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Analysis of the association of the *PRDM12* gene with pain sensitivity in individuals with psychoactive substance dependence

Early diagnosis of susceptibility to psychoactive substance (PAS) use and addiction is a pressing problem of addictology. The development of PAS dependence involves a reward system that also plays a key role in the modulation of nociception. The *PRDM12* gene associated with congenital insensitivity to pain is involved in neurogenesis and affects the properties of nerve cells.

Objective: to comparatively assess pain sensitivity in mental and behavioral disorders caused by the use of PASs in healthy individuals and subjects with their occasional uses according to the genotype of rs10121864 in the *PRDM12* gene.

Patients and methods. Examinations were made in 103 patients with addiction to PAS (F1x.2), in 114 apparently healthy individuals (a control group) and in 36 subjects who occasionally used PASs (a risk group). The pain sensitivity threshold and pain tolerance were determined by tensoalgometry; a subjective assessment of pain thresholds was made using a visual analogue scale. Genotyping was performed using the *PRDM12* rs10121864 polymorphism.

Results and discussion. The distribution of the genotypes of *PRDM12* rs101218 was statistically significantly different in the comparison groups. Odds ratio (OR) calculation showed that in the subjects who occasionally used PASs, the risk of their dependence was several times greater than that in carriers of the mutant A allele (OR, 2.52; 95% confidence interval (CI), 1.42–4.50) of rs10121864 and its homozygous genotype AA (OR, 6.66; 95% CI, 1.50–29.54) and in those of alternative genotypes. The *PRDM12* was also found to be associated with the parameter of subjective assessment of pain sensitivity in PAS-dependent subjects. Thus, this parameter was significantly lower in the carriers of the mutant A allele than in those of the GG genotype.

Conclusion. The A allele and AA genotype of *PRDM12* rs10121864 were established to be associated with the risk of PAS dependence and with the parameter of subjective perception of the upper pain threshold.

Key words: addiction; nociception; *PRDM12* gene.

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Introduction. The transition from accidental drug use to addictive disorder in people depends on the confluence of congenital traits, such as biological gender, impulsivity, sensitivity, anxiety, risk-taking behavior, and social and environmental influences, such as socioeconomic status, education, and exposure to trauma, peer pressure, drug availability, family drug use [1, 2]. In addition to these factors, neural chains and molecular mechanisms involved in the development and support of addiction [3, 4]. The development of dependence on psychoactive substances (PAS) can be described as a three-stage cycle: 1. initiation, 2. negative affect and 3. craving [5]. A key step in the addiction cycle is the transition from initiation to forced drug use [6, 7]. One aspect of this transition is the transition from drug use as targeted behavior to compulsive behavior, which is believed to be related to the transition from ventral corticostriate chains involving the prefrontal cortex and ventromedial striatum to a more dorsal chain including the dorsolateral striatum [8].

In the development of dependence on PAS, a reward system is involved, in which dopamine plays a leading role. The mesocorticolimbic pathway of dopamine, including the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex, is identified as a common neural substrate of all drugs [9, 10, 11].

Clinical and preclinical studies show that the brain's reward center plays a key role in modulating nociception, and adaptation in the dopaminergic system can affect several sensory and affective components of pain syndromes [12, 13, 14]. These adaptations include changes in the levels of released dopamine, as well as postsynaptic changes in the levels of expression of receptors and the concentration of molecules that regulate signal transmission [15]. It was previously shown that the formation of dependence on opioids and other PAS is associated with a change in pain sensitivity [16]. These data prompt further study of the molecular mechanisms by which the brain's reward center modulates pain.

In a 2015 study, Ya-Chun Chen et al. [17] identified a new gene, *PRDM12*, associated with congenital insensitivity to pain in humans. The genes of the *PRDM* family play an important role in various processes of the development of the organism [18], including the differentiation of primary germ cells [19, 20, 21], the development of the embryo [22] and meiotic recombination of adult cells [23]. The *PRDM12* gene encodes an epigenetic regulator, which is key in the process of meiosis, participates in neurogenesis, and affects the properties of nerve cells [18, 24]. *PRDM12* is required for the development of sensory neuron and pain perception [17, 25–27]. The involvement of the *PRDM12*

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Table 1. *Frequency distribution of rs10121864 PRDM12 genotypes and alleles in PAS-dependent groups, with occasional PAS use and in the control group of healthy individuals*

Group	GG (n=81)	Genotypes AG (n=121)	AA (n=51)	G	A	Alleles	Hardy-Weinberg equilibrium χ^2 , p-value	Group comparison result, χ^2 , p-value
Healthy individuals	37 (32.5%)	57 (50.0%)	20 (17.5%)	131 (57.5%)	97 (42.5%)		0.060, p=0.810	11.372, p=0.023*
Occasional PAS users	17 (47.2%)	17 (47.2%)	2 (5.6%)	51 (70.8%)	21 (29.2%)		0.730, p=0.390	
PAS-dependent	27 (26.2%)	47 (45.6%)	29 (28.2%)	101 (49.0%)	105 (51.0%)		0.780, p=0.380	

* – p-value <0,05.

gene in modulation of nociceptors and sensory neurons in *Xenopus* embryos has been shown [17]. In mice, the gene is necessary for normal embryogenesis, and it plays an important role during postnatal development [28].

Early diagnosis of predisposition to the use of PAS and the formation of addiction is an urgent problem of clinical and biological addictology [29]. A predisposition to addictive behavior is associated with the need for excessive sensory stimulation. The genetic factor is widely studied as a predisposition factor for addictive disorders [30].

The aim of the study was to conduct a comparative assessment of pain sensitivity, taking into account the genotype of the polymorphic variant rs10121864 of the *PRDM12* gene in individuals with mental and behavioral disorders caused by the use of PAS, in healthy individuals, and in the group of individuals with occasional PAS use.

Materials and methods. We examined 103 patients (85 men and 18 women) with signs of mental and behavioral disorders caused by the use of PAS (F1x.2) in the post-withdrawal period, the average age was 24 [18; 27] years (Me [Q25; Q75]). The control group consisted of 114 conditionally healthy individuals (48 men and 66 women), comparable in age. As an additional risk group, people who occasionally and accidentally use PAS according to the classification of E.E. Bechtel were examined (1986) (36 people: 17 men and 19 women). The study was conducted in

compliance with the principles of informed consent of the Helsinki Declaration of the World Medical Association.

Thresholds of pain sensitivity and pain tolerance were determined using our own patented version of tensoalgometry (TAM) [31]. To analyze the subjective assessment of the upper and lower thresholds of pain sensitivity, a visual analogue scale (VAS) was used. As a result of tensoalgometry, the thresholds of pain sensitivity were evaluated – the minimum pain sensation that the subject is able to recognize (lower threshold of pain) (PL), as well as the threshold for tolerance of pain (upper threshold of pain) (PU). The results of two tensoalgometric methods were expressed in arbitrary units (conventional units) and newtons (N). VAS allows you to evaluate the subjective assessment of the upper and lower thresholds of pain sensitivity.

The polymorphic variant rs10121864 *PRDM12* was genotyped using the real-time polymerase chain reaction method using a StepOnePlus™ Real-Time PCR System (Applied Biosystems, USA) using TaqMan Validated SNP Genotyping Assay kits (Applied Biosystems, USA).

Statistical processing of the results was performed using the SPSS 21.0 program. using nonparametric methods. The non-parametric Kruskal – Wallis, Mann – Whitney criteria were used. To compare qualitative characteristics, the χ^2 criterion was used. Analysis of the correspondence of genotype frequencies to those expected at Hardy-Weinberg equilibrium will be performed using Fisher's exact test.

Results. Data were obtained on the frequency distribution of the genotypes and alleles of rs10121864 *PRDM12* in three comparison groups (in the groups dependent on PAS, with occasional use of PAS and the control group). The distribution of genotypes in all groups was consistent with Hardy-Weinberg's law. The frequencies of the rs10121864 *PRDM12* genotypes and alleles in the three comparison groups differed statistically significantly (p = 0.023) (Table 1).

Further analysis revealed no statistically significant differences when comparing a group of healthy individuals with a group of individuals with a dependence on PAS ($\chi^2=3.629$, p=0.489) and with a group of people occasionally consuming PAS ($\chi^2=4.381$, p=0.336). At the same time, in a pairwise comparison, it was found that in the group of PAS-dependent individuals and in the group of individuals occasionally consuming PAS, the frequency distribution of the rs10121864 genotypes differs at the level p=0.021, and the frequency distribution of the alleles of the studied polymorphic variant of the *PRDM12* gene is different at the significance level p=0.003 (Fig. 1) (pairwise comparisons were carried out using the Bonferroni correction).

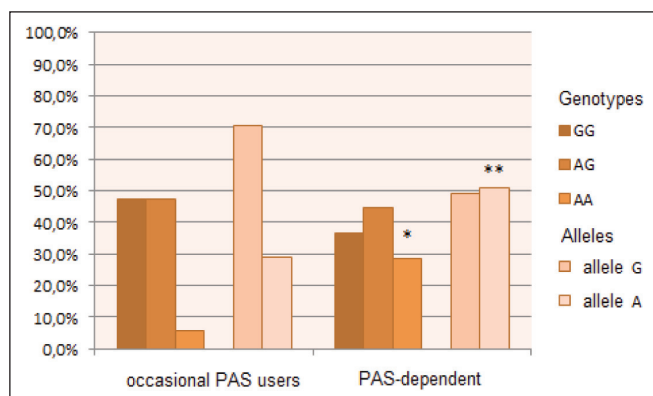


Figure 1. *Frequency distribution of rs10121864 genotypes and alleles in the group of PAS dependent and the group of individuals with occasional PAS use.*

Note: * – p = 0.021, ** – p = 0.003. The p value was calculated with Bonferroni correction for multiple comparisons.

Table 2. *Parameters of tensoalgometry in individuals dependent on PAS (men) [Median (Q25–Q75)]*

Parameter	Carriers of genotype GG rs10121864 <i>PRDM12</i> (n=22)	Carriers of genotype AG rs10121864 <i>PRDM12</i> (n=38)	Carriers of genotype AA rs10121864 <i>PRDM12</i> (n=25)	χ^2 , p-value
PL, conventional units	10.0 (7.0–12.0)	10.0 (7.0–13.5)	12.0 (9.0–12.0)	$\chi^2=1.370$, p=0.504
PU, conventional units	15.0 (15.0–16.0)	15.0 (15.0–16.0)	15.0 (15.0–17.0)	$\chi^2=3.608$, p=0.165
PL VAS, conventional units	3.5 (2.0–5.0)	3.0 (1.5–4.0)	2.0 (1.0–4.0)	$\chi^2=2.205$, p=0.332
PU VAS, conventional units	7.0 (6.0–8.0)	5.5 (4.0–6.5)	5.5 (4.0–6.0)	$\chi^2=7.361$, p=0.025*

* – p-value <0,05

An analysis of the data when comparing the group of PAS-dependent and the risk group — the group of individuals episodically using PAS — showed that the OR odds ratio for the mutant A allele rs10121864 was 2.52 (95% CI=1.42–4.50), and homozygous genotype AA OR=6.66 (95% CI=1.50–29.54). The obtained OR indices can be interpreted in such a way that among individuals who occasionally use PAS, the risk of developing addiction to PAS is several times higher in carriers of the mutant A allele rs10121864 and its homozygous AA genotype than in carriers of alternative genotypes.

Next, an analysis of the results of tensoalgometry was carried out depending on the carriage of one or another genotype of rs10121864 *PRDM12*.

Comparison in the group of men with a dependence on PAS revealed significant differences for the index of PU VAS in carriers of various rs10121864 *PRDM12* genotypes (Table 2). Thus, in carriers of the mutant allele A (genotypes AA and AG), this indicator was significantly lower than in carriers of the GG genotype.

We obtained similar results in a group of women. Comparison in terms of PU VAS for carriers of different genotypes of the polymorphic variant rs10121864 *PRDM12* revealed differences in the level of statistical trends in female subjects dependent on PAS ($\chi^2=4.752$, p=0.093; Table 3). So, among individuals with dependence for carriers of the GG genotype, this indicator was 6.0 (4.0–7.0), and for carriers of the heterozygous AG allele, it was 5.5 (4.5–6.5) (indicated [Median (Q25–Q75)]). From table 3 it is seen that the value of PU VAS in carriers of the mutant allele A (with genotypes AG and AA) is lower than in carriers of the GG genotype of the studied locus. Differences in this

indicator in people with different genotypes indicate a possible contribution of the *PRDM12* gene to the subjective perception of pain.

Other indicators of pain sensitivity did not statistically differ in the groups of men and women, depending on the genotype at the rs10121864 *PRDM12* locus.

Discussion. Based on the obtained data, it can be assumed that the minor allele A of rs10121864 of the *PRDM12* gene, associated with pain insensitivity [17], can contribute to the perception of pain in women with addiction to PAS, as well as in women at risk with episodic use of PAS influencing the subjective perception of pain.

The obtained results suggest that the polymorphic variant rs10121864 of the *PRDM12* gene can contribute to the subjective perception of the upper pain threshold, which makes this locus more interesting and relevant for the study of nociception in various pathological conditions associated with changes in pain sensitivity indicators, in particular, in addictive disorders.

More and more evidence suggests that genetic factors contribute significantly to the individual differences in pain sensitivity. In an early study with a subjective perception of pain at the level of a statistical trend, an association of the *SCN9A* gene was detected. The *SCN9A* gene encodes the sodium channel NaV1.7, which is predominantly expressed in nociceptive primary sensory neurons, where it enhances depolarization. [32].

The data on the influence of the genetic component on the change in pain sensitivity in addictive disorders make it possible to suggest a conjugation of a predisposition to the development of dependence on PAS and the innate properties of adaptive mechanisms, including mechanisms that modulate

Table 3. *Parameters of tensoalgometry for PAS-dependent (women) [Median (Q25 – Q75)]*

Parameter	Carriers of genotype GG rs10121864 <i>PRDM12</i> (n=5)	Carriers of genotype AG rs10121864 <i>PRDM12</i> (n=9)	Carriers of genotype AA rs10121864 <i>PRDM12</i> (n=4)	χ^2 , p-value
PL, conventional units	8.0 (5.0–11.0)	4.0 (2.0–6.5)	4.0 (2.0–6.0)	$\chi^2=2.103$, p=0.349
PU, conventional units	14.0 (12.0–15.0)	12.0 (9.0–15.0)	9.0 (7.0–12.5)	$\chi^2=0.902$, p=0.637
PL VAS, conventional units	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (1.5–3.0)	$\chi^2=0.591$, p=0.744
PU VAS, conventional units	9.5 (9.0–10.0)	6.0 (4.5–7.0)	6.0 (5.5–6.5)	$\chi^2=4.752$, p=0.093

pain. The predisposition to addiction to PAS is explained by the lack of dopamine neuromediation in the reward system, which can be genetically determined [33, 34]. The *PDRM12* gene involved in neurogenesis [18, 24] can affect the development of diseases caused by impaired neuromediation. At the same time, it has been shown that both heroin addicts and people who are on long-term therapy with narcotic analgesics have a decrease in pain sensitivity thresholds [35–38]. Thus, genes associated with pain, including the *PDRM12* gene, can be included in the mechanisms involved in the pathogenesis of addictive disorders.

Individual differences in the pain response can be used as a tool for studying nociceptive mechanisms in various pathologies, including addictive disorders, and be relevant as part of a personalized approach to patients.

The search for factors predisposing to the development of dependence on PAS has not only a socially important role, but also is of great importance in the practice of using narcotic analgesics. Therefore, research on the study of a group of people with experience in the use of PAS, but not having a diagnosis of addiction, occupy a special place. In this work, the association of the polymorphic variant rs10121864 of the *PRDM12* gene with the development of dependence on PAS among people with experience in the use of such substances was revealed.

Study Limitations. The study was carried out at one point, therefore, it is impossible to exclude the possibility of the future transfer of any of the examined persons from the risk

group to the group of patients with PAS dependence, and from the control group to other groups. The frequencies of alleles of gene polymorphisms in different populations may differ; therefore, the results obtained are most relevant for the Siberian region, where the respondents who make up the sample in this study live.

Conclusion. In the course of the work, it was shown that the A allele and the AA rs10121864 genotype of the *PRDM12* gene are associated with a risk of developing addiction to PAS, which makes this locus interesting to study as a factor in predisposition to the development of addictive behavior. Also, as part of the study, it was shown that in the group of people who use PAS, carriers of allele A show lower rates of subjective perception of the upper pain threshold than carriers of the homozygous GG genotype. The data obtained indicate the significance of sensitivity indicators in the development of addictive disorders and the contribution to the change in pain perception in these disorders of the genetic component.

Statement of Interest. *The authors declare no conflict of interest.*

The authors confirm that the results presented in the article were not previously published.

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Declaration about financial and relationships.

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