in patients was 35.0 % versus 24.5 % in the control ($p = 0.172$).

The results of the study indicate that the studied polymorphic variants are probably not significant risk factors for the development of VD. However, the identified trends justify the need for further study on larger and ethnically heterogeneous samples. The obtained data expand the understanding of the molecular genetic basis of VD and can be used in developing personalized approaches to predicting the risk of developing occupational diseases. A promising direction is the study of additional genetic markers and their pathogenetic role in the development of the disease.

Keywords: *vibration disease, occupational diseases, genetic polymorphisms, genetic predisposition, IRX1, SMAD3, TEAD1, risk.*

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Vibration disease (VD) holds a leading place among occupational pathologies. Most frequently, it is diagnosed in workers employed in construction, shipbuilding, aircraft building, mining, metallurgy, agriculture and transport. VD is a poly-syndrome disease with persistent progression; it is caused by long-term exposure to occupational vibration beyond safe standards. VD development involves a set of pathological changes including neurovascular and neuromediator disorders as well as vestibular and coordination dysfunction. Overall, the pathological process can be considered close to angiotrophoneurosis, which, unless treated, can progress and spread onto other systems in the body. As a result, serious complications are rather likely, right up to persistent loss of work ability [1–3].

Hereditary predisposition makes a significant contribution to determining how susceptible a person is to harmful occupational exposures; it is also a significant factor promoting onset and progression of occupational diseases. Contemporary research more and more frequently corroborates effects produced by genetic factors on risks associated with onset and progression of occupational diseases [4–6]. The iroquois homeobox gene 1 (*IRX1*) is particularly interesting in this respect; it belongs to the iroquois homeobox gene family involved in embryonic development and cell differentiation [7]. This gene encodes the IRX1 transcription factor, which can regulate the vessel ability to dilate. The intracellular signal protein SMAD3 plays a significant role in transferring signals from the receptors of the transforming growth factor beta (TGF-β) to the nucleus and in regulating transcription of target genes [8]. Some studies have reported that the *SMAD3* gene, which codes this protein, is known to play a role in bone remodeling and cartilage maintenance. They have also confirmed differentiated expression of *SMAD3* in intact and degraded cartilage of the knee and hip [9]. TEA domain transcription factor 1 (TEAD1) is a key factor of transcription in the Hippo signaling pathway, an evolutionarily conserved protein kinase cascade, which regulates neurodevelopment and is involved in pathogenesis of diseases of the nervous system through neuroinflammation modulation, neuronal differentiation and cell death [10]. When the nervous system is developing, the *TEAD1* gene is necessary for proliferation of neural stem cells and survival of neural precursor cells [11, 12]. All aforementioned genes are involved in key pathological processes typical for VD including vascular disorders, fibrosis-degenerative changes in the connective tissue and neurological dysfunction. The *IRX1* gene, which regulates vascular dilation, might be associated with developing angiospasms and microcirculatory disorders observed in VD patients. The *SMAD3* gene, which mediates transfer of TGF-β signals, plays a significant role in fibrosis and tissue remodeling, which can explain degenerative changes in cartilage and joint tissues upon long-term vibration exposure. The *TEAD1* gene as the key transcription factor of the Hippo signaling pathway regulates neuroinflammation, neural differentiation and cell death, which can cause onset of peripheral neuropathy as a typical VD symptom. Therefore, polymorphisms of these genes are especially interesting as potential genetic VD markers since their functional significance is directly associated with basic pathogenetic components of the disease.

Up-to-date diagnostic approaches allow identifying predictors indicating elevated risks of occupational diseases. These advances promote implementation of effective prevention programs. However, despite considerable success in the sphere, many aspects of molecular-genetic pathways of specific occupational pathologies have not been given enough attention.

The aim of this study was to assess possible associations between polymorphisms of the *IRX1, SMAD3, TEAD1* genes and the risk of developing vibration disease (VD).

Materials and methods. The study involved 80 patients with diagnosed VD aged between 23 and 79 years (the average age was 59.9 ± 1.6 years), who were treated at the department for neurology and occupational pathology, the hospital of the Ufa Research Institute of Occupational Health and Human Ecology. The control group was made of 105 people aged between 23 and 79 years (the average age was 53.5 ± 1.1 years) without any contacts with occupational vibration. All participants permanently resided in the Republic of Bashkortostan; they gave their written consent to participate in the research after having been provided with complete information about the study aims and methods.

Venous blood stabilized with K_3EDTA was used in the experiment. DNA was extracted with 'Magno-sorb' commercial kit produced by Rospotrebnadzor's Central Scientific Research Institute for Epidemiology. Real-time polymerase chain reaction was used to genotype polymorphic variants of rs12653958 of the *IRX1* gene, rs7163797 of the *SMAD3* gene, and rs3993110 of the *TEAD1* gene. To do that, we applied specifically designed primers and DNA probes synthesized by DNA-Synthesis, a Moscow-based company.

Statistical data analysis was performed in IBM SPSS Statistics 21 and Microsoft Excel using the χ^2 test for comparing distribution of alleles and genotypes in two groups. A relationship between gene polymorphisms and the risk of the disease was quantified by calculating the odds ratio (OR) with a 95 % confidence interval (95 % CI). OR > 1 indicated higher likelihood of the disease whereas OR < 1 was considered a protective effect. Differences were considered significant at $p < 0.05$.

Results and discussion. The study investigated possible associations between polymorphisms of the *IRX1, SMAD3, TEAD1* genes and the risk of developing vibration disease (VD). Distribution of genotypes established for all analyzed polymorphisms in the control group conformed to the Hardy – Weinberg equilibrium. But the equilibrium was not met in the examined VD patients. Analysis of the rs12653958 of the *IRX1* gene established the G/G genotype in 12.2 % of the VD patients whereas its frequency equaled only 8.6 % in the healthy participants; however, these differences were not confirmed to be significant ($p = 0.593$). The A/A genotype was found in 63.5 % of the VD patients and 61.9 % of the controls but these differences were not significant either ($p = 0.951$). The heterozygous A/G genotype turned out to be a bit less frequent among the VD patients (24.3 %) against the healthy controls (29.5 %) but the *p*-value (0.550) again did not reach statistical significance.

Frequency of the G allele (24.3 %) among the VD patients had practically similar to that among the healthy controls (23.3 %) with the *p*-value being 0.929, which indicated any significant intergroup differences were absent.

The *IRX1* gene is thought to act as possible vasodilatation regulator by changing sensitivity to prostaglandin and / or bradykinin [13]. An assumed role played by this polymorphism in vasodilatation / vasoconstriction can explain its association with cardiovascular diseases. Elevated expression of the *IRX1* gene can activate genes that prevent constricted vessels from relaxing as it usually happens. Studies with their focus on rs12653958 polymorphism of the *IRX1* gene revealed its association with some cardiovascular diseases, including myocardial infarction [14] and coronary artery disease [15] as well as its influence on Raynaud syndrome onset [13]. Nevertheless, we were

Table 1

Frequency of alleles and genotypes of rs12653958 of the *IRX1* gene in the analyzed groups

Genotypes and alleles	VD		Control		χ^2	*p*	OR (95 % CI)
	n	%	*n*	%			
A/A	47	63.5	65	61.9	0.001	0.951	1.07 (0.58–1.98)
A/G	18	24.3	31	29.5	0.36	0.550	0.77 (0.39–1.51)
G/G	9	12.2	9	8.6	0.29	0.593	1.48 (0.56–3.92)
A	112	75.7 %	161	76.7	0.01	0.929	0.95 (0.58–1.55)
G	36	24.3 %	49	23.3	0.01	0.929	1.06 (0.65–1.73)

Note: *n* is the number, χ^2 is the chi-square test, *p* is significance, OR is odds ratio, 95 % CI is 95 % confidence interval.

not able to establish a significant relationship between this polymorphism and the VD risk in our study.

Next, we analyzed how genotypes of rs7163797 of the *SMAD3* gene were distributed in two groups. The analysis established the A/A genotype in 47.4 % of the VD patients whereas its frequency was 45.0 % in the healthy controls; however, the difference was not significant (Table 2). The heterozygous C/A genotype tended to be less frequent among the VD patients (30.8 %) against the healthy controls (37.4 %) but the *p*-value (0.461) was above the threshold of statistical significance. The homozygous C/C genotype was a bit more frequent in the VD patients (21.8 %) against the controls (17.6 %) but this difference was not significant either ($p = 0.621$). Our analysis of allele distribution did not establish any significant intergroup differences either ($p = 0.952$).

The *SMAD3* gene is known to be involved in inflammation in osteoarthritis (OA) progression [16]. According to available data, the *SMAD3* gene has a predominantly regulatory effect on development of localized hip OA variants [17]. J.Y. Yao with colleagues confirmed an association between the *SMAD3* gene mutations and OA [18]. A meta-analysis revealed that *SMAD3* gene rs12901499 polymorphism increased the risk of osteoarthritis [19]. C.L. Miller and

Table 2

Frequency of alleles and genotypes of rs7163797 of the *SMAD3* gene in the analyzed groups

Genotypes and alleles	VD		Control		χ^2	*p*	OR (95 % CI)
	n	%	*n*	%			
A/A	37	47.4	41	45.0	0.02	0.878	1.10 (0.60–2.02)
C/A	24	30.8	34	37.4	0.54	0.461	0.75 (0.39–1.42)
C/C	17	21.8	16	17.6	0.24	0.621	1.31 (0.61–2.80)
A	98	62.8	116	63.7	0.001	0.952	0.96 (0.62–1.50)
C	58	37.2	66	36.3	0.001	0.952	1.04 (0.67–1.62)

Note: *n* is the number, χ^2 is the chi-square test, *p* is significance, OR is odds ratio, 95 % CI is 95 % confidence interval.

Table 3

Frequency of alleles and genotypes of rs3993110 of the *TEAD1* gene in the analyzed groups

Genotypes and alleles	VD		Control		χ^2	p	OR (95 % CI)
	n	%	*n*	%			
A/A	28	35.0	24	24.5	1.87	0.172	1.66 (0.87–3.18)
C/A	30	37.5	51	52.0	3.19	0.074	0.55 (0.30–1.01)
C/C	22	27.5	23	23.5	0.20	0.658	1.24 (0.63–2.44)
A	86	53.8	99	50.5	0.25	0.616	1.14 (0.75–1.73)
C	74	46.2	97	49.5	0.25	0.616	0.88 (0.58–1.34)

Note: *n* is the number, χ^2 is the chi-square test, *p* is significance, OR is odds ratio, 95 % CI is 95 % confidence interval.

other reported an association between rs17293632 polymorphism of the *SMAD3* gene and elevated risks of coronary artery disease (CAD). They also found an association between this polymorphism and elevated expression of the *SMAD3* gene in smooth muscle cells in human arteries [20]. In addition, a full-genome associative study found an association between rs17228212 polymorphism of the *SMAD3* gene and CAD development [21]. However, we have not managed to find any available publications with their focus on investigating effects produced by rs7163797 polymorphism of the *SMAD3* gene on development of the foregoing diseases. Our study did not establish a significant correlation between this polymorphism and VD.

Our analysis of distribution of the *TEAD1* gene rs3993110 polymorphism revealed certain intergroup differences, although not significant. Thus, the homozygous A/A genotype was more frequent in the VD patients being detected in 35 % of them against 24 % in the control group ($p = 0.172$). The heterozygous C/A genotype showed an inverse trend as its frequency was lower among the VD patients (37.5 %) against the control (52.0 %) but this difference was not significant either ($p = 0.074$). Frequency of the C/C genotype was practically the same in both groups (27.5 % in the VD patients and 23.5 % in the healthy controls) ($p = 0.658$). Our analysis of allele frequencies did not establish any significant intergroup differences either ($p > 0.05$).

Experiments on super-expression and knockdown showed the *TEAD1* gene to have direct influence on the neural tube development, neuron generation and fate, cell apoptosis and migration [11, 12, 22]. The *TEAD1* gene is the most prevalent in the heart and plays a specific role in its development [23]. Mutation in the *TEAD1* gene leads to Aicardi syndrome (AIC), a congenital neurodevelopmental disorder characterized by intellectual disability, enlarged cerebral cavities, agenesis of the corpus callosum, and disrupted neuron migration [24]. As association was established between rs3993110 polymorphism of the *TEAD1* gene and changes in joints that carry major weight burden in patients with osteoarthritis [25]. However, our findings do not confirm any significant contribution made by rs1800795 to the VD risk.

Conclusion. In this study, we assessed possible associations between polymorphisms of the *IRX1* gene (rs12653958), *SMAD3* gene (rs7163797) and *TEAD1* gene

(rs3993110) and the risk of vibration disease. Analysis of allele and genotype distribution did not find any significant differences between the VD patients and the control. This indicates that the studied polymorphic variants do not have any significant effect on the VD risk. However, the trends identified in distribution of allele and genotype frequencies justify the need for further study on larger and ethnically heterogeneous samples. The obtained data expand the understanding of the molecular genetic basis of VD and can be used in developing personalized approaches to predicting the risk of developing occupational diseases. A promising direction is investigating additional genetic markers and their pathogenetic role in the development of the disease.

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Competing interests. The authors declare no competing interests.

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