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PECULIARITIES OF THE CYP2C19 GENOTYPE AND INFLUENCE ON THE EFFECTIVENESS OF PHARMACOTHERAPY

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✓ ***Resume***

The article presents the results of a genotypic study of patients with chronic gastritis in the Bukhara region by polymorphism of the CYP2C19 gene for the polymorphic marker G681A. It turned out that in the present region, patients with the G/G genotype prevail and, according to the prevalence, type B of chronic gastritis associated with Helicobacter pylori prevails.

Key words: CYP2C19 gene, polymorphism, chronic gastritis, polymorphic marker G681A of the CYP2C19 gene, proton pump inhibitors.

ОСОБЕННОСТИ ГЕНОТИПА ГЕНА CYP2C19 И ВЛИЯНИЕ НА ЭФФЕКТИВНОСТЬ ФАРМАКОТЕРАПИИ

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✓ ***Резюме***

В статье приводятся результаты генотипического исследования больных с хроническим гастритом в Бухарском регионе по полиморфизму гена CYP2C19 по полиморфному маркеру G681A. Оказалось, что в настоящем регионе превалируют больные с генотипом G/G и по встречаемости превалирует тип В хронического гастрита, ассоциированный с Helicobacter pylori.

Ключевые слова: ген CYP2C19, полиморфизм, хронический гастрит, полиморфный маркер G681A гена CYP2C19, ингибиторы протонового насоса.

CYP2C19 GENOTIPI VA FARMAKOTERAPIYA SAMARADORLIGIGA TA'SIRI

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Buxoro davlat tibbiyot instituti

✓ ***Rezyume***

Maqolada G681A polimorfik markeri uchun CYP2C19 genining polimorfizmi bilan Buxoro viloyatida surunkali gastrit bilan og'rigan bemorlarni genotipik o'rganish natijalari keltirilgan. Ma'lum bo'lishicha, ushbu regionda G/G genotipiga ega bemorlar ko'proq bo'lib, Helicobacter pylori bilan bog'liq bo'lgan surunkali gastrit B tipidagi kasallik keng tarqalgan.

Kalit so'zlar: CYP2C19 geni, polimorfizm, surunkali gastrit, CYP2C19 genining G681A polimorfik markeri, proton pompasi ingibitorlari.

Relevance

Recently, the concept of personalized medicine has become increasingly common in the literature [15, 17]. It is an integrated medicine that includes the development of personalized treatments based on genomics, testing for predisposition to diseases, prevention, combining diagnosis with treatment, and monitoring treatment [2, 9, 24]. The goal of personalized medicine is to find a suitable drug for a particular patient and, in some cases, even to develop a treatment regimen for the patient according to his genotype [5, 12, 23].

Enzymes of the P-450 family play an important role in the metabolism of both endogenous compounds (steroids, bile acids, fatty acids, prostaglandins (thromboxane A2, prostacyclin I2), leukotrienes, biogenic amines) and exogenous ones: drugs, poisons, industrial pollution products, pesticides, carcinogens, mutagens, etc.: they are membrane proteins primarily associated with intracellular membranes [14, 26]. Along with the liver, where the greatest amount of cytochrome P-450 is found, it is also found in the intestine,

adrenal glands, kidneys, lungs, some parts of the brain, skin, placenta, and myocardium [13].

Unlike other hemoproteins, which, as a rule, have only one activity and a strictly defined function in the cell, P450, along with monooxygenase, can also exhibit oxidase activity, generating reactive oxygen species in the form of superoxide and hydroxyl radicals, hydrogen peroxide. In this regard, P-450 is sometimes referred to in the literature as a mixed-function oxidase. Currently, more than 1000 isoforms of cytochrome P-450, called isoenzymes, have been isolated. The genes of cytochrome P-450 isoenzymes are located in different chromosomes and occupy different loci in them. To date, about 500 different genes encoding P450 have been identified (Padalko V. I., et al., 2005). There are a large number of polymorphic genes in the human genome, and many of them encode enzymes that metabolize drugs and xenobiotic agents, including carcinogens. According to R. M. Ward and G. L. Kearns (2013), these enzymes are immature at birth and reach the level of adult activity at 5-6 months of life. Among the most well-known are several isoenzymes of the microsomal oxidative system P450 - CYP3A4, CYP2C9, CYP2C19, etc [4, 22]. There are more than 200 variants of alleles of cytochromes involved in the metabolism of drugs in a living organism [11, 21].

Substrates for cytochrome P-450 are almost all medicinal substances, while its isoforms differ from each other in substrate specificity and activity regulators (inhibitors and inducers).

One of the main isoenzymes of cytochrome P-450 is CYP2C19.

In 1994, De Marais et al. for the first time, cytochrome P450 polymorphism was studied on the gene encoding the structure of the enzyme CYP2C19 [25].

The CYP2C19 gene encodes a member of the cytochrome P450 enzyme superfamily, which is an important phase I enzyme widely expressed in endothelial and smooth muscle cells. It is a key enzyme responsible for the metabolism of many therapeutic drugs, and is thought to play an important role in detoxifying or inactivating potential carcinogens and bioactivating some environmental procancerogens to form toxic DNA-binding metabolites [3].

Genetic polymorphism defines the three main phenotypes of metabolizers (drug users): extensive, slow, and fast [1]. Extensive metabolizers are individuals with a normal metabolic rate of the drugs in question. They are most often homozygous for the wild allele of the corresponding enzyme Examples of cytochrome P450 genes involved in drug metabolism [8]. Slow metabolizers (sometimes zero) are characterized by a reduced metabolic rate of the drug in question. From the genetic point of view, they are homozygous (with an autosomal recessive type of inheritance) or heterozygous (with an autosomal dominant type of inheritance) for the mutant (slow) allele of the corresponding enzyme. In such individuals, the synthesis of the enzyme is absent or an inactive (defective≫) enzyme is synthesized, as a result of which the drug accumulates in high concentrations, which leads to the appearance of undesirable side reactions [7]. Hence, it is clear that for slow metabolizers, the dose of the drug should be lower or another drug is prescribed. Fast (or overactive) metabolizers are characterized by an increased metabolic rate of certain drugs. Basically, these are homozygotes (with an autosomal recessive type of inheritance) or heterozygotes (with an autosomal dominant type of inheritance) for the fast allele of the corresponding enzyme [16].

Thus, the polymorphic variability of this gene determines the different enzymatic activity of the CYP2C19 isoenzyme and, accordingly, the presence of slow, intermediate, fast, and ultrafast xenobiotic metabolizers in the population [10, 18].

Proton pump inhibitors (PPIs), such as omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprazole, are metabolized by cytochrome P450 (CYP2C19) isoenzyme 2C19 in the liver. There are genetic differences that affect the activity of this enzyme [6].

Thus, the use of proton pump inhibitors in people with peptic ulcer disease may be less effective if the patients are carriers of a genetic variant associated with a high metabolic rate of the drug. In this case, the drug will be quickly disposed of by the enzyme [20].

Thus, the CYP2C19 gene is the main factor that ensures the metabolism of proton pump inhibitors [19].

However, there are no studies on the influence of the patient's genotype based on the allelic variant of the SUR2C19 gene on the type and course of chronic gastritis (HCG) in patients living in the Bukhara region, which was the basis for this study.

Material and method

To solve the tasks set a comprehensive examination of 100 patients with chronic gastritis who were on inpatient treatment and follow-up in the Bukhara regional IPKB was conducted. The control group consisted of 96 healthy people who did not have a history of pathology from the digestive tract, living in the Bukhara region,

corresponding by sex and age to the examined group of patients with chronic gastritis.

The age of patients with chronic gastritis ranged from 18 to 67 years.

The initial stage of our work was the selection and optimization of the system of oligoprimes for the detection of the rs4244285 polymorphism of the CYP2C19 gene by the polymorphic marker G681A. The nucleotide sequences of detection of the rs4244285 polymorphism of the SUR2C19 gene were selected using the program "Oligo v. 6. 31" (Molecular Biology Insights Inc., USA) and synthesized in Sintol LLC and NPF “Litech” (Moscow). The rest of the components were purchased from the world's leading manufacturers - Serva (Germany), Sigma (USA), Helikon NPF Litekh, Sibenzim (Russia), etc.

The adaptation of primer systems for standard PCR analysis was carried out using PCR analyzers “AppliedBiosystems 2720” (USA) and Rotor-Gene 6000 (Corbett Australia). For amplification, a reaction mixture with a volume of 25 µl was used, which contained 2.5 µl of 1 OxTaq buffer (67 mMtris-HCl (pH 8.8), 16.6 mM (NH4) 2S04>, 2.5 mM MgCl2, 0.01% Tween-20), 0.1 µg of genomic DNA, a mixture of dNTP (dATP, dGTP, dCTP, dTTP of 200 µm each), 1 unit. Termusaquaticus DNA polymerase (manufactured by Silex, Moscow) and 5-10 pM locus-specific oligonucleotide primers. The temperature and time parameters were changed depending on the pairs of oligoprimes.

For detection of rs4244285 of the SUR2C19 gene: preliminary denaturation-940C (1 min. 1 cycle), 35 amplification cycles: 930C (10 sec.) – denaturation, 640C (10 sec.) – annealing of primers, 720C (20 sec.) – elongation, and final synthesis-720C (1 min. 1-cycle), 10 min. storage.

Polymorphic regions of the SUR2C19 gene were detected using the PCR-SSP method.

The specificity and number of amplified fragments were tested by agarose gel electrophoresis.

Results and discussion

It is known that one of the variants of the CYP2C19*2 (rs4244285) gene under study consists in replacing guanine (G) with adenine (A) at the 681 (681G-A) position in exon 5. Using a modified detection method, we investigated the polymorphism G681A of the gene CYP2C19, which has variants of the genotypes A/ A, GG, G/A.

The distribution of genotypes of the polymorphic locus G681A of the CYP2C19 gene in the Bukhara population did not correspond to the expected Hardy-Weinberg equilibrium, X2 =7.0 p=0.008.

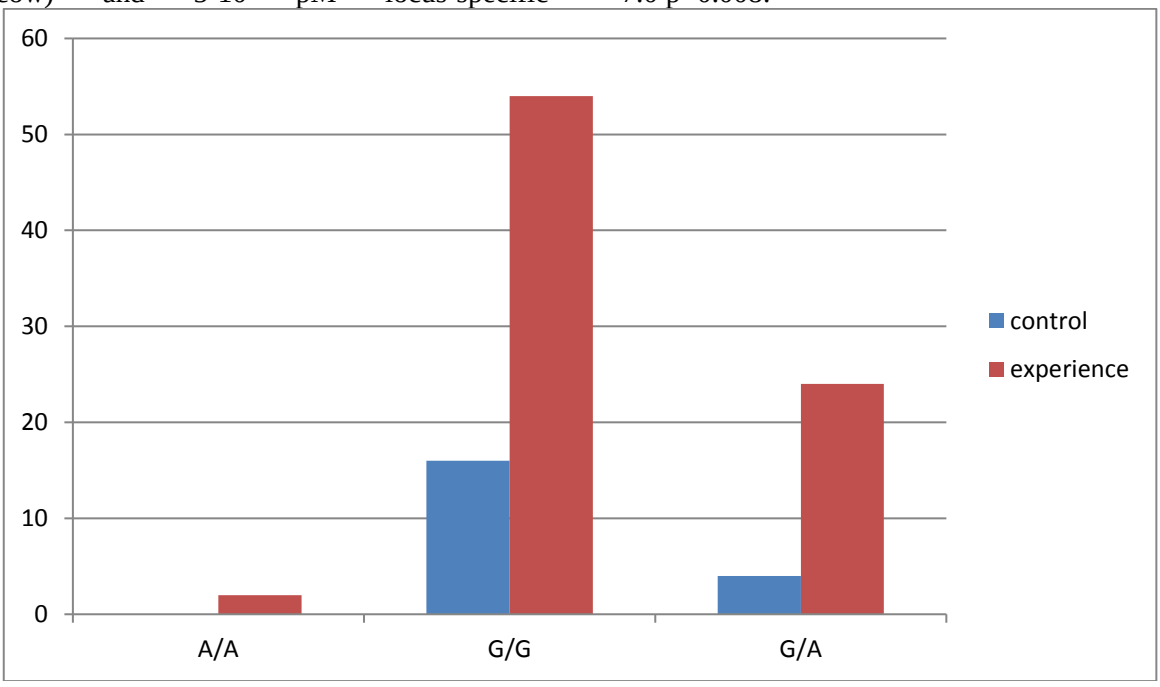

Figure 1 . The frequency of distribution of the genotypes of the CYP2C19 gene in patients with chronic gastritis, regardless of the type of gastritis

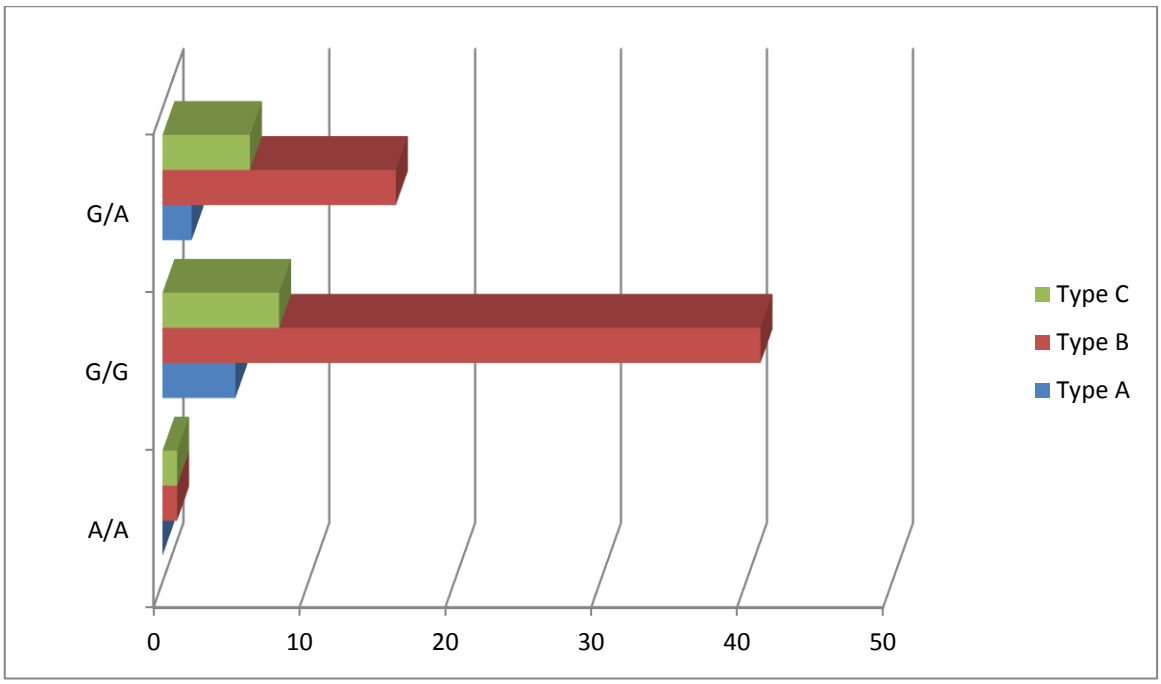

Figure 2. Distribution of types of chronic gastritis depending on the genotypes of the CYP2C19 gene

It should be noted that, in the structure of the group of patients with chronic gastritis (HCG) studied by us, regardless of the type of gastritis, it was revealed (Figure 1) that carriers of the "wild type" allele CYP2C19 GG made up more than 67%, carriers of the heterozygous allele CYP2C19 G/A made up 30%, carriers of the homozygous allele CYP2C19 A/A made up 2.5%. Thus, the frequency of occurrence of the G allele corresponded to 82%, while the frequency of occurrence of the A allele was about 17% in patients with chronic gastritis

It should also be noted that the A/A genotype of the CYP2C19 gene was not detected in the representatives of the control-healthy group.

When determining the occurrence of types of CG by allelic variants of the CYP2C19 gene, it turned out (Figure 2) that type B CG occurs in all genotypic variants: in patients with the G/G genotype – about 76%, in patients with the G/A genotype – about 67 %, in patients with the A/A genotype – 50% of cases, while type C CG is more detected in patients with the A/A genotype – 50%, and in heterozygous genotypic variant G/A-25% and in patients with the homozygous genotype G/G is about 15%. If type A HCG in patients with genotypes G/G and G/A is determined in the range of 8-9%, then in patients with genotype A/A, ot was not determined.

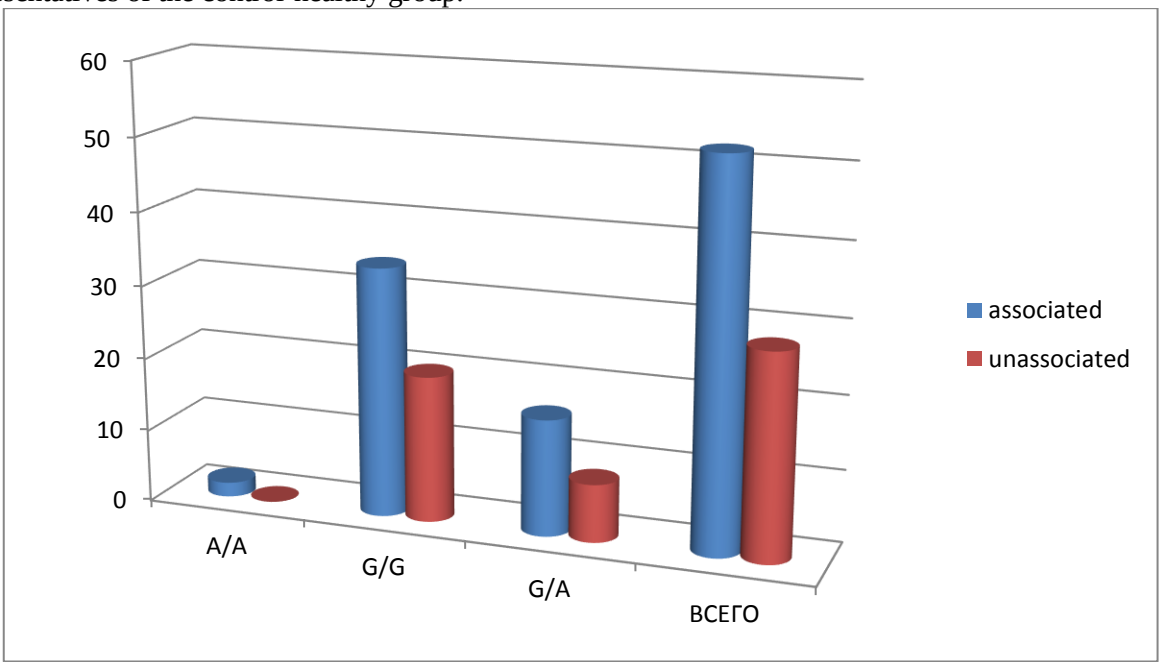

Figure 3. Frequency of distribution of the genotypes of the CYP2C19 gene in chronic gastritis, depending on the association of Helicobacter pylori

It should be noted that in the development of hCG, a special place is occupied by the bacteria Helicobacter pylori (HP) and such HCG is called "associated HP HCG". There is also a distinction between "unassociated HP hCG". When determining the genotype of the SUR2C19 gene by the polymorphic variant G681A comparatively (Figure 3), in patients with associated HP HCG, the heterozygous genotype G/A was detected in about 67% of cases, and the homozygous genotype G/G in 63% of patients, while in the non-associated group of patients, these genotypes were present in 33 and 37% of cases. It should be noted that the A/A genotype is found only in patients with associated HP HCG.

Our studies have shown that in the development of HCG, the presence and activity of the patient's genotype of the SUR2C19 gene for the allelic variant G681A for the duration of the disease occurs (Fig. 4).

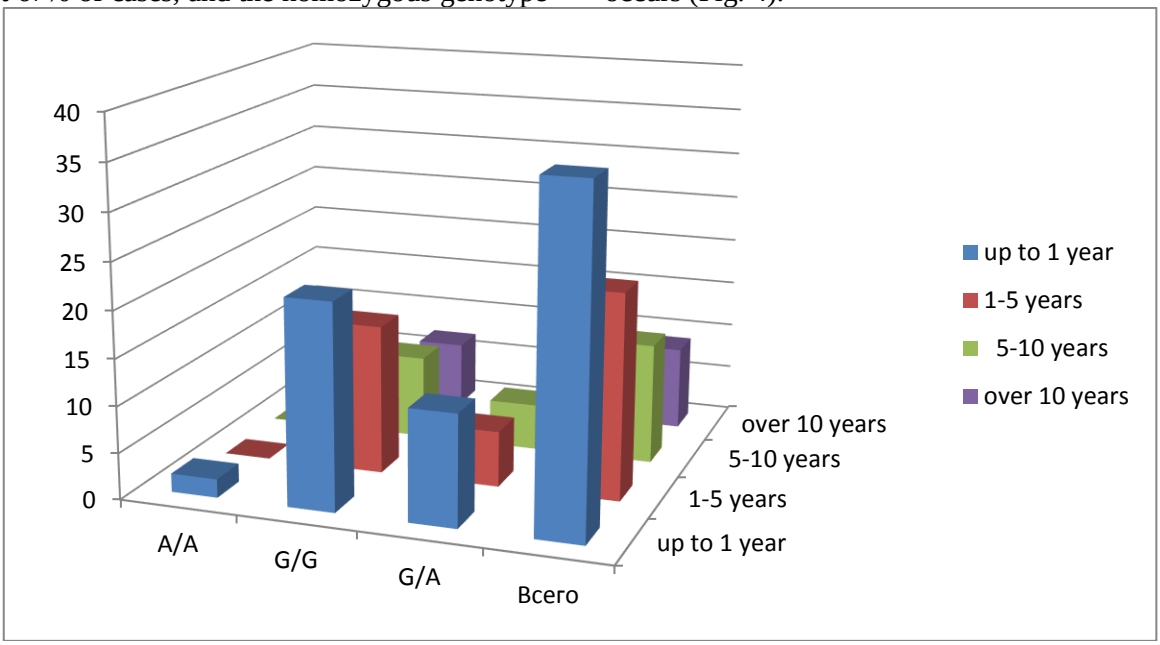

Figure 4. Frequency of distribution of the genotypes of the SUR2C19 gene in chronic gastritis, depending on the duration of the medical history

It turned out that patients with genotype G/A make up exactly half of patients who are ill for less than 1 year; ¼ of patients who are ill for up to 5 years; about 21% of patients with 5-10 years of "experience" of the disease and 4% of patients who suffer from HCG for more than 10 years. So, patients with genotype G / G in patients with a history of the disease up to 1 year are about 40%, patients with a similar genotype and with an established diagnosis of HCG with a 5-year history are about 30%; patients with a history up to 10 years are about 17% and with a history over 10 years are about 13%. And the A/A genotype is found only in patients with an established diagnosis of HCG for less than 1 year.

Conclusions

Thus:

- the occurrence of carriers of the "wild type" genotype G / G of the gene SUR2C19 for the allelic variant G681A is the main number of patients with HCG in the Bukhara region and this genotype differs in the duration of the disease;

- in all genotypic variants of the allelic variant of the CYP2C19 gene, type B HCG is found and Helicobacter pylori-associated HCG is determined.

LIST OF LITERATURE:

1. Arvanitidis K. Genetic polymorphisms of drug-metabolizing enzymes CYP2D6, CYP2C9, CYP2C19 and CYP3A5 in the Greek population // K. Arvanitidis, G. Ragia, M. Iordanidou et al. // Fundam. Clin. Pharmacol. 2007. Vol. 21 №4. P. 419 - 426.
2. Dawood S. Pharmacology, pharmacogenetics, and pharmacoepidemiology: three ps of individualized therapy. Cancer Invest. 2009. Oct. Vol.27, №8. P. 809-815.
3. Efrén Martínez-Quintana, Fayna Rodríguez-González, José María Medina-Gil, Paloma Garay-Sánchez, Antonio Tugores // Actividad de CYP2C19 y factores de riesgo cardiovascular en pacientes con síndrome coronario agudo. Medicina Clínica. Volume 149. Issue 6. 2017. Pages 235-239.

4. Gaikovitch E.A., Cascorbi I., Mrozikie- wicz P.M., Brockmöller J., Frötschl R., Köpke K., Gerloff T., Chernov J.N., Roots I. Polymorphisms of drug-metabolizing enzymes CYP2C9, CYP2C19, CYP2D6, CYP1A1, NAT2 and of P-glycoprotein in a Russian population//Eur. J. Clin. Pharmacol. 2003, Aug. Vol.59, №4. P. 303-312.
5. Gomez A., Ingelman-Sundberg M. Pharmacoepigenetics: its role in interindividual differences in drug response//Clin. Pharmacol. Ther. 2009, Apr. Vol.85, №4. P. 426-430.
6. Isakov V.A. Farmakogeneticheskiy analiz metabolizma i klinicheskoy effektivnosti ingibitorov protonnogo nasosa / V. A. Isakov // Klin. farmakol. ter. 2003. № 1. S. 32 - 37.
7. Kantemirova B.I., Griganov V.I., Dubina D.SH., Aliyeva Z.G. // Polimorfizm gena CYP2C19 u detey, prozhivayushchikh v astrakhanskom regione. Meditsinskiy vestnik Bashkortostana. Tom 7 №4 2012. 29-32 S.
8. Kitayeva Ye. Yu., Shprakh V.V., Mirzayev K.B., Ryzhikova K.A., Shuyev G.N., Sozayeva Zh.A., Pimenova Yu.A., Kogay V.V., Sychev D.A. //Chastota polimorfizmov genov CYP2C19 i ABCB1, assotsiirovannykh s izmeneniyem antiagregantnogo deystviya klopidogrela, u russkikh i buryat. Sibirskoye meditsinskoye obozreniye. 2018 №3 43-50 S.
9. Kukes V.G. Metabolizm lekarstvennykh sredstv: kliniko-farmakologicheskiye aspekty. - M.: Reafarm, 2004. - S. 113-120.
10. Ieiri I., Higuchi S. Pharmacogenomics: inter-ethnic and intra-ethnic differences in pharmacokinetic and pharmacodynamic profiles of clinically relevant drugs //Yakugaku Zasshi. 2009, Feb. Vol.129, №2. P. 231-235.
11. Miguel A. López-García, Iris A. Feria-Romero, Héctor Serrano, Darío Rayo-Mares, Pietro Fagiolino, Marta Vázquez, Consuelo Escamilla-Núñez, Israel Grijalva, David Escalante-Santiago, Sandra Orozco-Suarez // Influence of genetic variants of CYP2D6, CYP2C9, CYP2C19 and CYP3A4 on antiepileptic drug metabolism in pediatric patients with refractory epilepsy. Pharmacological Reports. Volume 69. Issue 3. 2017. Pages 504-511
12. Musayeva D.M., Ochilov A.K., Ochilova G.S. Korrektsiya farmakometaboliziruyushchey funktsii pecheni antioksidantami //Dostizheniya nauki i obrazovaniya. – 2018. – №. 10 (32).
13. Nebert D.W., Dalton T.P. The role of cyto- chrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. //Nat Rev Cancer. 2006. Dec; 6(12):947-60.
14. Ochilov A.K. Vazhnost' tsitokhromov P450 dlya gastroenterologii // Novyy den' v meditsine. – 2020. – №2 (30/2). – S. 57-59.
15. Ochilova G.S. Kharakteristika glikoproteina-P kak belka transportera lekarstvennykh veshchestv // New Day Medicine. – 2020. – №2 (30/2). – S. 60-63.
16. Ochilov A. K., Musayeva D. M. LECHENIYe KHRONICHESKOGO GASTRITA V ZAVISIMOSTI OT ALLEL'NYKH VARIANTOV GENA CYP2C19 //dlya provedeniya I-mezhdunarodnoy nauchno-prakticheskoy onlayn-konferentsii «Aktual'nyye voprosy meditsinskoy nauki v XXI veke». – 2019. – S. 267.
17. Ochilova D.A., Rakhmonkulova N.G., Effectiveness of combination therapy in the treatment of hypertensive disease//New Day in Medicine 1(29)2020 305-307 https://cutt.ly/hvNY7VE
18. Ochilov A.K., Musayeva D.M. Osobennosti gena CYP2S19 dlya induvidualizitsii farmakoterapii // Novyy Den' v Meditsine 1 (29) 2020. 65-68 s.
19. Ochilov A.K., G.S.Ochilova. “Znacheniye gena CYP2C19 v farmakoterapii pri khronicheskikh gastritakh» // Problemy biologii i meditsiny, 2019, № 4 (113) 250-252 s.
20. Ochilov A.K., Ochilova G.S. Klinicheskaya znachimost' polimorfizmov gena CYP2C19 // Universitetskaya nauka: vzglyad v budushcheye. Sbornik nauchnykh trudov po materialam Mezhdunarodnoy nauchnoy konferentsii, posvyashchennoy 85-letiyu Kurskogo gosudarstvennogo meditsinskogo universiteta (7 fevralya 2020 goda) Tom I. 2020. 376-379 S.
21. Romodanovskiy D.P., Khapayev B.A., Ignat'yev I.V., Kukes V.G., Karkishchenko V.N. Chastoty «medlennykh» allel'nykh variantov genov, kodiruyushchikh izofermenty tsitokhroma R450 CYP2D6, CYP2C19, CYP2C9 u karachayevtsev i cherkesov. BIOMEDITSINA. 2010;1(2):33-37.
22. Sara Vélez Gómez, Isaura Torres, Rubén Darío Manrique, Mauricio Duque, Juan Esteban Gallo // Aplicación farmacogenómica de los genes CYP2C19, CYP2C9 y VKORC1 implicados en el metabolismo de los fármacos clopidogrel y warfarina. Revista Colombiana de Cardiología. Volume 25. Issue 6. 2018. Pages 396-404.
23. Saliyeva M. KH., Azizov YU. D., Mirzayeva M. M. Puti modernizatsii mediko-sanitarnoy pomoshchi sel'skomu naseleniyu // Re-health journal. – 2019. – №. 2.
24. Saliyeva M. KH. i dr. Ob uluchshenii mediko-sanitarnoy pomoshchi //Dostizheniya nauki i obrazovaniya. – 2018. – №. 12 (34).
25. Sychev D.A., Ramenskaya G.V., Ignat'yev I.V., Kukes V.G. Klinicheskaya farmakogenetika /Pod redaktsiyey Kukesa V.G., Bochkova N.P. M.: Geotar-Media, 2007. 248 s.
26. Wooten J. Reporting adverse drug reactions//South Med. J. 2009, Apr. Vol.102, №4. P. 345-346.

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