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Molecular Genetic Studies of Hereditary Predisposition to Alcoholism

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ABSTRACT

The article presents a literature review on the results of molecular genetic studies of predisposition to alcoholism. Major molecular genetic studies of alcoholism conducted for identifying associations polymorphisms neurotransmitter system and ethanol - metabolizing enzymes in populations of different ethnic groups. Identification of gene polymorphisms association with the risk of developing alcoholism will promote preventive addictology and technologies of personalized therapy.

Keywords: alcoholism, genetic predisposition, serotonin, dopamine, ethanol - metabolizing enzymes.

Heredity has a big role in the development of alcoholism. On the incidence of alcoholism among children of alcohol-dependent people attention was paid in the XIX century [36]. Since the second half of XX century modern genetic researches began. Thus, J.Seixas et al. (1985) reported that children of the alcohol-dependent people develop alcoholism in 4 times more likely than children whose parents do not suffer from alcohol dependence, even if they are raised in different families, and the risk of disease in the sons of alcoholics is higher than in daughters. It was confirmed in further studies.

Back in 2000 a group of researchers [5] has been studied elevated basal level of gene activity Tryptophan in alcohol preferring mice C57BI. In C57B1 mice basal activity of this enzyme was elevated, which presumably was the probable cause of the reduced level of tryptophan in the blood and serotonin in the brain associated with a predisposition to the alcoholism.

Ten years of research (Anstee QM et al., 2013) in a mouse model, it was found that mutation of two types of base pair substitutions in Gabrb1 - the gene encoding the beta- subunit of one of the two GABA- receptor responsible for the body's response to major inhibitory neurotransmitter CNS gamma- aminobutyric acid - lead to permanent preference experimental animals ethanol water.

Even in the XX century has been proven that psychoactive substances stimulate the «reinforcement system" of the brain, central to which is occupied dopaminergic and serotonergic systems [1].

Recent advances in molecular genetic studies of substance dependence, the most common of which is alcohol, showed that the basis of the formation of the disease state is the individual features of activity of neurotransmitter systems and their compensatory potential for prolonged effects of these substances on the body. An important role in dopaminergic neurotransmission plays dopamine transporter DAT1 (encoded by the gene *SLC6A3*), limiting the activity of dopaminergic neurotransmission by reuptake of the neurotransmitter into the presynaptic terminals.

The results of molecular genetic studies VNTR polymorphism in the gene *SLC6A3* revealed that allele 9 repeat units, primarily in the homozygous state, is associated with an early form of alcoholism (the beginning of 35 years) and with the development of acute alcoholic psychosis [8, 24, 34].

In the literature there is a single study of polymorphic marker 2319G> A gene *SLC6A3* in alcoholism, which reports on its involvement in the development of alcohol dependence [23]. Other authors [14, 17] established the role of the polymorphic locus VNTR DRD4 gene in the development of alcohol and drug addiction and the formation of personality traits in healthy individuals. At the same time, a comparative analysis of the distribution of allele frequencies VNTR locus of the *DRD4* gene found similarities in the group Yakut and Evenks with East Asians (Chinese, Japanese), while all ethnic groups studied statistically significantly different from the people of Africa [33]. The study identified markers of increased risk of alcohol and drug abuse only in individuals Tatar and Russian ethnicity genotype *DRD4**S/*S and/or allele of DRD4*S. The analysis of gene polymorphism of the dopaminergic system in patients with alcoholism Yakut and Chukchi ethnicity [4] analyzed the association of *SLC6A3* gene haplotypes with alcoholism in the population of the Yakut Republic of Sakha (Yakutia) and the Tatars of the Republic of Bashkortostan [10]. Various results can be explained by the difference in the geographical origin of the individuals involved in the study and ethnic heterogeneity of samples.

On the territory of the Republic of Sakha (Yakutia), a group of researchers [2, 13, 18] studied polymorphism 1342 A/G in exon 9 of the dopamine transporter DAT1 (SLC6A3) in samples Yakuts, dependent on alcohol and healthy individuals. The study has been found close to the statistically significant association of polymorphism A/G (p= 0,015) with alcoholism in the Yakut population. Genetic variability of the studied loci not linked with alcoholic psychosis [18]. Statistically significant differences between the control groups Yakut and Evenks were found in the frequency distribution of genotypes and alleles of polymorphic loci 25G> A *DRD3* gene and 5 -HTTLPR of the 5 – *HTT* gene [17].

A.O.Kibitov [16] in 2013 established the molecular genetic profile of the dopamine neurotransmitter system in addicted patients. Other authors [6] studied polymorphism RS1611115 (-1021C / T) gene dopamine -β- hydroxylase (DBH) in patients with alcoholic psychosis and healthy donors from Kemerovo region.

The next authors [12] tested the hypothesis of an association of polymorphic variants rs9373085, 743964, rs1743966, rs1057293 *SGK1* gene with alcoholism, comparison of the frequencies of genotypes and alleles in groups of alcoholics and controls revealed no significant differences.

Thus, it is possible to suppose that polymorphic variants of dopaminergic systems genes may lead to the development of alcoholism, modulating alcohol action on brain "reinforcement system". For more thorough and accurate assessment of the role of these genes will require further molecular genetic studies of polymorphic variants in different populations of the world, as well as the study of the functional significance of the protein products in the pathogenesis of alcohol dependence.

Further review of the literature allows us to establish that the molecular genetic studies in the field of Addiction, revealed the correlation between polymorphisms of genes regulating serotonin exchange with the risk of formation of alcoholic psychosis often conducted among the Slavic population, which examined the role of hormonal parameters, genetic markers and psychometric parameters in the regulation of aggressive behaviors in patients with alcoholism [3].

The serotonin 5- hydroxytryptamine, 5 -HT is one of important hormones, which has the role of neurotransmitter of the CNS. Chemical structure of serotonin relates to biogenic amines, tryptamine class. Physiological functions of serotonin are extremely diverse. Serotonin controls so many functions in the body. The metabolism of serotonin is involved alcohol dehydrogenase; serotonin may participate in the formation of endogenous opiates, reacts with acetaldehyde (a decay product of ethanol). Serotonin itself is formed from the amino acid tryptophan. However, this reaction only occurs in natural light. Lack of ultraviolet in the winter season and the reason for the widespread seasonal depression (R.Sandyk, 1999), including the indigenous population of the Arctic North, where the end of November start polar night. In this regard, it is assumed that the reduction in the level of serotonin in the brain is one of the factors in the formation of depressions under the Arctic North, which may be the direct cause of substance abuse. Analysis of published data indicates failure association study of serotonin receptor gene polymorphism with the development of alcoholism in Alaska Arctic North.

Aggression in alcohol-dependent individuals is now widely studied, but yet the question why in response to alcohol intake in some individuals there is the desire to commit aggressive acts, while others have not such a reaction has not resolved, the role of biological factors in the mechanisms of criminal aggression patients with alcoholism is not defined. For this purpose, Tomsk scientists [3,7] carried a comprehensive study of the role of hormonal indicators of genetic markers and psychometric parameters in the regulation of aggressive behavior in 450 people, including 193 patients with alcoholism. The study of genetic markers revealed associations with their psychometric characteristics. So convicted patients with alcoholism wrongful conduct, media S/S genotype of 5HTTLPR polymorphism of the serotonin transporter gene, characterized by low levels of depression questionnaire Beck compared with genotype L/L. This result corresponds to the data in the literature and has a biological explanation. S allele reduces the promoter strength and as a consequence , the level of expression of the transporter in the brain, acting essentially as an antidepressant - selective serotonin reuptake inhibitors, which may lead to disruption in signaling synaptic 5 -HT in people with genotype S / S, and S / L as compared with native genotype L / L [21].

Ethanol-oxidizing systems have great importance in the genesis of alcoholism. Many Mongoloids have their identity [15, 35]. Studies in Eskimos and Indians of Alaska, Evenksof Yakutia, showed a high frequency of "abnormal" AlDG1 isoenzymes and (alcohol dehydrogenase) ADH. According to researchers, this leads to a greater possibility of developing alcoholism.

In ethanol metabolism two enzymes play an important role - alcoholdehydrogenase (ADH) and aldehydedehydrogenase (ALDH). The cytochrome system takes a main position, and a relatively small role takes a catalase. Currently 6 *ADH* classes are revealed [38]. *ADH* classification was based on differences in electrophoretic mobility. These differences were significant ones in the respective structures and functions of enzymes. Seven *ADH* genes are located on chromosome 4 (4q21-q25), within a portion size of 380 kB. Independent studies revealed the presence of clutch of this site with alcoholism [22, 27]. *ADH* enzymes of classes I, II and IV influence significantly on the metabolism of ethanol. Class I enzymes are encoded by three genes: *ADH1A, ADH1B* and *ADH1C*, highly expressed in human liver.

ADH oxidizes ethanol to acetaldehyde. As a biologically active molecule, acetaldehyde induces a range of pathological processes, damaging a number of enzymes, supramolecular structures, membranes, etc. Acetaldegidrogenazes, *ALDH1* and *ALDH2* have a major role in the metabolism of acetaldehyde. *ALDH2* gene is mapped to chromosome 12 (12q24.2), contains a

polymorphism G1510A, which results in an aminoacid substitution Glu487Lys. *ALDH2 * Lys* allele is found only in Asian populations. Enzyme, resulting in a heterozygous individual has only 20% of normal enzyme activity. To explain this, a model of partial dominance allele *ALDH2 * Lys* was proposed towards to *ALDH2* Glu* [21]. Genotype *ALDH2 *Lys/*Lys* is associated with the occurrence of the flush-syndrome (discomfort, facial flushing, nausea, vomiting) after the intake of ethanol, due to elevated levels of acetaldehyde. Therefore, this genotype is considered to be a protective against the development of alcohol dependence [31].

In research of H. Shoshana et al. [32], conducted in 2001 by students of the University of California in San Diego (USA), they revealed that in the population of Asians change in the level of the enzyme alcohol dehydrogenase gene ADH2 was correlated with alcohol consumption.

ADH1B gene contains two actively studied functional polymorphisms: *Arg47His* and *Arg369Cys*, which are the result of transitions *143A> G* and *1108T>C*, respectively. The enzyme encoded by *ADH1B *A*, has improved activity provides a more rapid accumulation of acetaldehyde, which has a toxic effect on many tissues of the body [31]. *ADH1B *A* allele and the corresponding atypical *ADH* are rarer among alcohol-dependent patients than among healthy individuals. Among alcoholics allele carriers use smaller doses of ethanol than the individuals in whom it is absent. Thus, the allele may be considered as protective against alcohol abuse. Frequency of allele *ADH1B * A* in different populations varies from values of more than 70% of indigenous peoples of Southeast Asia to 7.5 % and below in the peoples of Europe. Among indigenous peoples from Africa and America this allele is virtually absent. Several researchers suggest that the frequency of allele *ADH1B*A* increased by the positive selection [25].

In addition, a polymorphic marker *143A> G* (rs1229984, *Arg47His*) *ADH1B* gene has an interest in the study of alcoholic etiology of carcinogenesis [26, 29].

In research of M.V. Osier et al. [30] the role of alcoholdehydrogenase gene (ADH) in alcoholism has shown, namely that gene polymorphism *ADH1B Arg47His*, associated with the *ADH1B * 47His*, carries a protective effect.

Other researchers [2, 13, 18] studied the distribution of allele and genotype frequencies of polymorphisms of two genes ethanol - metabolizing enzymes *ADH1B * Arg47His* and *CYP2E1 Pst I (G/C)*, length polymorphism of tandem repeats (VNTR) in the 3'-noncoding region (3 '-UTR) in samples from three Yakut populations in comparison with the group of patients with alcoholism Yakuts. In this case, in the Yakuts no connection of ethanol-metabolizing enzymes polymorphism with susceptibility to alcoholism was found.

Established markers of increased risk of alcoholic psychosis, which accounted for polymorphisms in the genes of enzymes of alcohol metabolism: ADH1C 272 R> G, ALDH2 357 A>G, CYP2E1 7632 T> A Russian population in the Belgorod region of Central Black Earth region of the Russian Federation [9].

Thus, analysis of published data on the polymorphism of candidate genes for alcoholism in humans indicates the existence of population differences in the frequency distribution of genotypes and alleles of these genes, and the genetic background of alcohol dependence. Use of polymorphic loci as genetic markers of genes whose expression products may at neurotransmitters and enzymes involved in the metabolism of alcohol, especially determine reactions to alcohol, as well as provoke potentially pathogenic changes in the light of ethnicity, will provide comprehensive information on the molecular genetic mechanisms of formation of alcohol dependence. It must be emphasized that the study of candidate genes for alcohol dependence was conducted on samples from Western Europe, North America and some Asian populations, while in Russia, according to an analysis of literature, such studies have relatively small amount [9, 14, 17, 19, 20].

Conducted clinical and genetic analysis of ethanol - metabolizing enzymes polymorphism with susceptibility to alcoholism and alcoholic psychosis persons of indigenous nationalities (Yakut) revealed no statistically significant association. Low frequency of alleles having a protective effect (8.0 and 12.0%), possibly contributes to the high prevalence of alcoholism among the Yakut [16].

It was revealed that markers of increased risk for alcoholism in Yakut is allele *ADH1B * 143G*, a marker of low risk - *MAOA *H*T* haplotype, whereas in the Evenks marker of reduced risk of chronic alcoholism is a heterozygous genotype *HTR1B * 861C/G*, as well as increased risk of alcoholism markers in the combined sample of the Sakha (Yakutia) is *ADH1B * 143G* allele and genotype *ADH1B * 143G/G*, low-risk markers - genotype *DRD4*L/ L* and the haplotype *MAOA*H*T* [17].

Analysis of intergenic interactions among the Yakut from Republic of Sakha (Yakutia) allowed us to establish a statistically significant ($p<0.05$) model the interactions of genes affecting the formation of alcohol dependence: 1) *ADH1C* rs698, *PDY*N 68 no VNTR; 2) *ADH 1B* rs2966701, *PDYN* 68 n.o. VNTR, *OPRM1* rs3823010 [4].

Pharmacogenetic investigations (Chamorro A.J. et al., 2012) established the role of G allele polymorphism *A118G OPRM1* at naltrexone treatment of patients with alcohol dependence [37].

Despite a proven role of genetic factors, it is extremely difficult to establish its contribution to the formation of alcoholism in the entire population of patients with alcohol dependence. This is due to the fact, that always selected patient populations are examined in which the disease occurs more rapidly and proceeds more unfavorably. The largest number of alcohol-dependent persons never seeks medical help due to the rather good adaptation and relatively benign course of the disease. It is possible that these patients groups differ significantly in environmental, ethnocultural and genetic factors on the formation of alcoholism. In this regard, further molecular genetic investigations in populations of indigenous peoples of the Arctic North are very important problem of the modern addictology. Also, revealing the association of gene polymorphisms with the risk of alcoholism will promote preventive addictology and technologies of personalized therapy.

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