

NEUROLOGICAL VIEWS ON THE RELATIONSHIP BETWEEN POLYMORPHISM RS1544410 OF THE DRD4-A GENE AND NOCTURNAL ENURESIS

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Abstract: Children of adolescence represent a high-risk group. During this period, active changes in hormonal status occur and a mature and independent personality is formed. Excessive tension of the mental sphere and violation of the mechanisms of social adaptation lead to increased anxiety, decreased self-control, irresponsibility, unscrupulousness, cruelty and aggressiveness, consolidation of unfavourable traits in the formation of personality. Lack of timely psychological help to such children contributes to the development of neuroses, deviant and addictive behavior.

Key words: Comparative analysis, contradictory data, polymorphism, nocturnal enuresis.

Introduction. [6].

Various forms of mental maladaptation are noted in 83 per cent of older girls and 62 per cent of boys. They include prenosological, initial mental health disorders. These functional states on the verge of norm and pathology have an independent significance for the hygiene of children and adolescents in terms of assessing their impact on the child's development and improving primary prevention measures [4]. It is the prenosological states that are the main forms of mental health disorders of schoolchildren [3]. The reasons for the development of deviant forms of behaviour are not only environmental and social factors, but also genetic predisposition [1]. Unfavourable ecological, economic, political and social factors of human interaction with the environment, constant increase of neuropsychic tension adversely affect the state of physical and mental capabilities of a person, contribute to the formation of personal maladaptation, leading to the formation of neurotic states, which, in turn, interfere with the processes of optimal life activity. According to modern research, the differences between people in basic psychological characteristics are equally determined by the influence of genes and the external environment [7]. With unfavourable influence of both factors on character development, high degrees of deviation, up to pathological forms, may develop. With a favourable combination, even a strong genetic predisposition to the development of abnormality may not be realized or at least not lead to pathological character deviations [8]. According to modern psychogenetic concepts of personality development, the features of human behaviour are implemented through the interaction of CNS neurotransmitters, the most important of which are dopamine, serotonin and noradrenaline [10]. Currently, there is a large number of studies devoted to the study of the relationship of neurotransmitter gene polymorphisms with the peculiarities of human behaviour and personality.

The aim of the study was to investigate the frequency of alleles and genotypes distribution of polymorphic markers of DRD4-a gene (rs1544410) in the group of NE patients and conditionally healthy donors (control sample).

Materials and methods of the study. A total of 93 patients with HE (main group) were examined. This group of patients was divided into 2 subgroups depending on the severity of the disease:

1. NE patients (n=45);
2. Patients with enuresis (n=48).

The control sample consisted of 93 conditionally healthy donors from Uzbekistan.

The frequency distribution of alleles and genotypes of polymorphic marker rs1544410 of DRD4- α gene in the main group and subgroups of EI patients and control sample was analysed. The cytokine gene DRD4- α is located at the 6p21.1-6p21 locus.3. The coupling map of the main human histocompatibility complex containing the genes of tumor necrosis factors ProcNatlAcadSciUSA 84: 8535–8539doi:10.1073/pnas.84.23.8535 has identified several functional polymorphic loci to date (-863, -857, -850, -575, -375, -74, -308, -237, -162), among which the most important is the option of replacing guanine with adenine G-308A. The international polymorphism code is rs1544410.

The allele variant 308A of this gene affects the level of mRNA transcription and, accordingly, the biosynthesis of this cytokine in the body. (Wilson A.G., di Jovin F.S., Blakemore A.I. and Duff G.V., "Single-base polymorphism in the tumor necrosis alpha factor gene can be detected using NcoI restriction of PCR product", Human Molecular Genetics, Volume 1, No. 5, 1992, p. 353.doi:10.1093/hmg/1.5.353, Wilson A.G., Symons J.A., McDowell T.L., McDevitt G.W, Duf, H.O., 1997a. The effect of polymorphism in the promoter of human tumor necrosis factor alpha on transcription activation. Proc. Natl. Acad. Sci. 94, 3195–3199. DOI: 10.1073/pnas.94.7.3195; Wilson, A.G., Symons, J.A., McDowell, T.L., McDevitt, H.O., Duff, J.W., 1997b. The effect of polymorphism in the promoter of human tumor necrosis factor- α on transcription activation. Proc. Natl. Acad. Sci. U.S. A. 94, 3195–3199.). The distribution of alleles and genotypes of the DRD4- α rs1544410 gene in the study groups of patients in the main and control groups was checked by the Hardy-Weinberg equilibrium.

Tables 1 and 2 present the theoretical and actual (Hexp and Obs, respectively) frequencies of alleles and genotypes, as well as indicators of gene diversity in the primary and control samples of patients. The frequencies of the G and A alleles in the studied patients and the control group were 0.82/0.18 and 0.90/0.1, respectively.

Analysis of the distribution of genotypic variants of the DRD4- α rs1544410 gene showed that the actual distribution of genotypes in the groups of TE patients and controls for this polymorphism corresponded to the theoretically expected Hardy-Weinberg equilibrium ($p < 0.05$).

That the observed distribution of the homozygous G/G genotype in the patient group was significantly reduced compared to the theoretical one (0.80 vs. 0.81, respectively; $\chi^2=0.013$; $p=0.3$). On the contrary, the observed frequency of the heterozygous G/A genotype is statistically significantly higher than expected (0.2 vs. 0.18, respectively; $\chi^2=0.2$; $p=0.3$). The relative deviation of Hobes and Heexp turned out to be positive and amounted to: $D = +0.1$. As expected, no unfavorable homozygous genotype A/A was found in the studied groups.

In the control sample, the observed and expected frequencies of the homozygous genotype G/G were Hobes=0.88 and Heexp=0.89 ($\chi^2=0.001$ and $p=0.5$), and the heterozygous genotype G/A-Hobes=0.115 and Heexp=0.011. fainted. $\chi^2=0.038$ and $p=0.5$). The relative deviation of Hobes and Heexp in this group also turned out to be positive $D=+0.04$.

Table 1 Expected and observed frequencies of genotype distribution of the rs1544410 locus of the DRD 4- α gene in the control sample.

Alleles	Frequency of alleles			
of G	0.94			
A	0.06			
genotypes	Frequency of genotypes	genotypes	P	Df

	<i>Observed</i>	<i>Expected</i>			
Y/Y	0.88	0.89	0,001	0.5	1
Y/A	0.115	0.11	0,038		
A/A	0,00	0,003	0,315		
total	1,00	1,00	0,355		

Table №2 The difference between the expected and observed frequencies of heterozygosity by the polymorphism locus rs1544410 of the DRD4-a gene in the studied groups of patients and the control group.

Groups	H _o	H _e	D *
The main group	0.2	0.18	+0.1
The control group	0.115	0.11	+0.04

Note: $D = (H_o - H_e) / H_e$

Thus, the obtained population-genetic data on the polymorphism rs1544410 of the DRD4-a gene are reliable. There was no heterogeneity between the actually observed and theoretically expected values of the rs1544410 polymorphism of the DRD4-a genotypes in the studied groups of patients of the main and control groups. The unfavorable A/A genotype was not detected in both studied samples. In the studied samples, the distribution of ancestral G/G and unfavorable G/A genotypes of this locus was expected, that is, the Hardy-Weinberg equilibrium was performed in both cases, which indicates the homogeneity of the studied samples and qualitative genotyping of this locus (absence of genotyping errors).

We analyzed the relationship of allelic and genotypic variants of the rs1544410 polymorphism of the DRD4-a gene with the formation and development of NE.

Associative analysis of the rs1544410 locus of the DRD4-a gene was performed using the studied groups of patients with NE and control, as well as using the case-control scheme. The results of determining the obtained data are presented in Table 1 and show that there is a contribution of the unfavorable allele A and the corresponding genotype G/A in the development of TE.

From the table. 1 and 2 show that the proportions of G and A alleles in the studied patients and the control group were 89.8% and 10.2%, respectively, compared with 94.3% and 5.7%. Statistical analysis revealed a significant trend towards an increase in the frequency of the unfavorable A allele (with high coefficients) and a decrease in the dominant, foreign G allele in patients with NE compared with conditionally healthy donors, despite unreliable differences. The calculated coefficients showed that the probability of detecting a functionally unfavorable A allele in respondents with NE was 1.9 times higher than in the control group ($x^2 = 2.6$; $P = 0.1$; $OR = 1.9$; 95% CI 0.8653-4.05). The calculated relative risk of pathology was 1.8 with a confidence interval of 95% CI 0.8726–3.643.

Conclusions: Thus, the polymorphism rs1544410 of the DRD4-a gene is one of the main reasons for the insufficient regulation of the inflammatory and immune response of the body, and according to our data, the foreign variant G/A (associated with the overproduction of proinflammatory cytokines TNF). It is interesting to note that the negative effect of this genotype was observed only in patients with Enuresis, whereas the frequency of this genotype in patients with NPDR did not differ compared to the control group, that is, there is a tendency to increase the severity of pathology in the genotype. Since this study is one of the few studies on the association of rs1544410 of the DRD4-a gene with the risk of developing NE, our data may be the subject of further discussion.

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