Molecular-genetics aspects of migraine

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Молекулярно-генетические аспекты мигрени

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***Abstract**: 109 sick with migraine are examined, which were divided into 2 groups: Genotyped was conducted by means of PCR study Migraine with and without aura is thought to be genetically complex with aggregation in families due to a combination of environmental and genetic tendencies. Twin studies are most important in establishing the multifactorial nature of migraine with heritability approaching 50 %, and the MTHFR Ala222Val polymorphism in common forms of migraine are clear examples.*
***Аннотация:** проведен анализ на наличие ассоциаций с мигренью наиболее распространенной мутации Ala222Val в гене MTHFR. В результате молекулярно-генетического исследования 109 больных с мигренью и 39 родственников больных узбекской национальности.*

***Keywords:** migraine without aura, migraine with aura, polymorphism, genotype, PCR (polymerase chain reaction).*
***Ключевые слова:** мигрень без ауры, мигрень с аурой, полиморфизм, генотип, ПЦР (полимеразная цепная реакция).*

Migraine - a chronic disease characterized by recurrent attacks of throbbing headache, lasting from 4 to 72 hours, usually unilateral localized in the fronto-temporal region, which is accompanied by increased sensitivity to light - photophobia and sound - phonophobia, and - nausea, and sometimes vomiting.

In the last decade, notions of migraine has undergone significant changes due to the rapid growth of scientific research on the epidemiology, genetics, pathogenesis and treatment of this disease. According to epidemiological studies conducted in different countries, migraine suffer from 3 to 16 %, and according to some estimates up to 30 % of the population. Thus men range from 2 to 15 %, and women from 6 to 25 % of the population. Male to female ratio is 1: 2.5 or 2: 4 [1, 2, 3]. About 68 % of people suffering from migraines, are aged between 25 and 54 years, in 22 % of cases - over 55 years of age and 10% are under the age of 25 years. The most common migraine occurs between the ages of 35-40 years. Recent epidemiological studies suggest that the prevalence of migraine in the population tends to grow. Thus, according to the US National Center of health, in the period from 1981 to 1989, the number of people suffering from migraine headaches, increased by 60 % (from 25.8 to 41.0 to 1000.0 of the population) [6, 7]. Epidemiological studies conducted in the UK, show that in 34 % of patients with migraine can be at least once a month, 27 % of patients - once a month, 17 % of patients - 2 times a month, 12 % is 3 -4 attack per month, 6 % 5.10 attacks per month and 4 % of migraine patients is more than 10 times per month. Similar results were obtained in the United States. Thus, in the result of the epidemiological studies have shown that 40 % of patients report if they have one and less migraine per month, 35 % of patients have from 1 to 3 episodes per month, 25 % of patients appears more 4 seizures per month [6, 7]. The duration of a migraine attack is very variable, as a reliable estimate of this indicator is difficult due to the use of antimigraine drugs that affect the duration of the attack. In 80 % of the migraine attack lasts for more than 6 hours, and 32 % for more than 24 hours. The average duration of an attack is 18 hours [5, 6, 7].

The role of heredity in the origin of migraine has long attracted the attention of researchers. Frequent indications of migraine in several generations of the next of kin, as well as the occurrence of the disease at an early age indicate the important role of inherited genetic factors in the origin of this disease. These genealogical studies show that if the migraine attacks were both parents, the risk of offspring incidence reaches 60-90 %. If only the mother was suffering from migraine, the incidence of the risk is 72 % if only the father – 20 % [1, 2]. Studies in twins have shown that the concordance rate was significantly higher in monozygotic than in dizygotic twins, as, indeed, and in twins living together, rather than separately [1, 3, 5, 7]. These data led the authors to conclude that approximately 50 % of the variability in appearance migraine due to genetic factors and not due to

the influence of external factors. Another step to the proof of the genetic origin of migraine were the results of molecular biological studies in patients with familial hemiplegic migraine form. It has been established that the responsible for the manifestation of this form of migraine is the 19p13 chromosome [1, 7].

Later it was shown that a gene mutation CACNA1A, localized on chromosome 19r13.1 and determines the status of specific cerebral P / Q - type calcium channels responsible for the emergence of this form of migraine and other diseases, called «channelopathies» [3, 4, 5]. There work showing engagement CACNA1A gene in the origin of migraine with aura and without aura [2, 6, 7]. Very interesting are comparative studies of migraine with such «channelopathies» as hyperkalemic and hypokalemic periodic paralysis, paramyotonia Eulenburg, episodic ataxia with myokymia episodic ataxia with cerebellar atrophy, CADASIL syndrome (cerebral autosomal dominant arteriopathy with subcortical in facts and leukoencephalopathy). It has been established that these diseases form a paroxysmal course, the absence of symptoms in between attacks, as well as the data of molecular genetic studies indicating the presence of mutations in the gene SACNA1A 19 chromosomes in these conditions. Moreover, many patients with «channelopathies» are migraine cephalgia.

Serotonin plays a central role in the pathophysiology of migraine, and therefore the genes of serotonin (5HT) receptors are targets for scrutiny. However, studies performed in families of migraine sufferers and healthy subjects did not reveal the direct involvement of genes 5HT2A and 5HT2C receptors in migraine origin [7].

In this regard, the main importance is further genetic study of migraine.

At present, the use of PCR blood diagnostics to detect the presence of associations with migraine Ala222Val the most common mutation in the MTHFR gene (metilentetragidofolatreduktazy) for early diagnosis of migraine.

Materials and methods. The studies were conducted on a sample of patients with migraine, in the amount of 109 people. The selection of specific individuals do not take into account their gender, age; collection of materials was performed in unrelated individuals. All probands were persons of Uzbek nationality. Probands living in the Aral Sea region (Khorezm, Karakalpakstan and Tashkent city).

Also Ala222Val analysis of mutations in the MTHFR gene in two groups of comparisons was carried out, they made a group of related entities migraine patients (39 people) and a group of healthy subjects 22 people, not suffering from this pathology. Previously all probands were examined for the establishment of the verification of the diagnosis of migraine. A survey conducted members of the department of neurology and psychiatry Urgench branch of TMA, it included history and numerous clinical tests.

The studies were conducted at the Center for Genomic Technology (CGT) at the Institute of Genetics and Experimental Biology of Plants (IGiEBR) of the Academy of Sciences of the Republic of Uzbekistan (Uzbek Academy of Sciences) and the laboratory of the Academy of Mamun in Khiva. The project was analyzed for the presence of associations with migraine Ala222Val the most common mutation in the MTHFR gene.

Results. As a result of molecular-genetic study 109 patients with migraine and 39 relatives of patients Uzbeks, the following indices of genotypes and alleles of MTHFR gene polymorphisms on Ala222Val (Table 1).

Table 1. Genotyping of patients with migraine and their relatives on the frequency of occurrence of alleles genotypes MTHFR gene polymorphisms on Ala222Val

Results of the study	Patients with migraine n=109	Relatives of patients n=39
Pathology	18 16,5%	4 10,2%
Heterozygote	62 56,9%	23 58,9%
Norm	25 22,9%	2 5,1%
Error thermocycler	4 3,7%	10 25,6%

As evidenced by the materials of Table 1, the Uzbek population is a polymorphic allele of the studied gene MTHFR polymorphism for more Ala222Val allele. Among patients with migraine incidence pathology and heterozygotes is 73.4 %, and among relatives - 69.1 %. Thus, the genotype of MTHFR gene allele polymorphism Ala222Val is genetic predictor of migraine in the Uzbek population of persons living in the Aral Sea region.

Conclusion. Detection of PCR-diagnostics genotype alleles of MTHFR gene polymorphism on Ala222Val can be used for early diagnosis and differential diagnosis of migraine in Uzbek people.

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