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 tensiometry; 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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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 TM 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 nonparametric Kruskal – Wallis, Mann – Whitney criteria were used. To compare qualitative characteristics, the χ² 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 (χ²=3.629, p=0.489) and with a group of people occasionally consuming PAS (χ²=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).
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 (χ²=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 2. **Parameters of tensoalgometry in individuals dependent on PAS (men) [Median (Q25–Q75)]**

| Parameter | Carriers of genotype GG rs10121864 PRDM12 (n=22) | Carriers of genotype AG rs10121864 PRDM12 (n=38) | Carriers of genotype AA rs10121864 PRDM12 (n=25) | χ², p-value |
|-----------|------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------|
| PL, conventional units | 10.0 (7.0–12.0) | 10.0 (7.0–13.5) | 12.0 (9.0–12.0) | χ²=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) | χ²=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) | χ²=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) | χ²=7.361, p=0.025* |

* – p-value <0.05

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

| Parameter | Carriers of genotype GG rs10121864 PRDM12 (n=5) | Carriers of genotype AG rs10121864 PRDM12 (n=9) | Carriers of genotype AA rs10121864 PRDM12 (n=4) | χ², p-value |
|-----------|------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------|
| PL, conventional units | 8.0 (5.0–11.0) | 4.0 (2.0–6.5) | 4.0 (2.0–6.0) | χ²=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) | χ²=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) | χ²=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) | χ²=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 PRDM12 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 PRDM12 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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