International Journal of Biomedicine 11(3) (2021) 367-371
http://dx.doi.org/10.21103/Article11(3)_OA15

ORIGINAL ARTICLE

Population Genetics

INTERNATIONAL JOURNAL OF BIOMEDICINE

C3435T Polymorphism of the *ABCB1* gene in the Yakut Population

Nadezhda I. Pavlova[1*], PhD; Aleksandra T. Diakonova[1]; Vladislav A. Alekseev[1]; Yigulana P. Borisova[1]; Vladimir V. Dodokhov[2], PhD; Tuyara I. Dmitrieva[2]; Khariton A. Kurtanov[3], PhD

[1]Yakut Science Center of Complex Medical Problems
[2]Arctic State Agrotechnological University
[3]Institute for Biological Problems of Cryolithozone of SB of RAS
Yakutsk, the Republic of Sakha (Yakutia), Russia

Abstract

Background: The *ABCB1* gene is responsible for resistance to various cytotoxic drugs. The product of the *ABCB1* gene, P-glycoprotein (P-gp), acts as a transmembrane pump and influences the action of many drugs. More than 40 SNPs of the *ABCB1* gene that alter the expression of P-gp have been identified. The *ABCB1* rs1045642 SNP, designated as C3435T (C-the wild-type allele, T-the variant allele), correlates with the activity of P-gp. The aim of our research was to study the distribution of alleles and genotypes of the *ABCB1* C3435T polymorphism in Yakuts, in comparison with other human populations.

***Methods and Results*:** The studied cohort included 149 healthy Yakut volunteers (36 men and 113 women). The average age of participants was 30.67±0.06 years. The *ABCB1* gene is a highly polymorphic gene; the allele frequency of the C3435T polymorphism differs widely among the studied populations. The frequency of the mutant T-allele among the Yakuts was 51% .In the studied group of Yakuts, we revealed the prevalence of the heterozygous CT genotype (75.8%). The Yakuts have a relatively low frequency of CC (10.7%) and TT (13.4%) genotypes. This preliminary study did not include the objective of proving the relationship between the *ABCB1* C3435T polymorphism and addictive disorders in Yakuts. The further search for functional polymorphisms of the *ABCB1* gene and associations with addictive behavior using a systematic approach on larger samples is of great practical importance.**(International Journal of Biomedicine. 2021;11(3):367-371.)**

Key Words: ABCB1 • single nucleotide polymorphism • multidrug resistance • P-glycoprotein

For citation: Pavlova NI, Diakonova AT, Alekseev VA, Borisova YP, Dodokhov VV, Dmitrieva TI, Kurtanov KhA. C3435T Polymorphism of the ABCB1 gene in the Yakut Population. International Journal of Biomedicine. 2021;11(3):367-371. doi:10.21103/Article11(3)_OA15

Abbreviations

AD, addictive disorders; **HWE**, Hardy-Weinberg equilibrium; **ABCB1**, ATP-Binding Cassette Subfamily B Member 1; **MDR**, multidrug resistance; **P-gp**, P-glycoprotein; **SNPs**, single nucleotide polymorphisms

Introduction

Since its first description by R. Juliano and V. Ling, the ATP-binding cassette (ABC) protein P-gp has become the object of special attention as a key player in one of the drug resistance mechanisms.(1) Multidrug resistance (MDR) is a biological phenomenon that significantly increases the survival of tumor cells under the treatment of cytostatic drugs, which ultimately negatively affects the life expectancy of patients with malignant neoplasms. The MDR phenotype is associated with the functioning of the products of the ABC-transporter family of genes, a function that is associated with a major drug resistance mechanism.(2)

P-glycoprotein (P-gp), a protein encoded by the *ABCB1* gene, is an important transporter for many drugs, and is also associated with many immunological processes and apoptosis. (3) The P-gp is a very broad-spectrum efflux pump that is present in a variety of endothelia: liver, jejunum, or brain

capillary endothelial cells. P-gp plays an important role in the blood-brain barrier, protecting neurons from xenobiotics.

The *ABCB* gene family includes the *ABCB1* and *ABCB2* genes. The *ABCB1* gene is responsible for resistance to various cytotoxic drugs; the exact functions of the *ABCB2* gene, however, remain unknown.[4] The product of the *ABCB1* gene, P-gp, acts as a transmembrane pump and influences the action of many drugs.[5] The *ABCB1* gene is localized on chromosome 7q21. More than 40 SNPs of the *ABCB1* gene that alter the expression of P-gp have been identified. Three SNPs (1236C>T, 2677G>T and 3435C>T) have been repeatedly shown to predict changes in P-gp function. It has been shown that the frequencies of these polymorphisms in a population are ethnically related.

The *ABCB1* rs1045642 SNP, designated as C3435T (C-the wild-type allele, T-the variant allele), correlates with the activity of P-gp. In individuals homozygous for the T-allele, the expression of P-gp is more than four times lower than in individuals with the CC genotype.

The relationship of P-glycoprotein with the resistance of cancer cells to chemotherapy has been identified. The polymorphisms in the *ABCB1* gene can affect the pharmacokinetics of many drugs, including cytostatic anticancer drugs.[3-5]

The expression and function of some xenobiotic carriers vary depending on the time of the day, causing time-dependent changes in the distribution and toxicity of the drug. P-gp is highly expressed in the kidneys and is involved in the excretion of various drugs. The elimination of several P-gp substrates was demonstrated to vary depending on administration time, but the underlying mechanism remains unclear.[6-8]

Lopez and co-authors found that *ABCB1* in the adrenal glands can regulate the adaptation to stress. They identified previously unknown subpopulation cells Abcb1b+ involved in stress adaptation in the adrenal glands. This finding was confirmed using a mouse stress model, adrenal tissues of patients with Cushing's syndrome, adrenal cell lines and peripheral cortisol, as well as genotyping data from patients with depression.[9]

There are also reports showing that the *ABCB1* gene participates in forming human resistance to various infections as a result of acquiring resistance to bacterial toxins or viruses.[10]

Muderrisoglu et al.[11] demonstrated that the genetic polymorphism of the *ABCB1(MDR1)* gene is significantly associated with non-smoking status in a cohort of Turkish people. In particular, the frequency of the *ABCB1* 1236TT-2677TT-3435TT haplotype was significantly higher in non-smokers than in smokers (21.5% vs. 10.8, respectively; *P*=0.018). This haplotype and associated allelic variants may serve as a biomarker of protection against nicotine addiction if confirmed by other studies in different populations.[11]

Another group of researchers suggest that the rs1045642 SNP has an adaptive significance, or is linked to other polymorphic sites that have an adaptive significance.[10]

In 2013, Isaza and colleagues[12] determined the prevalence of some genetic markers involved in addictive behavior in a group of addicts to derivatives of coca (cocaine/crack) or heroin and a control group of non-addicted people matched for gender, age, and ethnicity. Significant differences were found between drug addicts and the control group in relation to SNP 3435C>T of the *ABCB1* gene (*P*=0.001). The results showed that the 3435CC genotype is associated with addiction to heroin or cocaine.

Identification of these genetic markers will allow early identification of people at risk in order to take appropriate preventive measures and offer better treatment options for those suffering from AD.

The aim of our research was to study the distribution of alleles and genotypes of the *ABCB1* C3435T polymorphism in Yakuts, in comparison with other human populations.

Materials and Methods

The study of the *ABCB1* C3435T polymorphism was carried out in the Department of Molecular Genetics at YSC CMP. The studied cohort included 149 healthy Yakut volunteers (36 men and 113 women). The average age of participants was 30.67±0.06 years. All study participants filled out a questionnaire approved by the local committee on biomedical ethics at YSC CMP and voluntarily signed an informed consent to conduct genetic research.

Genomic DNA was isolated from the whole blood samples using a commercial DNA extraction and purification kit (Newteryx, Russia). All DNA samples were deposited to YSC CMP biomaterial collection "The Genome of Yakutia" (No. USU_507512).

Allelic variants of the *ABCB1* rs1045642 SNP were tested by PCR-RFLP assay. PCR conditions, sequences of oligonucleotide primers, the restriction enzymes used and lengths of restriction fragments are shown in Table 1.

Table 1.

Conditions of PCR-RFLP assay

Gene	Primer	AL, bp	AT, °C	RE	RFL, bp
ABCB1 (rs1045642)	F:5′-TTG ATG GCA AAG AAA TAA AGC-3′	207	54	DpnI	CC – 130,76 CT – 206,130,76 TT – 206
	R:5′-CTT ACA TTA GGC AGT GAC TCG-3′				

AL - amplicon length; AT - annealing temperature; RE - restriction enzyme; RFL - restriction fragment length

Genotypes were identified by analyzing the size of the resulting fragments by 4% agarose gel electrophoresis with ethidium bromide using a standard tris-acetate buffer at 120V for 1 hour. Restriction products were visualized using the Bio-Rad gel imaging system.

The study was approved by the Ethics Committee of the Yakut Science Center of Complex Medical Problems (YSC CMP). Written informed consent was obtained from each research participant (or the participant's parent/guardian).

Statistical analysis was performed using the Statistica 8.0 software package (Stat-Soft Inc., USA). The correspondence

of the distributions of genotypes to the expected values at HWE and comparison of the frequencies of allelic variants/genotypes were performed using the chi-square test. A probability value of $P<0.05$ was considered statistically significant.

Results

The *ABCB1* gene is a highly polymorphic gene; the allele frequency of the C3435T polymorphism differs widely among the studied populations. In terms of the allele frequency, the Yakuts are similar to the southern Kyrgyz, Russians, and Tuvans, and when compared to the data of other researchers and the open-source data of the 1000 Genomes Project, the frequency is observed to be similar to that of Caucasian populations (Table 2).

The greatest difference in the allele frequency between the studied group and other ethnic groups was observed with Africans, Peruvians, and Chinese (C allele: 60-88%). The highest frequency of the wild C allele was observed in Esan in Nigeria (88%). The frequency of the mutant T-allele among the Yakuts was 51%, which is comparable with previously published data on the southern Kyrgyz (51%),(10) as well as with the 1000 Genome Project data on the Punjabi Pakistanis (51%). The highest frequency of the T-allele (61%) was observed in Bengalis and northern Kyrgyz. The lowest frequency of the T-allele (12%-19%) was observed in African populations. We assume that the presence of the T-allele, as a result of acquiring resistance to bacterial toxins and viruses, helped to establish resistance to various diseases; at the same time, the presence of the C allele favored the assimilation

Table 2.

The frequency distribution of alleles and genotypes in of the ABCB1 C3435T polymorphism in different ethnic populations

Populations	n	Allele frequency		Genotype frequency			H_o	H_e	Fis	References
		C	T	CC	TC	TT				
Yakuts (Russia)	149	0.49	0.51	10.7	75.8	13.4	0.76	0.50	-0.52	Current study
Russians (Russia)	90	0.43	0.57	-	-	-	0.44	0.49	0.10	[10]
Tuvans (Russia)	142	0.43	0.57	-	-	-	0.46	0.49	0.06	
Northern Kyrgyz (Kyrgyzstan)	41	0.39	0.61	-	-	-	0.60	0.47	-0.28	
Southern Kyrgyz (Kyrgyzstan)	44	0.49	0.51	-	-	-	0.42	0.50	0.16	
Jordanians (Jordan)	337	0.57	0.43	33.2	47.5	19.3	0.47	0.49	0.04	[21]
Brazilians (Brazil)	278	0.55	0.45	23.7	61.5	14.7	0.61	0.50	-0.22	[22]
Maharashtrians (India)	222	0.42	0.58	18.0	47.3	34.7	0.47	0.49	0.04	[23]
Macedonians (Macedonia)	107	0.51	0.49	25.2	52.3	22.4	0.52	0.50	-0.04	[24]
Ashkenazi Jews (USA)	101	0.50	0.50	30.7	38.6	30.7	0.36	0.50	0.28	[25]
African in Caribbean in Barbados	96	0.85	0.15	71.9	26.0	2.1	0.26	0.26	0.00	[26]
Descendants of Africans from the Southeastern States (USA)	61	0.81	0.19	67.2	27.9	4.9	0.28	0.31	0.10	
Esan (Nigeria)	99	0.88	0.12	77.8	21.2	1.0	0.21	0.20	-0.05	
Gambians (Gambia)	113	0.81	0.19	66.4	29.2	4.4	0.29	0.31	0.06	
Luhya (Kenya)	99	0.86	0.14	72.7	26.3	1.0	0.26	0.24	-0.08	
Mende (Sierra Leon)	85	0.85	0.15	70.6	29.4	0.0	0.70	0.46	-0.52	
Yoruba (Nigeria)	108	0.87	0.13	77.8	19.4	2.8	0.19	0.22	0.14	
Colombians (Colombia)	94	0.44	0.56	31.9	47.9	20.2	0.48	0.49	0.02	
Mexicans (Mexico)	64	0.52	0.48	25.0	54.7	20.3	0.55	0.50	-0.10	
Peruvians (Peru)	85	0.62	0.38	36.5	51.8	11.8	0.52	0.47	-0.11	
Puerto Ricans (Puerto Rico)	104	0.57	0.43	35.6	43.3	21.2	0.43	0.49	0.12	
Daians (China)	93	0.57	0.43	34.4	46.2	19.4	0.46	0.49	0.06	
Han (Beijing)	103	0.62	0.38	41.7	40.8	17.5	0.41	0.47	0.13	
Han (South China)	105	0.69	0.31	50.5	38.1	11.4	0.38	0.42	0.10	
Japanese (Japan)	104	0.52	0.48	24.0	55.8	20.2	0.56	0.50	-0.12	
Kinh (Vietnam)	99	0.60	0.40	37.4	44.4	18.2	0.44	0.48	0.08	
Utahs of Northern and Western European Descent (USA)	99	0.43	0.57	18.2	50.5	31.3	0.51	0.49	-0.04	
Finns (Finland)	99	0.42	0.58	14.1	56.6	29.3	0.57	0.49	-0.16	
British (England and Scotland)	91	0.47	0.53	22	50.5	27.5	0.51	0.50	-0.02	
Iberians (Spain)	107	0.54	0.46	29.9	47.7	22.4	0.48	0.50	0.04	
Tuscan (Italy)	107	0.53	0.47	29.9	46.7	23.4	0.47	0.50	0.06	
Bengalis (Bangladesh)	86	0.39	0.61	14	50	36	0.50	0.48	-0.04	
Gujaratis living in Houston, exas (USA)	103	0.43	0.57	19.4	47.6	33	0.48	0.49	0.02	
Telugu (UK)	102	0.41	0.59	19.6	42.2	38.2	0.42	0.48	0.13	
Punjabi (Pakistan)	96	0.49	0.51	22.9	52.1	25	0.52	0.50	-0.04	
Tamils Sri Lanka (UK)	102	0.41	0.59	19.6	42.2	38.2	0.42	0.48	0.13	

H_o - observed heterozygosity, H_e - expected heterozygosity, Fis - Wright's fixation index.

of various drugs. However, this hypothesis needs further investigation.

The SNP genotyping of the *ABCB1* gene in the studied group of Yakuts revealed the prevalence of the heterozygous CT genotype (75.8%). Among all compared ethnic groups, the Yakuts had the highest heterozygosity. The level of genetic differentiation of populations in terms of frequencies, calculated using the F_{is} coefficient, was -0.52. Possibly the high heterozygosity of this polymorphism is associated with adaptation since carriers of both alleles experience their effects simultaneously. The Yakuts have a relatively low frequency of CC (10.7%) and TT (13.4%) genotypes. The lowest heterozygosity was observed in Yoruba (19.4%). A high frequency of the CC genotype was observed in African populations (66.4%-77.8%). Among Asian populations, a high frequency of the CC genotype was found in the Chinese (41.7%-50.5%).

The *ABCB1* C3435T polymorphism is a silent mutation, albeit with functional implications. Hoffmeyer observed a significant correlation of a polymorphism in exon 26 (C3435T) of *MDR-1* with expression levels and function of *MDR-1*. TT homozygous for this polymorphism showed significantly lower duodenal P-gp expression, higher in vivo activity of Pgp and increased digoxin plasma levels.[13] In a study by Wang et al.,[14] it was found that the abundant 3435C>T SNP appears to be a main factor in allelic variation of *ABCB1* mRNA expression in the liver, by changing mRNA stability.

A recent population pharmacokinetic study investigated the functional effects of common combinations of SNPs (C1236T, G2677T/A, and C3435T) and haplotypes of the *ABCB1* gene in vivo, measuring the apparent bioavailability of digoxin, which is a substrate of *ABCB1*. Carriers of CGC/CGT and TTT/TTT had 35% higher apparent bioavailability compared to the reference group CGC/CGC, while no difference was seen in CGC/TTT carriers.[15] The obtained results support the use of digoxin as a phenotyping substrate of intestinal P-gp activity. These results are also consistent with another report, showing about twice the frequency of the all-variant TT-TT-TT haplotype in non-smokers, since *ABCB1* is involved in the transport of endogenous compounds such as opioid peptides, steroids, glutamate and endorphin, which act as modulators of neurons in the central nervous system and may play a role in substance addiction mechanisms.[11]

It has been reported that the *ABCB1* polymorphism has an effect on substance abuse. For example, the *ABCB1* polymorphism affects methadone dosage in the treatment of opioid or heroin addiction.[16,17] In addition, nicotine has been shown to alter the expression of *ABCB1*[18,19] and long-term exposure to the carcinogen 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK) found in tobacco smoke plays a role in head and neck squamous cell carcinoma by increasing anti-apoptosis and therapeutic resistance via the Snail-RKIP signaling pathway.[20]

Therefore, it can be assumed that genetic polymorphisms of the *ABCB1* gene have an effect on the mechanisms associated with substance addiction, including nicotine addiction. However, the association of molecular and biological mechanisms has not been investigated. Our study was limited due to the inability to study the C1236T(rs1128503) and G2677T/A(rs2032582) polymorphisms for haplotype analysis and due to a relatively small cohort of studied people.

In conclusion, the comparative analysis of our results with literature data on other human populations showed a high observed heterozygosity (75.8%) in the Yakut population. The frequencies of the CC and TT genotypes in the studied group were relatively low: 10.7% and 13.4%, respectively. This preliminary study did not include the objective of proving the relationship between the *ABCB1* C3435T polymorphism and addictive disorders in Yakuts. The further search for functional polymorphisms of the *ABCB1* gene and associations with addictive behavior using a systematic approach on larger samples is of great practical importance.

Competing Interests

The authors declare that they have no competing interests.

Sources of Funding

The study was carried out within the framework of the project “The study of the genetic structure and burden of hereditary pathology of populations of the Republic of Sakha (Yakutia).” All DNA samples were deposited to YSC CMP biomaterial collection “The Genome of Yakutia” (No. USU_507512).

References

1. Juliano RL, Ling V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta. 1976 Nov 11;455(1):152-62. doi: 10.1016/0005-2736(76)90160-7.
2. Gillet JP, Gottesman MM. Overcoming multidrug resistance in cancer: 35 years after the discovery of ABCB1. Drug Resist Updat. 2012 Feb-Apr;15(1-2):2-4. doi: 10.1016/j.drup.2012.03.001.
3. Rokhlina FV, Novik GA, Kalinina NM, Bychkova NV, Filippova YuN, Zarayskiy MI. [Influence of C3435T polymorphism of the MDR1 gene on the effectiveness of therapy for juvenile idiopathic arthritis]. Pediatric Pharmacology. 2013; 10 (5): 46–51. [Article in Russian].
4. Chin JE, Soffir R, Noonan KE, Choi K, Roninson IB. Structure and expression of the human MDR (P-glycoprotein) gene family. Mol Cell Biol. 1989 Sep;9(9):3808-20. doi: 10.1128/mcb.9.9.3808-3820.1989.
5. Stavrovskaya AA. [Tumor cell on the defensive]. Soros educational journal. 2001;7(7):17-23. [Article in Russian].
6. Omata Y, Yamauchi T, Tsuruta A, Matsunaga N, Koyanagi S, Ohdo S. RNA editing enzyme ADAR1 governs the circadian expression of P-glycoprotein in human renal cells by regulating alternative splicing of the ABCB1 gene. J Biol Chem. 2021 Jan-Jun;296:100601. doi: 10.1016/j.jbc.2021.100601.

***Corresponding author:** Nadezhda I. Pavlova, PhD. Yakut Science Center of Complex Medical Problems. Yakutsk, the Republic of Sakha (Yakutia), Russia. E-mail: solnishko_84@inbox.ru*

7. Choi JS, Park HJ. Circadian changes in pharmacokinetics of cyclosporin in healthy volunteers. Res Commun Mol Pathol Pharmacol. 1999 Jan;103(1):109-12.
8. Ferrazzini G, Sohl H, Robieux I, Johnson D, Giesbrecht E, Koren G. Diurnal variation of methotrexate disposition in children with acute leukaemia. Eur J Clin Pharmacol. 1991;41(5):425-7. doi: 10.1007/BF00626363.
9. Lopez JP, Brivio E, Santambrogio A, De Donno C, Kos A, Peters M, et al. Single-cell molecular profiling of all three components of the HPA axis reveals adrenal ABCB1 as a regulator of stress adaptation. Sci Adv. 2021 Jan 27;7(5):eabe4497. doi: 10.1126/sciadv.abe4497.
10. Pels YaR, Marusin AV, Spiridonova MG, Stepanov VA. [Polymorphism of the human MDR1 gene in the populations of Siberia and Central Asia]. Molecular Biology. 2007;6(41):982-988. [Article in Russian].
11. Muderrisoglu A, Babaoglu E, Korkmaz ET, Ongun MC, Karabulut E, Iskit AB, Emri S, Babaoglu MO. Effects of Genetic Polymorphisms of Drug Transporter ABCB1 (MDR1) and Cytochrome P450 Enzymes CYP2A6, CYP2B6 on Nicotine Addiction and Smoking Cessation. Front Genet. 2020 Nov 30;11:571997. doi: 10.3389/fgene.2020.571997.
12. Isaza C, Henao J, Beltrán L, Porras L, Gonzalez M, Cruz R, et al. Genetic variants associated with addictive behavior in Colombian addicted and non-addicted to heroin or cocaine. Colomb Med (Cali). 2013 Mar 30;44(1):19-25.
13. Hoffmeyer S, Burk O, von Richter O, Arnold HP, Brockmöller J, Johne A, Cascorbi I, Gerloff T, Roots I, Eichelbaum M, Brinkmann U. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A. 2000 Mar 28;97(7):3473-8. doi: 10.1073/pnas.050585397.
14. Wang D, Johnson AD, Papp AC, Kroetz DL, Sadée W. Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C>T affects mRNA stability. Pharmacogenet Genomics. 2005 Oct;15(10):693-704.
15. Hsin CH, Stoffel MS, Gazzaz M, Schaeffeler E, Schwab M, Fuhr U, Taubert M. Combinations of common SNPs of the transporter gene ABCB1 influence apparent bioavailability, but not renal elimination of oral digoxin. Sci Rep. 2020 Jul 27;10(1):12457. doi: 10.1038/s41598-020-69326-y.
16. Levran O, O'Hara K, Peles E, Li D, Barral S, Ray B, Borg L, Ott J, Adelson M, Kreek MJ. ABCB1 (MDR1) genetic variants are associated with methadone doses required for effective treatment of heroin dependence. Hum Mol Genet. 2008 Jul 15;17(14):2219-27. doi: 10.1093/hmg/ddn122.
17. Yuferov V, Levran O, Proudnikov D, Nielsen DA, Kreek MJ. Search for genetic markers and functional variants involved in the development of opiate and cocaine addiction and treatment. Ann N Y Acad Sci. 2010 Feb;1187:184-207. doi: 10.1111/j.1749-6632.2009.05275.x.
18. Pal D, Kwatra D, Minocha M, Paturi DK, Budda B, Mitra AK. Efflux transporters- and cytochrome P-450-mediated interactions between drugs of abuse and antiretrovirals. Life Sci. 2011 May 23;88(21-22):959-71. doi: 10.1016/j.lfs.2010.09.012.
19. Takano M, Naka R, Sasaki Y, Nishimoto S, Yumoto R. Effect of cigarette smoke extract on P-glycoprotein function in primary cultured and newly developed alveolar epithelial cells. Drug Metab Pharmacokinet. 2016 Dec;31(6):417-424. doi: 10.1016/j.dmpk.2016.08.006.
20. Nieh S, Jao SW, Yang CY, Lin YS, Tseng YH, Liu CL, Lee TY, Liu TY, Chu YH, Chen SF. Regulation of tumor progression via the Snail-RKIP signaling pathway by nicotine exposure in head and neck squamous cell carcinoma. Head Neck. 2015 Dec;37(12):1712-21. doi: 10.1002/hed.23820.
21. Al-Diab O, Yousef Al-M, Manassrah EAl, Masadeh A, Olemat M, Qosa H, et al. Genotype and Haplotype Analysis of ABCB1 at 1236, 2677 and 3435 among Jordanian Population. Tropical Journal of Pharmaceutical Research. 2015 Apr;14(6):1013-1019. doi: 10.4314/tjpr.v14i6.11
22. Scheiner MA, Damasceno AM, Maia RC. ABCB1 single nucleotide polymorphisms in the Brazilian population. Mol Biol Rep. 2010 Jan;37(1):111-8. doi: 10.1007/s11033-009-9547-x.
23. Pramanik S, Surendran ST, Devi S, Krishnamurthi K, Chakrabarti T. Frequency and genotype distribution of ABCB1 gene polymorphisms among Maharashtrian population of Central India. Xenobiotica. 2014 Jun;44(6):579-82. doi: 10.3109/00498254.2013.866300.
24. Naumovska Z, Nestorovska AK, Sterjev Z, Filipce A, Dimovski A, Suturkova L. Genotype variability and haplotype profile of ABCB1 (MDR1) gene polymorphisms in Macedonian population. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2014;35(3):121-33. doi: 10.1515/prilozi-2015-0016.
25. Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, Gottesman MM. A "silent" polymorphism in the MDR1 gene changes substrate specificity. Science. 2007 Jan 26;315(5811):525-8. doi: 10.1126/science.1135308. Epub 2006 Dec 21. Erratum in: Science. 2007 Nov 30;318(5855):1382-3. Erratum in: Science. 2011 oCT 7;334(6052):39.
26. GSR and the 1000 Genomes Project [Internet]. Available from: https://www.internationalgenome.org.