Epilepsy Research 158 (2019) 106221

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Lack of association of SCN2A rs17183814 polymorphism with the efficacy of lamotrigine monotherapy in patients with focal epilepsy from Herzegovina area, Bosnia and Herzegovina

Natasa Pejanovic-Skobic[a,*], Ivana Markovic[b], Nada Bozina[c], Silvio Basic[b]

[a] Clinic of Neurology, University Clinical Hospital Mostar, 88000 Mostar, Bosnia and Herzegovina
[b] Clinic of Neurology, Clinical Hospital Dubrava, 10000 Zagreb, Croatia
[c] Department of Laboratory Diagnostics, University Hospital Centre Zagreb, 10000 Zagreb, Croatia

ARTICLE INFO

Keywords:
Epilepsy
Gene polymorphism
SCN2A
Lamotrigine

ABSTRACT

Objective: We assessed the influence of the SCN2A gene polymorphism c.56 G > A rs17183814 on the response to lamotrigine monotherapy in patients with focal epilepsy in Herzegovina area, Bosnia and Herzegovina.
Material and methods: For SCN2A polymorphism c.56 G > A rs17183814, one hundred patients with epilepsy who were receiving lamotrigine in monotherapy and seventy-one age and sex matched healthy controls were genotyped using TaqMan assay. All patients were Caucasians from the region of Herzegovina, Bosnia and Herzegovina. Genotyping was conducted using a polymerase chain reaction in real time. Patients were divided into two groups: responders and non-responders.
Results: Of all patients with epilepsy, 33% were non-responders, and 67% were responders. The mean age of non-responders was 38.8 vs. group of responders in which it was 35.2. Mean age of onset of seizures in epilepsy patients was 26.7 for non-responders and 25.4 for responders. In patients with epilepsy, the mean age of seizure onset was 26.7 for non-responders and 25.4 for responders. For SCN2A c.56 G > A gene polymorphism, we did not observe any significant differences in genotypic or allelic frequency between patients with epilepsy and healthy controls. Genotype or allelic frequencies of SCN2A c.56 G > A gene polymorphism did not significantly differ for AG or GG genotypes in the non-responders vs. responders.
Conclusion: There was no significant association in patients with focal epilepsy between studied genotypes and response to lamotrigine monotherapy in Herzegovina patients with focal epilepsy. However, we need studies in a bigger cohort of patients with epilepsy to be assessed in the future.

1. Introduction

Epilepsy is a common and heterogeneous neurological disorder with the important etiological role of genetics. It is also recognized that genetic factors have an impact on the response and effectiveness of antiepileptic drugs (AEDs). There have been reports of several single nucleotide polymorphisms (SNPs) correlated with AED dosage and drug resistance (Goldstein et al., 2007; Chmielewska et al., 2013). Lamotrigine (LTG) is one of the most commonly prescribed new-generation AEDs used in monotherapy or in combination with other AEDs to treat focal and generalized seizures in adults and children (Pellock, 1997; Cohen et al., 1987).

Sodium channels play a major role in generating and spreading of action potentials in neuronal and other excitable cells (Kaplan et al., 2016). Their structure as heteromultimeric complexes consists of a big, pore-forming α-subunit responsible for the function of sodium channels and smaller accessory β-subunits (Yu and Catterall, 2003; George, 2005). Eleven genes (SCN1A – SCN11A) encrypt the α-subunit targeting some of the most commonly used sodium channel blockers such as carbamazepine (CBZ), oxcarbazepine (OXZ), phenytoin (PHT), and lamotrigine (LTG) (Plummer and Meisler, 1999; Kuo, 1998). Genetic variations in the α-subunit may affect sodium channel electrophysiological features in drug-resistant patients with epilepsy (Loscher et al., 2009).

It is clear that, based on prior studies, pharmacoresistance mechanisms are most probable to be multifactorial, including environmental, genetic and disease-related conditions as well as factors related to antiepileptic drugs (Sisodiya et al., 2002; Depondt, 2006). Recent trials analyzing target pharmacoresistance hypothesis in patients with epilepsy often included a heterogeneous group of patients with different

* Corresponding author at: Clinic of Neurology, University Clinical Hospital Mostar, Kralja Tvrtka bb, 88000 Mostar, Bosnia and Herzegovina.
E-mail address: natasa.pejanovic@gmail.com (N. Pejanovic-Skobic).

https://doi.org/10.1016/j.eplepsyres.2019.106221
Received 8 August 2019; Received in revised form 12 October 2019; Accepted 17 October 2019
Available online 23 October 2019
0920-1211/

monotherapy or polytherapy with varying etiologies, making it hard to determine the precise cause of pharmacoresistance in these patients. We therefore decided to examine the impact of one gene polymorphism on the efficacy of single AED, and in this case it was LTG in a monotherapy as it is one of the most popular antiepileptic drugs prescribed globally.

Common variation within distinct genes is likely to contribute significantly to drug resistance mechanisms (Sisodiya, 2005; Ma et al., 2014). However, studies surveying the effect of SNPs of a variety of genes on specific metabolism of AEDs in different populations showed some contradictory findings, likely owing to geographical/genetic differences between the populations studied (Manna et al., 2011; Hashi et al., 2015; Shaheen et al., 2014; Seven et al., 2014; Seo et al., 2006; Lakhan et al., 2009).

Polymorphism c. SCN2A 56 G > A causes amino acid substitution (Arg19Lys) in a cytoplasmic portion of the sodium channel and this Arg19 is a residue that is moderately preserved. Based on prior findings and present understanding that changes in voltage-gated sodium channel genes are involved in susceptibility to epilepsy and could influence interindividual differences in response to AEDs, our research intended to explore the influence of SCN2A gene polymorphism c.56 G > A (rs17183814) on lamotrigine monotherapy response in patients with focal epilepsy in the population of Herzegovina area, Bosnia and Herzegovina.

2. Material and methods

2.1. Patients and healthy controls

This was a two-center survey of patients from the Herzegovina region (Bosnia and Herzegovina) treated at University Clinical Hospital Mostar, Bosnia and Herzegovina, and Clinical Hospital Dubrava in Zagreb, Croatia. The current research included 100 patients with epilepsy who were followed up for at least one year as outpatients in these two clinical hospitals. Experienced neurologist diagnosed seizures and epilepsy syndromes and classified them according to the new epilepsy classification of International League Against Epilepsy-ILAE from 2017 (Fisher et al., 2017; Scheffer et al., 2017).

The study's inclusion criteria were: 1) focal epilepsy diagnosis according to ILAE criteria, 2) neuroimaging (brain MRI) without pathological substrate. The exclusion criteria were: 1) generalized epilepsy, 2) history of non-epileptic seizures, 3) brain MRI pathological finding, 4) progressive or degenerative neurological disorder, 5) abuse of alcohol and/or drugs, 6) serious mental illnesses.

During the study period, 71 healthy participants with no proof of epilepsy were appointed as controls, independently matched to patients with epilepsy based on gender and age.

Demographic and clinical informations were gathered from questionnaires for all participants. We reported gender, age, age of onset of epilepsy, medical and neurological history, seizure type, classification of epilepsy, seizure frequency, electroencephalographic recording, neuroimaging information, and AED therapy, on the first visit.

Medical records were subsequently gathered up to the end of the research every three months. Every participant was provided all necessary information about the research before the blood collection and informed consent from all participants was received. The Ethic Committee of both research centers, University Clinical Hospital Mostar and Clinical Hospital Dubrava in Zagreb approved this prospective observational study, and it is in accordance with the Helsinki Declaration of 1964 and its subsequent amendments.

The primary criterion for unresponsiveness was the occurrence of seizures in patients getting maximum tolerated doses of lamotrigine over a period of one year and these patients were included in the group of non-responders. Patients with epilepsy, who had complete seizure freedom for at least one year before the last visit, including that visit, were regarded drug responsive and those patients were placed in the group of responders.

Based on clinical judgment, AED dosage was adjusted according to routine clinical practice. In patients who continued to have seizures, despite the current antiepileptic treatment, AED dosage was titrated to that level considered to be maximally tolerated by the patient before being evaluated as failing owing to insufficient efficacy and switched to another monotherapy or polytherapy regiment.

2.2. DNA analysis

The manufacturer (Qiagen AS, Oslo, Norway) suggested method was used for extracting genomic DNA from 5 ml of venous blood with a DNA extraction kit. The SCN2A polymorphism rs17183814 was assessed using TaqMan assay by allelic discrimination in accordance with the protocols of the manufacturer (Applied Biosystems, Foster City, CA, USA). ABI 7500 real-time PCR (polymerase chain reaction) system was used for genotyping (Applied Biosystems, Foster City, CA, USA).

Sequence: CCTGACAGCTTCCGCTTCTTTACCA **[A/G]** GGAATCCCT TGCTGCTATTGAACAA

2.3. Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 20 (IBM). Chi-square test was used to evaluate differences between patients with epilepsy and healthy controls in genotypic and allelic frequencies. When P-value was < 0.05, the association was considered significant. Using binary logistic regression, the relationship between different genotypes and responsiveness was examined. Association was expressed as odds ratios (OR) or risk estimates with confidence intervals (CI) of 95 %.

3. Results

3.1. Demographic profiles of epilepsy patients

Of all epilepsy patients, 33% were non-responders and 67 % were good responders. Mean duration of disease was the longest in the non-responder group, while the responders had the shortest duration of

Table 1
Demographic profile of epilepsy patients, responders and non-responders.

	All patients (100)	Responders (67)	Non-responders (33)
Male gender	48 (48%)	31 (46%)	17 (52%)
Female gender	52 (52%)	36 (54%)	16 (48%)
Mean age at onset of disease (years)	25.61	25.36	26.73
95% CI	$P(22.50, 28.72) = 0.95$	$P(21.52, 29.20) = 0.95$	$P(20.58, 32.87) = 0.95$
Mean disease duration (years)	10.78	9.87	12.03
95% CI	$P(8.79, 12.77) = 0.95$	$P(7.68, 12.05) = 0.95$	$P(7.78, 16.28) = 0.95$
Mean age of epilepsy patients (years)	36.34	35.24	38.76
95% CI	$P(33.36, 39.44) = 0.95$	$P(31.43, 39.05) = 0.95$	$P(33.58, 43.94) = 0.95$

CI, confidence interval.

Table 2
Analysis of patient's age, age of epilepsy onset and disease duration for responders and non-responders.

	Non-responders		Responders	
	Mean value	SD	Mean value	SD
Age of epilepsy onset	26.73	17.33	25.36	15.74
Disease duration	12.03	11.99	9.87	8.97
Age	38.76	14.61	35.24	15.62

SD, standard deviation.

Table 3
Analysis of responders/non-responders in a regard to gender structure.

Chi-square test: Responders-nonresponders and gender	Value	*df*	P-value
Pearson's Chi-square	0.244	1	0.621
Yates correction	0.079	1	0.779
OR	0.244	1	0.622
Total number of patients	100		
Fi – coefficient	0.049		0.621

OR, odds ratio; *df*, degree of freedom.

disease. The mean non-responder's age was longer than in the responder group. The mean age of seizure onset was almost the similar for responders and non-responders (Table 1 and 2). Statistical analysis revealed that there was no statistical difference between two groups of patients with epilepsy, responders and non-responders in the gender structure (Table 3).

3.2. Correlation of SCN2A c.56 G > A gene polymorphism and susceptibility to epilepsy

In 100 sporadic patients with epilepsy and 71 healthy controls, we determined the genotypic and allelic frequencies. The frequency of genotypes in patients with epilepsy and healthy controls did not show statistically significant differences for GA or GG genotypes (Table 4). It is important to note that AA genotype was not determined in epilepsy patients from our studied population, and only one subject in the control group had AA genotype.

3.3. Correlation of SCN2A c.56 G > A polymorphism with responsiveness on lamotrigine in responders and non-responders group

Statistical analysis reveals no statistically significant difference in genotype frequency between non-responders and responders for GA or GG genotype (Table 5).

4. Discussion

We analyzed one genetic polymorphism, SCN2A c.56 G > A, in our research. We did not found an association of SCN2A c.56 G > A gene polymorphisms with long-term susceptibility to epilepsy.

There was no increased risk of developing epilepsy in patients with this SCN2A polymorphism in a research by Lakhan et al. (2009). This polymorphism was previously analyzed in German patients with idiopathic generalized epilepsy and that study did not demonstrate any

Table 4
Genotype frequency GA/GG/AA in epilepsy patients and healthy controls.

Genotype	Epilepsy patients	Healthy controls	OR (95% CI)	P-value
GA	13 (13%)	9 (12.7%)	0.989 (0.447, 2.186)	0.978
GG	87 (87%)	61 (85.9%)	1.002 (0.890, 1127)	0.987
AA	0 (0%)	1 (1.4%)	0 (0.000, 0.000)	0.306

OR, odds ratio; CI, confidence interval.

Table 5
Genotype frequency GA/GG in responders and non-responders.

Genotype	Non-responders	Responders	OR (95% CI)	P-value
GA	3 (9%)	10 (15%)	0.609 (0.180, 2.065)	0.570
GG	30 (91%)	57 (85%)	1.069 (0.922, 1.238)	0.317

OR, odds ratio; CI, confidence interval.

correlation with susceptibility to epilepsy (Haug et al., 2001). A similar research conducted by Nakayama et al. (2002) in the Japanese population also discovered no correlation between this specific SCN2A polymorphism and epilepsy susceptibility in patients with FS.

Changes in drug targets, based on mechanisms engaged in the development of pharmacoresistant epilepsy, make them less susceptible to AEDs according to the target hypothesis (Remy and Beck, 2006). Targets for antiepileptic drugs include voltage-gated channels and neurotransmitter receptors related to neuronal excitation. It has been suggested that modifications in the structure, function or expression of particular sodium channel subunits may affect the clinical response to multiple AEDs (Ragsdale and Avoli, 1998). The disease can facilitate transcriptional or post-transcriptional alterations in the acquired drug resistance that cause modifications in voltage-gated sodium channels and alter their sensitivity to AEDs (Beck, 2007).

Li et al. (2016) found that VPA responses were significantly associated with three SNPs: rs1731017 (ABAT), rs2304016 (SCN2A) and rs1054899 (ALDH5A1). Further analysis of interaction in this study showed that the interaction between rs17183814 (ABAT) and rs1641022 (SCN2A) was also significantly associated with VPA response.

Markovic and Pejanovic-Skobic (2019) analyzed the effect of IVS5-91G > A (rs3812718) polymorphism of SCN1A gene on LTG efficacy in patients with non-lesional focal epilepsy and found no significant differences in the response to LTG between carriers of different genotypes. Haerian et al. (2013) conducted a genotype analysis of 39 polymorphisms found on the genes SCN1A, SCN2A and SCN3A in 1504 patients from Malaysia and Hong Kong treated with AEDs. Analysis of these patients showed no significant allelic, genotypic or haplotypic association of polymorphisms in the genes SCN1A, SCN2A, and SCN3A with responsiveness to AEDs. A meta-analysis of SCN1A rs3812718 and rs2298771 and SCN2A rs17183814 polymorphisms confirmed these findings.

In north Indian patients with epilepsy, the SCN2A c.56 G > A polymorphism (rs17183814) was observed to be independently associated with drug resistance in the study of Lakhan et al. (2009) but this association was pretty weak as it was only detected at the level of allels. The association only at the allelic level could be due to the small number of AA genotypes in drug-resistant and drug-responsive groups, the reason for AA genotype did not reach statistical significance. In our research, which included patients with epilepsy from Herzegovina, we did not have any patients with AA genotype in responders and non-responders groups, indicating that genetic variations between studied populations can play a significant role in interpreting different outcomes from pharmacogenomic studies, including patients with epilepsy from different areas. Because of the world population's significant heterogeneity, a specific genotype may be essential in determining drug response for one population, but not for the other. Therefore, in varying racial and ethnic groups, pharmacogenomic associations must be validated.

In regard to the ethnic heterogeneity, Yu et al. (2015) earlier suggested that ethnicity plays a role in the association between ABCB1 polymorphisms and drug resistant epilepsy showing significant associations in Asians while there was no association in Caucasians. We had a similar situation with ethnic heterogeneity regarding analyzed SCN2A polymorphism, since previously mentioned study of Lakhan et al. (2009) showed significant association between SCN2A c.56 G > A

polymorphism and drug resistance in north Indian patients with epilepsy, while we found no association between the same polymorphism and drug response in analyzed, Caucasian, population of epilepsy patients.

Discrepancies between studies can be explained by different variables, including genetic heterogeneity, sample size, population substructure, duration of treatment, variation in the definition of treatment results, type of AEDs used (sodium channel blockers or AEDs with multiple action mechanisms), interactions of AEDs in polytherapy and their competition for binding to ordinary targets, epilepsy etiology differences or dose regimens differences.

Analogously, epilepsy etiology may have an impact on the responsiveness to AEDs and the outcomes of studies. Most surveys were performed in patients with different types of epilepsy. Evidence suggested that pharmacoresistance in patients with recognized structural abnormality or inherent neurological lesion was more prevalent than in patients without such disturbances (Kwan and Brodie, 2000). Therefore, we only included patients with focal epilepsy who had no evidence of structural etiology of epilepsy.

It is probable that the causes of pharmacoresistance will be multiple, even in the case of only one AED with bad response. We have not discovered that SCN2A gene polymorphism rs17183814 impacts the efficacy of LTG in our population, so it is essential to examine other polymorphisms in the following studies that affect changes in the sodium channel or combinations of different polymorphisms for the same channel.

Whether the outcome of our research showing no impact of SCN2A gene polymorphism rs17183814 on the response to LTG in patients with epilepsy and other studies with similar outcomes means that the voltage-gated sodium channel genes do not contribute significantly to the pathogenesis of AED resistance is not totally clarified. An argument for such outcomes might be that the independent contribution of each gene to the development of AED pharmacoresistance may be too weak to be detected using conventional parametric statistical methods in limited sample settings or that the SNP chosen from each gene may not be a real representative of the gene in terms of its function. Thus, gene interaction may be more significant than the independent impacts of certain genes.

Our study limitations might be that the study population was screened for only one SNP in sodium channel genes, however, the impact and presence of other genetic variants in the very same gene or other candidate genes cannot be overlooked. Second, the small sample size of the epilepsy patients group might have resulted in possible false negative results and it would be beneficial to study this at the functional level and also to repeat the results in bigger cohorts.

There was no significant association in patients with focal epilepsy between studied genotypes and response to lamotrigine monotherapy in Herzegovina patients with focal epilepsy. However, we need studies in a bigger cohort of patients with epilepsy to be assessed in the future, because understanding the genetic impacts on the drug response make it possible to predict varying responsiveness to AEDs in patients with epilepsy and optimize the therapeutic approach for each individual patient.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Declaration of Competing Interest

None.

References

Beck, H., 2007. Plasticity of antiepileptic drug targets. Epilepsia 48 (Suppl. 1), 14–18.
Chmielewska, B., Lis, K., Rejdak, K., Balcerzak, M., Steinborn, B., 2013. Pattern of adverse events of antiepileptic drugs: results of the aESCAPE study in Poland. Arch.f Med. Sci.: AMS 9 (5), 858–864.
Cohen, A.F., Land, G.S., Breimer, D.D., Yuen, W.C., Winton, C., Peck, A.W., 1987. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin. Pharmacol. Ther. 42 (5), 535–541.
Depondt, C., 2006. The potential of pharmacogenetics in the treatment of epilepsy. Eur. J. Paediatric Neurol.: EJPN: Off. J. Eur. Paediatric Neurol. Soc. 10 (2), 57–65.
Fisher, R.S., Cross, J.H., D'Souza, C., French, J.A., Haut, S.R., Higurashi, N., et al., 2017. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 58 (4), 531–542.
George Jr, A.L., 2005. Inherited disorders of voltage-gated sodium channels. J. Clin. Invest. 115 (8), 1990–1999.
Goldstein, D.B., Need, A.C., Singh, R., Sisodiya, S.M., 2007. Potential genetic causes of heterogeneity of treatment effects. Am. J. Med. 120 (4 Suppl. 1), S21–5.
Haerian, B.S., Baum, L., Kwan, P., Tan, H.J., Raymond, A.A., Mohamed, Z., 2013. SCN1A, SCN2A and SCN3A gene polymorphisms and responsiveness to antiepileptic drugs: a multicenter cohort study and meta-analysis. Pharmacogenomics 14 (10), 1153–1166.
Hashi, S., Yano, I., Shibata, M., Masuda, S., Kinoshita, M., Matsumoto, R., et al., 2015. Effect of CYP2C19 polymorphisms on the clinical outcome of low-dose clobazam therapy in Japanese patients with epilepsy. Eur. J. Clin. Pharmacol. 71 (1), 51–58.
Haug, K., Hallmann, K., Rebstock, J., Dullinger, J., Muth, S., Haverkamp, F., et al., 2001. The voltage-gated sodium channel gene SCN2A and idiopathic generalized epilepsy. Epilepsy Res. 47 (3), 243–246.
Kaplan, D.I., Isom, L.L., Petrou, S., 2016. Role of sodium channels in epilepsy. Cold Spring Harb. Perspect. Med. 6 (6).
Kuo, C.C., 1998. A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuronal Na+ channels. Mol. Pharmacol. 54 (4), 712–721.
Kwan, P., Brodie, M.J., 2000. Early identification of refractory epilepsy. N. Engl. J. Med. 342 (5), 314–319.
Lakhan, R., Kumari, R., Misra, U.K., Kalita, J., Pradhan, S., Mittal, B., 2009. Differential role of sodium channels SCN1A and SCN2A gene polymorphisms with epilepsy and multiple drug resistance in the north Indian population. Br. J. Clin. Pharmacol. 68 (2), 214–220.
Li, X., Zhang, J., Wu, X., Yan, H., Zhang, Y., He, R.H., et al., 2016. Polymorphisms of ABAT, SCN2A and ALDH5A1 may affect valproic acid responses in the treatment of epilepsy in Chinese. Pharmacogenomics 17 (18), 2007–2014.
Loscher, W., Klotz, U., Zimprich, F., Schmidt, D., 2009. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 50 (1), 1–23.
Ma, C.L., Wu, X.Y., Zheng, J., Wu, Z.Y., Hong, Z., Zhong, M.K., 2014. Association of SCN1A, SCN2A and ABCC2 gene polymorphisms with the response to antiepileptic drugs in Chinese Han patients with epilepsy. Pharmacogenomics 15 (10), 1323–1336.
Manna, I., Gambardella, A., Bianchi, A., Striano, P., Tozzi, R., Aguglia, U., et al., 2011. A functional polymorphism in the SCN1A gene does not influence antiepileptic drug responsiveness in Italian patients with focal epilepsy. Epilepsia 52 (5), e40–4.
Markovic, I., Pejanovic-Skobic, N., 2019. The Lack of Influence of IVS5-91 G&A Polymorphism of the SCN1A Gene on Efficacy of Lamotrigine in Patients with Focal Epilepsy. pp. 1–6.
Nakayama, J., Yamamoto, N., Hamano, K., Iwasaki, N., Ohta, M., Nakahara, S., et al., 2002. Failure to find evidence for association between voltage-gated sodium channel gene SCN2A variants and febrile seizures in humans. Neurosci. Lett. 329 (2), 249–251.
Pellock, J.M., 1997. Lamotrigine. J. Child Neurol. 12 (Suppl. 1), S1.
Plummer, N.W., Meisler, M.H., 1999. Evolution and diversity of mammalian sodium channel genes. Genomics 57 (2), 323–331.
Ragsdale, D.S., Avoli, M., 1998. Sodium channels as molecular targets for antiepileptic drugs. Brain Res. Brain Res. Rev. 26 (1), 16–28.
Remy, S., Beck, H., 2006. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. Brain 129 (Pt 1), 18–35.
Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., et al., 2017. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 58 (4), 512–521.
Seo, T., Ishitsu, T., Ueda, N., Nakada, N., Yurube, K., Ueda, K., et al., 2006. ABCB1 polymorphisms influence the response to antiepileptic drugs in Japanese epilepsy patients. Pharmacogenomics 7 (4), 551–561.
Seven, M., Batar, B., Unal, S., Yesil, G., Yuksel, A., Guven, M., 2014. The drug-transporter gene MDR1 C3435T and G2677T/A polymorphisms and the risk of multidrug-resistant epilepsy in Turkish children. Mol. Biol. Rep. 41 (1), 331–336.
Shaheen, U., Prasad, D.K., Sharma, V., Suryaprabha, T., Ahuja, Y.R., Jyothy, A., et al., 2014. Significance of MDR1 gene polymorphism C3435T in predicting drug response in epilepsy. Epilepsy Res. 108 (2), 251–256.
Sisodiya, S.M., 2005. Genetics of drug resistance. Epilepsia 46 (Suppl. 10), 33–38.
Sisodiya, S.M., Lin, W.R., Harding, B.N., Squier, M.V., Thom, M., 2002. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. Brain: J. Neurol. 125 (Pt 1), 22–31.
Yu, F.H., Catterall, W.A., 2003. Overview of the voltage-gated sodium channel family. Genome Biol. 4 (3), 207.
Yu, L., Liao, W.P., Yi, Y.H., Qiu, G., 2015. ABCB1 G2677T/A polymorphism is associated with the risk of drug-resistant epilepsy in Asians. Epilepsy Res. 115, 100–108.