Pharmacogenetic and case–control study on potassium channel related gene variants and genetic generalized epilepsy

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Abstract

Potassium channels are the targets of antiepileptic drugs (AEDs), which play important roles in the etiology of epilepsy. KCNA1 and KCNA2 encode mammalian Kv1.1 and Kv1.2 channels, which are essential roles in the initiation and shaping of action potentials. KCNV2 encodes Kv8.2, which is a regional overlap with Kv2 subunits as functional heterotramers. In our study, we aim to investigate whether variants of KCNA1, KCNA2, and KCNV2 genes influence susceptibility to genetic generalized epilepsies (GGEs) and the efficacy of AEDs. Seven hundred sixty-seven subjects (284 healthy controls, 279 drug-responsive, and 204 drug-resistant GGE patients) were enrolled in our study. Eight variants of KCNA1, KCNA2, and KCNV2 were assessed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry method. Results showed that there were no statistically significant correlations between the 8 variants of KCNA1, KCNA2, and KCNV2 and the risk/drug resistance of GGEs. In conclusion, our study suggests that KCNA1, KCNA2, and KCNV2 variants may not be involved in the risk/drug resistance of GGEs. Further multicenter, multiethnic, and large sample size pharmacogenetic and case–control studies are warranted to confirm our negative results.

Abbreviations: AEDs = antiepileptic drugs, CAE = childhood absence epilepsy, EGTCS = epilepsy with generalized tonic-clonic seizures, GGEs = genetic generalized epilepsies, JAE = juvenile absence epilepsy, JME = juvenile myoclonic epilepsy, LD = linkage disequilibrium, OR = odds ratio, tagSNPs = tagged-single nucleotide polymorphisms.

Keywords: drug resistant, genetic generalized epilepsies, KCNA1, KCNA2, KCNV1

1. Introduction

Epilepsy is a clinical syndrome characterized by abnormal electrical activity and is a common type of neurological diseases.[1] Genetic generalized epilepsies (GGEs) are characterized by unprovoked generalized seizures. And GGEs have no evidence for an acquired cause that results in absences, generalized myoclonic seizures, or primary generalized tonic-clonic seizures.[2,3]

As we know, there are a series of gene mutations that can change the channel function. Most of them encode ion channels, which play important roles in the pathogenesis of epilepsy. Among them, the dysfunction mutations of potassium channels were also identified to be associated with the pathology of GGEs.[1,4] Because of genes related to the dysfunction mutations of potassium channels related genes, they are called “K” channelopathies.[5] Among potassium channels related genes, KCNA1 and KCNA2 encode mammalian Kv1.1 and Kv1.2 channels, which are closely related to the initiation and shaping of action potentials. KCNV2 encodes Kv8.2, which is a regional overlap with Kv2 subunits as functional heterotramers.[1,6,7]

Several KCNA1 knockout mouse models develop epileptic phenotypes that imply the importance of electrophysiological roles on brain neuron function.[8–10] KCNA1 gene loss-of-function mutations were reported in episodic ataxia type 1 patients, who have epileptic seizures.[11–15] The growing body of accepted evidence demonstrates that KCNA1 variants cause reduced current amplitude, thus contributing to the pathogenesis of epilepsy. Moreover, Kv1.2 knockout mouse model also shows the increased susceptibility of seizure.[16] Furthermore, recent studies found de novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy, ataxia, and myoclonic epilepsy.[17–20] Notably, KCNV2 encodes Kv8.2 potassium channel that are involved in mediating the suppression of Kv2.1 currents.[21] It has been reported that KCNV2 mutations are associated with febrile, afebrile partial seizures, and epileptic encephalopathy, because the 2 nonsynonymous variants R7K
and M285R can alter the function of Kv2.1/Kv8.2 heterotetrameric potassium channels.\(^{[21]}\)

Although there are sorts of antiepileptic drugs (AEDs) to control the onset of GGEs, still ports of seizures are not well controlled. Previously, studies found that variants of ion channel or drug transporters genes (SCN1A, SCN2A, ABCB1, ABCC2) contributed to the drug-resistant epilepsy and influenced the efficacy of AEDs.\(^{[12–24]}\) However, the results are not consistent and not fully understood. Only a case of severe refractory epileptic patient was reported to suffer from KCNV2 p.Met285Arg mutation.\(^{[21]}\) To our knowledge, no studies are reported about the relationship between the variants of KCNA1/ KCNA2 and drug-resistant epilepsy. On the basis of the important electrophysiological roles of Kv1.1, Kv1.2, and Kv8.2 potassium channels in the brain neurons, we hypothesized that the variants of these potassium channel related genes would affect the efficacy of AEDs.

Herein, we performed a pharmacogenetic and case-control study to investigate the relationships between KCNA1/KCNA2/ KCNV1 variants and AEDs efficacy and the risk of GGEs.

2. Methods

2.1. Subjects

The patients and controls were enrolled from Xiangya Hospital and the Second Xiangya Hospital of Central South University, from January 14, 2013, to February 2014. GGEs and the subtype definitions were created according to the guidelines of the International League Against Epilepsy and standardized protocols.\(^{[25,26]}\) GGEs inclusion criteria are as follows: patients have normal intelligence, psychomotoric development, normal neurologic examination status; electroencephalography results present generalized spike-wave discharges (2.5–5Hz) and normal background activity, and Han Chinese patients. GGEs exclusion criteria are as follows: patients have structural, metabolic, or degenerative brain disorders, exclusively stimulus-induced seizures, mental retardation, severe adverse drug reactions, unreliable or lacking records of seizure frequency, poor compliance with AEDs, a history of alcohol or drug abuse, the presence of degenerative brain disorders, exclusively stimulus-induced seizures in the brain neurons, and Han Chinese patients. GGEs exclusion criteria are as follows: patients have structural, metabolic, or degenerative brain disorders, exclusively stimulus-induced seizures, mental retardation, severe adverse drug reactions, unreliable or lacking records of seizure frequency, poor compliance with AEDs, a history of alcohol or drug abuse, the presence of degenerative brain disorders, exclusively stimulus-induced seizures in the brain neurons, and Han Chinese patients. GGEs exclusion criteria are as follows: patients have structural, metabolic, or degenerative brain disorders, exclusively stimulus-induced seizures, mental retardation, severe adverse drug reactions, unreliable or lacking records of seizure frequency, poor compliance with AEDs, a history of alcohol or drug abuse, the presence of degenerative brain disorders, exclusively stimulus-induced seizures in the brain neurons, and Han Chinese patients. GGEs exclusion criteria are as follows: patients have structural, metabolic, or degenerative brain disorders, exclusively stimulus-induced seizures, mental retardation, severe adverse drug reactions, unreliable or lacking records of seizure frequency, poor compliance with AEDs, a history of alcohol or drug abuse, the presence of degenerative brain disorders, exclusively stimulus-induced seizures in the brain neurons, and Han Chinese patients. GGEs exclusion criteria are as follows: patients have structural, metabolic, or degenerative brain disorders, exclusively stimulus-induced seizures, mental retardation, severe adverse drug reactions, unreliable or lacking records of seizure frequency, poor compliance with AEDs, a history of alcohol or drug abuse, the presence of degenerative brain disorders, exclusively stimulus-induced seizures in the brain neurons, and Han Chinese patients.

According to the inclusion and exclusion criteria, 767 subjects were enrolled in our study, consisting of 284 healthy controls and 483 Chinese GGE patients. Two hundred seventy-nine drug-responsive patients and 204 drug-resistant patients were identified according to the definition guideline. The characteristics of subjects are summarized in Table 1. There were no differences between drug-responsive and resistant patients in age, sex, at the onset, and in the distribution of subgroups. All relevant data were shown in the manuscript. For further information, please contact the corresponding author.

SNPs enrolled in our study are summarized in Table 2. The LD tests of tagSNPs with patients’ data are shown in Fig. 1. The results showed that KCNA1 rs2227910 and rs7974459 have significant LD relationship, and KCNV2 rs7029012 and rs19677058 have significant LD relationship (\(D' = 74\) and 70, respectively). The distributions of all tagSNPs in GGEs and healthy controls are summarized in Table 3. Notably, there was no mutation subject in GGEs and healthy controls about KCNA1 rs112561866, which is a missense (p.Met499Le) variant. The investigated SNPs were all in Hardy–Weinberg equilibrium among the case-controls. Sanger sequencing validated the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry results were 100% correct. Comparisons with GGEs and healthy controls showed no difference in the distributions of all selected SNPs. In addition, we analyzed the
The healthy controls [48.4% vs 37.9%, OR = 1.57 (1.004–2.35), P = .015]. KCNV2 rs10967705 was also associated with the risk of CAE (Table 4). No significant KCNA1 and KCNV2 haplotypes that are related with the risk of GGEs were observed (Table 5).

Moreover, we also found the frequency of KCNV2 rs10967728 GC + CC genotype was lower in EGTCs than that in the controls [83.1% vs 92.2%, OR = 0.90 (0.81–0.99), P = .015]. KCNV2 rs10967705 was also associated with the risk of CAE (Table 4). No significant KCNA1 and KCNV2 haplotypes that are related with the risk of GGEs were observed (Table 5).

We analyzed the distributions of KCNA1, KCNA2 and KCNV2 loci in 204 drug-resistant patients and 279 drug-responsive patients. The frequency of KCNV2 rs10967728 CC genotype was higher in drug-resistant patients than that in drug-responsive patients [55.9% vs 46.4%, OR = 1.21 (1.01–1.44), P = .039] (Table 6). After analyzing the frequencies of potassium channel related genes haplotypes in the drug-resistant and drug-responsive patients, we found that a KCNV2 haplotype CCAG was associated with the risk of drug resistance. The frequency of KCNV2 haplotype CCAG were lower in the drug-resistant patients than that in the drug-responsive patients [16.1% vs 21.9%, OR = 0.691 (0.494–0.967), P = .03] (Table 7).

However, there were no significant associations between the 8 variants of KCNA1, KCNA2, and KCNV2 genes and the risk or drug resistance of GGEs after a Bonferroni correction for multiple comparisons.

4. Discussion

Ion channels are the electrophysiological basis of neuron activity. Notably, potassium channels play important roles in neuronal excitability and are associated with the inward-negative resting membrane potential.[11] Whether potassium channel related genes KCNA1, KCNA2, and KCNV1 affect the risk of GGEs and the efficacy of AEDs is still not clear. In our study, we collected 767 subjects, including 284 healthy controls and 483 Chinese GGEs patients (consisting of 279 drug-responsive patients and 204 drug-resistant patients) to study the associations between KCNA1, KCNA2, KCNV1, KCNV2, and KCNV3 variants with the risk of drug resistance of GGEs.
drug-resistant patients) and assessed the 8 SNPs of KCNA1, KCNA2, and KCNV1. Before a Bonferroni correction for multiple comparisons, there were tendencies suggesting that rs7029012 and rs10967705 of KCNV2 might be associated with the susceptibility of JME; rs10967705 of KCNV2 might be associated with the risk of CAE; and KCNV2 rs10967728 might be associated with the risk of EGTCS. In addition, KCNV2 rs10967728 and a haplotype CCAG might be associated with the GGEs drug resistance. However, after a Bonferroni correction for multiple comparisons, no variants of KCNA1, KCNA2, and KCNV1 are found statistically significantly related to the risk and the drug resistance of GGEs.

KCNV2 encodes the K+ channel Kv8.2, which is electrophysiologically silent when assembled in homotetramer and

Table 3
The distributions of potassium channel related genes tagSNPs in the GGEs and the healthy controls.

| Gene  | SNPs     | Models          | GGEs (%) (N = 483) | Controls (%) (N = 284) | OR (95% CI)  | P     |
|-------|----------|-----------------|-------------------|------------------------|--------------|-------|
| KCNA1 | rs2227910| C/G             | 66.6/33.4         | 65.6/34.4              | 1.04 (0.84–1.30) | .70   |
|       |          | CC/GG           | 44.9/43.1/11.8    | 43.0/45.2/11.8         | 1.66 (0.86–3.19) | .16   |
|       |          | (C+C+GG)        | 88.2/11.8         | 88.2/11.8              | 0.99 (0.67–1.50) | .99   |
|       |          | CC/(GG+CG)      | 44.9/54.1         | 43/57                  | 0.97 (0.85–1.1) | .61   |
|       | rs112561866| A/G            | 100/0             | 100/0                  | —             | —     |
|       | rs794459 | C/T             | 41.5/58.5         | 41.5/58.5              | 1.0 (0.81–1.24) | .99   |
| KCNA2 | rs388720 | G/T             | 63.7/36.2         | 66.3/33.7              | 0.89 (0.72–1.11) | .31   |
|       |          | GG/GT/TT        | 40.6/42.3/13.1    | 40.3/49.1/10.6         | —             | .55   |
| KCNV2 | rs7029012| C/G             | 22.1/77.9         | 21.5/78.5              | 0.94 (0.77–1.14) | .56   |
|       |          | CC/CG/GG        | 4.2/35.9/59.9     | 5/33/62                | —             | .66   |
|       |          | (CC+CG)/GG      | 40.1/59.9         | 38/62                  | 0.97 (0.86–1.09) | .56   |
|       |          | CC/(CG+GG)      | 4.2/95.8          | 5/95                   | 1.01 (0.98–1.04) | .61   |
|       | rs10967705| C/G             | 23.8/76.2         | 23.8/76.2              | 0.99 (0.78–1.28) | .99   |
|       |          | CC/GG           | 5/37/56/74        | 6.4/34/58.9            | —             | .58   |
|       |          | (CC+CG)/GG      | 42.6/57.4         | 41.1/58.9              | 0.98 (0.86–1.11) | .71   |
|       |          | CC/(CG+GG)      | 5.9/6/3/6         | 6.4/33.6               | 1.02 (0.98–1.05) | .41   |
|       | rs13285989| A/G             | 81.1/18.9         | 81.1/18.9             | 0.96 (0.74–1.25) | .77   |
|       |          | AA/AG/GG        | 66.3/33.6/4.1     | 68.3/32.6/4.0          | —             | .66   |
|       |          | (AA+AG)/GG      | 95.8/4.2          | 95.1/4.9               | 0.84 (0.63–1.14) | .62   |
|       |          | AA/(AG+GG)      | 66.3/33.7         | 66.3/31.7              | 1.06 (0.86–1.31) | .57   |
|       | rs10967728| G/C             | 29.2/70.8         | 28.4/71.6              | 1.04 (0.83–1.31) | .73   |
|       |          | GG/GC           | 8.8/90.9/0.2      | 7/84/1/51.1             | —             | .89   |
|       |          | (GG+GC)/CC      | 49/50.4           | 49.8/51.1              | 0.99 (0.95–1.14) | .86   |
|       |          | (GG+GC+GG)      | 8.8/91.2          | 7/92.2                 | 0.99 (0.90–1.03) | .64   |

Homozygous wild-type patients served as the reference group. CI = confidence interval, GGEs = genetic generalized epilepsies, OR = odds ratio.

Table 4
Significant differences on the distributions of potassium channel related genes tagSNPs in the GGE subtype patients and the healthy controls.

| Subtypes/SNPs     | Patients | Controls | P     | OR (95% CI) |
|-------------------|----------|----------|-------|-------------|
| JME/rs7029012     | C 69 (0.274) | C 121 (0.215) | .046 | 1.68 (0.88–2.83) |
|                   | G 183 (0.726) | G 443 (0.785) |       |             |
|                   | GG 65 (0.516) | GG 175 (0.621) |       |             |
| JME/rs10967705    | C 76 (0.297) | C 134 (0.238) | .047 | 1.57 (1.004–2.35) |
|                   | G 180 (0.703) | G 430 (0.762) |       |             |
|                   | GG 62 (0.494) | GG 166 (0.589) |       |             |
| EGTCs/rs10967728  | C 76 (0.297) | C 134 (0.238) | .072 | 1.35 (0.97–1.89) |
|                   | G 180 (0.703) | G 430 (0.762) |       |             |
|                   | GG 62 (0.494) | GG 166 (0.589) |       |             |
| CAE/rs10967728    | C 61 (0.175) | C 134 (0.238) | .104 | 1.36 (0.94–1.96) |
|                   | G 287 (0.825) | G 430 (0.762) |       |             |
|                   | CC 4 (0.023) | CC 18 (0.064) |       |             |
|                   | CG+GG 180 (0.978) | CG+GG 264 (0.936) |    |             |

Homozygous wild-type patients served as the reference group. CAE = childhood absence epilepsy, G = confidence interval, EGTCs = epilepsy with generalized tonic-clonic seizures, JME = juvenile myoclonic epilepsy, OR = odds ratio.
modulates the properties of Kv2 and Kv3 channels to influence membrane translocation and channel properties.[1,21] Kv8.2 localizes with Kv2.1 as a contributor to the delayed rectifier potassium current in hippocampal pyramidal neurons, which is of particular importance for seizure generation.[30] Moreover, a potassium current in hippocampal pyramidal neurons, which localizes with Kv2.1 as a contributor to the delayed rectifier potassium current of particular importance for seizure generation.[30]

Clinical severity differs between these 2 variants of KCN2. Functional study found that the 2 variants could enhance Kv8.2-mediated suppression of Kv2.1 currents.[21] Variant. Functional study found that the 2 variants could enhance Kv8.2-mediated suppression of Kv2.1 currents.[21] However, studies found that the synonymous variants could change the function of their products protein.[31,32] The mechanisms were alteration in mRNA stability and induction of translational pausing to modify the protein abundance, structure, and activity. Synonymous variant rs10967705 does not change

associated with JME before a Bonferroni correction. Rs7029012 is a 5' UTR variant (c. -42C>G) within an exon, but not a translated 5' end of the gene. As a promoter region variant, it may influence the binding of acting element in inducing the expression changes of KCNV2. Further studies on whether the variant affect KCNV2 are warranted. Rs10967705 was found to be associated with the risk of JME and CAE, as a synonymous variant (p. Gly61Gly), before a Bonferroni correction was made. Synonymous variants do not produce altered coding sequences. Hence, they are not expected to change the function of the protein if they mutate. However, studies found that the synonymous variants could change the function of their products protein.[31,32] The mechanisms were alteration in mRNA stability and induction of translational pausing to modify the protein abundance, structure, and activity. Synonymous variant rs10967705 does not change

Table 6

| Genes | SNPs | Models | Drug-resistant (N = 204) (%) | Drug-responsive (N = 279) (%) | OR (95% CI) | P |
|-------|------|--------|-----------------------------|-----------------------------|-------------|---|
| KCNA1 | rs2227910 | C/G | 66.3/33.7 | 66.7/33.3 | 0.98 (0.75–1.29) | .90 |
| | | C/G | 46.6/43.5/11.9 | 45.2/43.0/11.8 | — | — |
| | | (GG+GC)/GG | 88.7/11.3 | 88.2/11.8 | 1.01 (0.61–1.66) | .97 |
| | | (CC+GG)/GG | 44.6/55.4 | 45.2/54.8 | 1.01 (0.86–1.19) | .98 |
| | rs112561866 | A/G | 100/0 | 100/0 | — | — |
| | | C/T | 42.1/57.9 | 41.1/58.9 | 1.04 (0.80–1.35) | .76 |
| | | CC/TT/TT | 18.3/47.5/34.2 | 17.5/47.3/35.3 | — | — |
| | | (CG+CC)/GG | 65.6/34.2 | 64.7/35.3 | 0.97 (0.76–1.24) | .80 |
| | | CC/CT/TT | 18.3/81.7 | 17.5/82.5 | 0.99 (0.91–1.08) | .81 |
| KCNA2 | rs3887820 | G/T | 64.5/35.5 | 63.2/36.8 | 1.06 (0.81–1.38) | .67 |
| | | GG/TT/TT | 41.9/45.3/12.8 | 39.7/46.9/13.4 | .89 |
| | | GG/TT/TT | 87.2/12.8 | 86.6/13.4 | 0.96 (0.60–1.53) | .86 |
| | | GG/TT/TT | 41.9/58.1 | 39.7/60.3 | 0.96 (0.83–1.12) | .63 |
| KCNV2 | rs7029012 | C/G | 19.5/80.5 | 24.1/75.9 | 0.76 (0.56–1.04) | .09 |
| | | CC/GG/GG | 4/65 | 4/65 | 4.3/39.5/56.2 | — |
| | | (CC+CG)/GG | 35/65 | 43.8/56.2 | 1.16 (1–1.34) | .05 |
| | | (CC+CG)/GG | 4/96 | 4/96 | 4.3/95.7 | 1.0 (0.97–1.04) | .83 |
| | rs10967705 | C/G | 21.3/78.7 | 25.5/74.5 | 0.79 (0.58–1.07) | .13 |
| | | CC/GG/GG | 4.9/32.8/62.3 | 5/41/54 | — | .17 |
| | | (CC+CG)/GG | 37.7/26.5 | 45/54 | 1.15 (0.99–1.34) | .07 |
| | | CC/GG/GG | 4.9/95.1 | 5/95 | 1.0 (0.96–1.04) | .95 |
| | rs13285989 | A/G | 80/20 | 81.8/18.2 | 0.89 (0.64–1.23) | .49 |
| | | AA/AG/GG | 64.5/31/4.5 | 67.6/28.4/4 | — | .78 |
| | | (AA+AG)/GG | 96/4 | 96/4 | 1.12 (0.47–2.65) | .80 |
| | | AA/AG/GG | 64.5/35.5 | 67.6/32.4 | 1.1 (0.85–1.41) | .48 |
| | | (GG+GT)/TT | 26/74 | 31.5/68.5 | 0.76 (0.57–1.01) | .06 |
| | | GG/CC/CC | 7.9/36.1/55.9 | 9.4/44.2/46.4 | 1.2 |
| | | (GG+GT)/TT | 44.1/55.9 | 53.6/46.4 | 1.21 (1.01–1.44) | .039 |
| | | GG/CC/CC | 7/92.1 | 9.4/90.6 | 1.02 (0.96–1.08) | .57 |

Homzygous wild-type patients served as the reference group.

CI = confidence interval, OR = odds ratio.
the amino acid of KCNV2. We hypothesized that it may influence the function of K+ channel Kv8.2 via these mechanisms. Moreover, Rs10967705 was a strong LD with rs7029012 and these 2 variants may jointly influence the function of Kv8.2. Rs10967728 was associated with the risk of EGTCs and drug resistance, as an intron variant. This variant may have the possibility of LD with functional SNPs.

KCNA1 and KCNA2 encode 2 Kv1 subfamilies called Kv1.1 and Kv1.2 subunits, which play essential roles in the initiation and shaping of action potentials in synaptic terminals, axons, soma, and proximal dendrites. Several heterozygous point mutations of KCNA1 were reported with generalized or partial seizures in episodic ataxia type 1, which is a neurological disease characterized by generalized ataxia attacks and spontaneous muscle quivering. KCNA2 was reported as having the risk of mild to severe epileptic encephalopathy and myoclonic epilepsy. In our study, we have not observed rs2227910, rs11256186, and rs7974459 of KCNA1 and rs3887820 of KCNA2 loci associated with the risk of GGEs and their subgroups.

Antiepileptic drug resistance is an important and complex problem. Although multiple drugs were used for the treatment, the conditions of some of the patients were not under good control. AEDs target multiple but not specific ion channels to play the pharmacological action, which creates complex electrophysiological situations in brain neurons. Previous research found that SCN1A gene polymorphism IVS5–91 rs3812718 G>A and SCN2A IVS7–32A>G rs2304016 might be associated with the drug-resistant epilepsy, which implies that the variants of the target genes of AEDs may influence the drug efficacy, as the potential drug target and the important electrophysiological roles in brain, KCNA1, KCNA2, and KCNV2 may influence the pharmacoresistance of AEDs. In our study, we also carried out the pharmacogenetic study to investigate the association between variants of KCNA1, KCNA2, and KCNV2 and GGEs drug resistance. We found that rs10967728 and a haplotype CCAG of KCNV2 might be related with GGEs drug resistance before a Bonferroni correction for multiple comparisons. But after a Bonferroni correction, the significant association has disappeared. Herein, further large-scale studies of whether and how the variant and haplotype affect the function of Kv8.2 are needed.

Some limitations exist in our study. First, the SNPs and genes selected for analysis in our study were limited and the sample size was relatively small. Second, the evaluation of AEDs’ efficacy and the definition of subgroups of GGEs were not as accurate as we had expected. All these limitations need further improvements in future research.

In conclusion, we have conducted a pharmacogenetic and case–control study to evaluate the role of the variants of KCNA1, KCNA2, and KCNV2 in the susceptibility and drug resistance of GGEs. Our results have revealed no significant association between 8 variants of KCNA1, KCNA2, and KCNV2 genes and risk or drug resistance of GGEs after a Bonferroni correction for multiple comparisons. Further larger sample clinical studies would be warranted to confirm our negative results.

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*Table 7*

| Gene | Haplotypes | Drug-resistant (n = 204) | Drug-responsive (n = 279) | Odds ratio (95% CI) | P |
|------|------------|--------------------------|--------------------------|---------------------|---|
| KCNA1 | CGT        | 0.987                    | 0.084                    | 1.041 (0.657–1.651) | .86|
|      | GGC        | 0.577                    | 0.325                    | 1.030 (0.783–1.356) | .83|
|      | GGT        | 0.333                    | 0.325                    | 1.030 (0.783–1.356) | .83|
| KCNA2 | CCAG       | 0.161                    | 0.219                    | 0.691 (0.494–0.967) | .03|
|      | CGG        | 0.094                    | 0.075                    | 1.296 (0.817–2.057) | .27|
|      | CGA        | 0.504                    | 0.509                    | 1.007 (0.773–1.311) | .96|
|      | GGC        | 0.185                    | 0.152                    | 1.281 (0.908–1.808) | .16|

*The polymorphisms are listed in the same order presented in Table 2. All polymorphisms with frequencies <-0.03 were ignored in this analysis.

CI = confidence interval. OR = odds ratio.
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