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ORIGINAL RESEARCH

Genetic Association of Epilepsy and Anti-Epileptic Drugs Treatment in Jordanian Patients

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Purpose: The aim of this study was to investigate the possible effects of single-nucleotide polymorphisms (SNPs) within SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 genes on response to anti-epileptic drugs (AEDs) and the genetic predisposition of epilepsy in Jordanian patients.

Patients and Methods: A total of 299 healthy individuals and 296 pediatric patients from the Jordanian population were recruited. Blood samples are collected, and genotyping was performed using a custom platform array analysis.

Results: The SLC1A1 rs10815018 and FAM131B rs4236482 polymorphisms found to be associated with epilepsy susceptibility. Moreover, SLC1A1 rs10815018 and GPLD1 rs1126617 polymorphisms were associated with generalized epilepsy (GE), while FAM131B rs4236482 is associated with the focal phenotype. Regarding the therapeutic response, the genetic polymorphisms of FAM131B rs4236482, GABRA1 rs2279020, and CACNG5 rs740805 are conferred poor response (resistance) to AEDs. There was no linkage of GLPD1 haplotypes to epilepsy, its subtypes, and treatment responsiveness.

Conclusion: Our findings suggested that SLC1A1, FAM131B, and GPLD1 polymorphisms increasing the risk of generating epilepsy, while FAM131B, GABRA1, and CACNG5 variants may play a role in predicting drug response in patients with epilepsy (PWE).

Keywords: pharmacogenetics, anti-epileptic drugs, generalized epilepsy, focal epilepsy, pharmacotherapy, Jordan

Introduction

Epilepsy is a common neurological condition that affects people of all ages.[1] Epilepsy is affecting more than70 million individuals worldwide, wherein the number of patients is growing in developing countries nowadays.[1] It also has a substantial impact on patients' morbidity and mortality.[2] Although the etiology of epilepsy remains unsettled, different evidences suggested that epilepsy could be generated due to genetic variants. It is believed that more than 70% of patients with epilepsy (PWE) have a genetic predisposition.[3] Genetic abnormalities can alter the electrical impulses, affect channels function, modify neuronal excitability, and may also disrupt pharmacokinetics of AEDs, and therefore affect treatment efficacy.[4]

Epilepsy have many different syndromes and types which have studied extensively. However, information regarding detailed genetic factors and AED selection for the individual patient is insufficient; hence, the importance of pharmacogenomic studies in this area rises considerably.[5] To date, there is a limited number of studies investigating the genetic and pharmacogenetic basis of common diseases, including epilepsy among the Jordanian population.[6–11] Recent studies found that epilepsy is

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associated with several chromosomal regions, where mutations in these regions cause neurological dysfunction.[12] The solute carrier gene, SLC1A1, is a high-affinity glutamate transporter that is associated with neurodevelopmental phenotypes, such as myoclonic-atonic epilepsy and schizophrenia.[13,14] The other family member, the SLC6A1 gene, encodes a voltage-dependent gamma-aminobutyric acid (GABA) transporter GAT-1, which is accounts for GABA reuptake from the synapse. The latter of which is an essential inhibitory neurotransmitter that stabilizes the brain's neuronal excitation.[15] Several mutations within the SLC6A1gene were reported in patients with myoclonic-atonic seizures.[15] The FAM131B gene is not well characterized yet; however, it is identified in patients with brain neoplasia such as astrocytoma and glioma.[16] The glycosylphosphatidylinositol phospholipase, D1GPLD1 is encoded as a plasma protein.[17] This gene is found mainly in the liver and brain, which may have a role in epilepsy pathology and pharmacology.[17] For the F2 gene, especially the rs1799963 SNP, it showed to has some linkage with vascular and thrombotic diseases.[18] Variants in the F2 gene are associated with increased production of prothrombin, which can lead to multiple neurological conditions.[19] GABRG2 gene is encoding GABA, one of the brain's main inhibitory neurotransmitters. Alteration in this gene is associated with epilepsy, as it may affect transcription, translation efficiency, as well as mRNA stability.[20] GABRG2 and GABRA1mutations can cause impairment in GABA receptor function and biogenesis, in addition to the association with receptor mobilization. For this, GABRG2 and GABRA1 are highly implicated in the etiology of epilepsy.[21] CACNG5 gene is encoding type II transmembrane AMPA receptor regulatory proteins (TARP). TARPs have a role in trafficking regulations and channel gating of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) receptors, which contribute to neuronal developmental and may play a role in the etiology of multiple neurological disorders.[22]

Thus, epilepsy is a crucial issue in clinical research, and there are promising results in its diagnosis and treatment. In the study, we aiming to assess the possible association between the targeted genetic variants of SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 genes in epilepsy susceptibility and AEDs response in Jordanian PWE.

Patients and Methods

Ethical Approval

This study was approved by the Ethics Committee of Jordan University of Science and Technology (16/111/2017), Queen Rania Al Abdullah Hospital (QRAH), and the Jordanian Royal Medical Services (JRMS). Informed written consent was provided by patients or their parents/guardians before enrolment in this study.

Participants and Treatment Approach

A total of 296 pediatric patients with epilepsy were recruited from the Pediatric Neurology Clinic at QRAH. Control subjects (299) were recruited from the Blood Bank at the JRMS. Participants' data and selection criteria have been reported previously in more detail.[10] The patients were classified according to the guidelines of the International League Against Epilepsy (ILAE, 2010).[23,24] The patients were aged less than 15 years, having two attacks of seizures within more than 24 hours apart, and receiving AEDs for a minimum of three months. The exclusion criteria rule out patients that have no sufficient medical records, unreliable seizure frequency, have liver disease, incompliant patients, or not visiting the clinics regularly for the follow-up. In addition, patients with abnormal psychometric development and neurological examination were also excluded.

According to the treatment protocol of QRAH, treatment of patients with generalized epilepsy (GE) starts at a dose of 10mg/kg valproic acid (VPA) (G.L. Pharma GmbH, Lannach, Austria). For patients with focal epilepsy (FE), patients were initially received 5 mg/kg of carbamazepine (CBZ) (Novartis Pharmaceuticals UK Ltd., Surrey, England). After the initiation of the treatment, the seizure was monitored for the first three to four weeks in order to evaluate the effectiveness of drug doses. During the follow-up visits, the therapeutic doses were increased gradually to reached 20 and 10 mg/kg of VPA and CBZ, respectively, to minimize seizure recurrence.

Regarding their response to AEDs, patients are classified into either drug-responsive or drug-resistant during the evaluation interval. On the one hand, if patients are seizure-free for at least three times the longest inter-seizure interval, or 12 months before starting a new intervention, regardless of which is longer, therefore, patient classified as responsive (124 subjects).[25] On the other hand, the resistant group (171 subjects) failed trials of

two adequately chosen AED to achieve sustained seizure freedom, whether as monotherapies or in combination.[25]

DNA Extraction and Genotyping

Nine SNPs (rs10815018, rs10510403, rs4236482, rs1126617, rs2076317, rs1799963, rs209337, rs2279020, and rs740805) were selected from SNP databases of the Applied Biosystems (http://www.appliedbiosystems.com), Ensembl (http://www.ensembl.org/index.html), and the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/SNP/). These SNPs are either previously studied in other ethnic groups or located in genes known to be associated with epilepsy phenotypes or affect treatment response. The peripheral blood of the participants was collected in EDTA tubes, and the genomicDNA was extracted using Wizard Genomic DNA purification kit according to the supplier's instructions (Promega Corporation, Madison, WI, USA). DNA samples were genotyped in association with the Australian Genome Research Facility (AGRF) using the MassARRAY (iPLEX GOLD) system (Sequenom, San Diego, CA, USA).

Statistical Analysis

The obtained data analysis has carried out using the Statistical Package for Social Sciences (SPSS) software version 22.0 (IBM Corporation, New York, USA) in addition to SNPStats Web Tool (https://www.snpstats.net/start.htm). Allele and genotype frequencies between patients and controls, as well as genotype frequencies deviation from Hardy–Weinberg equilibrium, were estimated by Chi-square (χ^2) test. A *P*-value of less than 0.05 was considered a significant value.

Table 1 The Distributions of SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 SNPs in Resistant and Responsive Patients

Gene	rs Number	Model	Resistant Patients%	Responsive Patients%	*P*-value
SLC1A1	rs10815018	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	62.7/27.8/9.5 62.7/37.3 90.5/9.5	56.3/38.7/5 56.3/43.7 95/5	0.088 0.27 0.15
SLC6A1	rs10510403	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	68.8/25.9/5.3 68.8/31.2 94.7/5.3	60.5/34.7/4.8 60.5/39.5 95.2/4.8	0.27 0.14 0.86
FAM131B	rs4236482	GG/GA/AA GG/(AG+AA) (GG+AG)/AA	67.8/26.9/5.3 67.8/32.2 94.7/5.3	54/33.1/12.9 54/46 87.1/12.9	0.018 0.016 0.021
GPLD1	rs1126617	CC/CT/TT CC/(CT+TT) (CT+CC)/TT	59.1/36.3/4.7 59.1/40.9 95.3/4.7	56.6/39.3/4.1 56.6/43.4 95.9/4.1	0.86 0.67 0.81
	rs2076317	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	49.2/42.7/8.1 49.2/50.8 91.9/8.1	48/42.1/9.9 48/52 90.1/9.9	0.86 0.83 0.91
F2	rs1799963	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	97.1/2.3/0.6 97.1/2.9 99.4/6	93.5/6.5/0 93.5/6.5 100/0	0.13 0.15 0.30
GABRG2	rs209337	CC/CA/AA CC/(CA+AA) (CC+CA)/AA	91.2/8.2/0.6 91.2/8.2 99.4/0.6	93.5/6.5/0 93.5/6.5 100/0	0.50 0.47 0.30
GABRA1	rs2279020	AA/GA/GG AA/(GA+GG) (AA+GA)/GG	27.4/56/16.7 27.4/72.64 83.3/16.7	41.3/43.8/14.9 41.3/58.7 85.1/14.7	0.044 0.013 0.68
CACNG5	rs740805	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	91.2/7.7/1.2 91.2/8.8 98.8/1.2	82.9/17.1/0 82.9/17.1 100/0	0.017 0.035 0.14

Results

In this study, a total of 296 Jordanian pediatric patients with epilepsy were enrolled (162, 54.8% males; 134, 45.2% females; mean±SD age: 7.1±4.1), in addition to 299 healthy controls of matched sex and ethnicity (152, 50.8% males; 147, 49.2% females; meanage±SD: 5.94 ±3.7) with no significant differences in terms of gender and age. More than half of the patients were drug-resistant (171, 58.1%), and 41.9% (124) were drug-responsive. The studied SNPs exhibited no association with response status to AEDs except for the FAM131B rs4236482, GABRA1 rs2279020, and CACNG5 rs740805 (Table 1). For the rs4236482, G allele (ie, in homozygous or heterozygous genotype) has emerged as a risk factor in drug-resistant patients (P= 0.018, 0.016, and 0.021), which is also seen in rs2279020 (*P*= 0.04, and 0.013). The AA genotype of rs740805polymorphism has a higher risk of developing drug resistance in patients (*P*= 0.017, and 0.035).

Genetic and allelic distribution of the polymorphisms between healthy controls and PWErevealed genetic association only in SLC1A1 rs10815018 and FAM131B rs4236482 SNPs (Table 2). It found that rs10815018AA genotype (*P*= 0.025) and rs4236482 G allele (*P*= 0.038, and 0.014) are risk factors for increasing epilepsy susceptibility. Furthermore, epileptic patients are classified into those with generalized epilepsy (172) and focal epilepsy (124). The analysis showed that rs1126617 SNP of GPLD1, and rs10815018 of the SLC1A1 gene are associated with the susceptibility to have GE (Table 3). As the latter SNP AA genotype is found earlier to be associated with epilepsy, it is further found to be associated with its generalized onset (*P*= 0.016, 0.004). In the case of focal

Table 2 The Distributions of SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 SNPs in PWE and Healthy Controls

Gene	rs Number	Model	PWE %	Control %	*P*-value
SLC1A1	rs10815018	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	60.2/32.2/7.6 60.2/39.8 92.4/7.6	51/39.2/9.8 51/49 90.2/9.8	0.08 0.025 0.35
SLC6A1	rs10510403	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	65.1/29.8/5.1 65.1/34.9 94.9/5.1	63/31.6/5.4 63/37 94.6/5.4	0.87 0.59 0.87
FAM131B	rs4236482	GG/GA/AA GG/(AG+AA) (GG+AG)/AA	61.8/29.7/8.4 61.8/38.2 91.5/8.4	62.5/33.8/3.7 62.5/37.5 96.3/3.7	0.038 0.86 0.014
GPLD1	rs1126617	CC/CT/TT CC/(CT+TT) (CT+CC)/TT	58.2/37.4/4.4 58.2/41.8 95.6/4.4	58.5/34.1/7.4 58.5/41.5 92.6/7.4	0.27 0.93 0.13
	rs2076317	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	48.6/42.2/9.1 48.6/51.4 90.9/9.1	48.5/40.5/11 48.5/51.5 89/11	0.72 0.97 0.44
F2	rs1799963	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	95.6/4/0.3 95.6/4.4 99.7/0.3	97/3/0 97/3 100/0	0.39 0.37 0.24
GABRG2	rs209337	CC/CA/AA CC/(CA+AA) (CC+CA)/AA	92.2/7.5/0.3 92.2/7.8 99.7/0.3	93.3/6.7/0 93.3/6.7 100/0	0.46 0.60 0.24
GABRA1	rs2279020	AA/GA/GG AA/(GA+GG) (AA+GA)/GG	33.5/50.7/15.9 33.5/66.5 84.1/15.9	34.3/48.5/17.2 34.3/65.7 82.8/17.2	0.85 0.82 0.67
CACNG5	rs740805	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	87.8/11.6/0.7 87.8/12.2 99.3/0.7	87.8/11.2/1 87.8/12.2 99/1	0.90 0.98 0.66

Table 3 The Distributions of SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 SNPs in Patients with Generalized Epilepsy (GE) and Healthy Controls

Gene	rs number	Model	GEP %	Control %	*P*-value
SLC1A1	rs10815018	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	64.7/28.2/7.1 64.7/35.3 92.9/7.1	51/39.2/9.8 51/49 90.2/9.8	0.016 0.004 0.31
SLC6A1	rs10510403	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	65.7/27.9/6.4 65.7/34.3 93.6/6.4	63/31.6/5.4 63/37 94.6/5.4	0.66 0.55 0.65
FAM131B	rs4236482	GG/GA/AA GG/(AG+AA) (GG+AG)/AA	61.6/31.4/7 61.6/38.4 93/7	62.5/33.8/3.7 62.5/37.5 96.3/3.7	0.28 0.84 0.12
GPLD1	rs1126617	CC/CT/TT CC/(CT+TT) (CT+CC)/TT	56.7/40.9/2.3 56.7/43.3 97.7/2.3	58.5/34.1/7.4 58.5/41.5 92.6/7.4	0.029 0.70 0.015
	rs2076317	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	45.4/47.7/7 45.4/54.6 93/7	48.5/40.5/11 48.5/51.5 89/11	0.17 0.51 0.14
F2	rs1799963	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	94.8/4.7/0.6 94.8/5.2 99.4/0.6	97/3/0 97/3 100/0	0.24 0.23 0.16
GABRG2	rs209337	CC/CA/AA CC/(CA+AA) (CC+CA)/AA	89.5/9.9/0.6 10.5/99.4 90.1/9.9	93.3/6.7/0 6.7/100 93.3/6.7	0.16 0.15 0.15
GABRA1	rs2279020	AA/GA/GG AA/(GA+GG) (AA+GA)/GG	33.7/50/16.3 33.7/66.3 83.7/16.3	34.3/48.5/17.2 34.3/65.7 82.8/17.2	0.94 0.89 0.80
CACNG5	rs740805	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	88.8/11.2/0 88.8/11.2 100/0	87.8/11.2/1 87.8/12.2 99/1	0.25 0.75 0.098

epileptic patients, none of the studied SNPs were associated, except for the FAM131B rs4236482, where the homozygous AA genotype increases the risk of its development (Table 4; P= 0.23, 0.008).

The three haplotypes of the GPLD1 gene failed to show any linkage with epilepsy, its broad types, or treatment response among the patients (Tables S1–S4).

Discussion

Several genetic and pharmacogenetic studies attempted to investigate the correlation of different gene polymorphisms with respect to the susceptibility to develop epilepsy, and response to AEDs treatment.[15,26–31] However, as most studies investigate previously examined candidate genes, we tend to include some genes associated with various neural pathways, different neurological disorders, and response to antipsychotic drugs.[15,32–35]

Although there are several different pharmacokinetic factors regulating drug metabolism at different stages (absorption, distribution, metabolism, and clearance), yet genetic polymorphisms are likely to alter the final phenotype.[36,37] To date, the gap between drug-resistant epilepsy prevalence and the explored genetic variants still considerable. Around 20% of pediatric patients with epilepsy are pharmacoresistant, as they exhibit resistance to multiple AEDs.[38] Epilepsy treatment response is characterized by the remission of seizures and responders to drug treatment, it is defined by the ILAE as "individuals being seizure-free for at least 12 months after starting AED therapy".[39] In our study, the examined SNPs rs10815018, rs10510403, rs1126617,

Table 4 The Distributions of SLC1A1, SLC6A1, FAM131B, GPLD1, F2, GABRG2, GABRA1, and CACNG5 SNPs in Patients with Focal Epilepsy (FE) and Healthy Controls

Gene	rs Number	Model	FEP %	Control %	*P*-value
SLC1A1	rs10815018	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	53.8/37.8/8.4 53.8/46.2 91.6/8.4	51/39.2/9.8 51/49 90.2/9.8	0.84 0.61 0.66
SLC6A1	rs10510403	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	64.2/32.5/3.2 64.2/35.8 96.8/3.2	63/31.6/5.4 63/37 94.6/5.4	0.63 0.81 0.33
FAM131B	rs4236482	GG/GA/AA GG/(AG+AA) (GG+AG)/AA	62.1/27.4/10.5 62.1/37.9 89.5/10.5	62.5/33.8/3.7 62.5/37.5 96.3/3.7	0.023 0.93 0.008
GPLD1	rs1126617	CC/CT/TT CC/(CT+TT) (CT+CC)/TT	60.2/32.5/7.3 60.2/39.8 92.7/7.3	58.5/34.1/7.4 58.5/41.5 92.6/7.4	0.95 0.76 0.99
	rs2076317	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	53.2/34.7/12.1 53.2/46.8 87.9/12.1	48.5/40.5/11 48.5/51.5 89/11	0.54 0.38 0.76
F2	rs1799963*	GA/AG	96.8/3.2	97/3	0.91
GABRG2	rs209337*	CC/CA	96/4	93.3/6.7	0.27
GABRA1	rs2279020	AA/GA/GG AA/(GA+GG) (AA+GA)/GG	33/51.7/15.2 33/67 84.8/15.2	34.3/48.5/17.2 34.3/65.7 82.8/17.2	0.82 0.80 0.63
CACNG5	rs740805	AA/AG/GG AA/(AG+GG) (AA+AG)/GG	86.3/12.1/1.6 86.3/13.7 98.4/1.6	87.8/11.2/1 87.8/12.2 99/1	0.84 0.67 0.62

Note: *Monomorphic SNP.

rs2076317, rs1799963, and rs209337 did not show any linkage with treatment response. Based on the genotype and allele analysis, the G allele was of significantly higher distribution in drug-resistant patients withrs4236482 and rs2279020 intronic variants (278, 81% and 150, 55%, respectively) compare to the responsive group (175, 71% and 89, 37%, respectively). To the best of our knowledge, rs4236482 did not show previously to be associated with the efficacy of AEDs treatment. As a result, FAM131Bvariantsare expected to interfere with any of the drug modulation steps, an issue that needs substantial investigation. The GABRA1receptor variants, such as rs2279020 were examined as a potential factor affecting treatment efficacy.[26–28,40] Our results support the association of rs2279020 with AEDsresistance, which contradicts the result in Chinese Han PWE,[40] but similar to Indian patients.[27] Moreover, as suggested that voltage-dependent calcium channels (VDCCs) genes are one of the major effectors in pharmacogenetics of epilepsy,[41–43] A allele of CACNG5 rs740805 appear to associated with the drug resistance phenotype with a higher rate in resistant patients (323, 95% vs 225, 91% in the responsive group). This finding suggested the idea that other VDCCs genes may play a role in epilepsy treatment outcomes.

In this study, we failed to show an association between the SLC6A, F2, and GABRA1 polymorphisms and vulnerability to develop epilepsy in general, its broad phenotypes, or treatment efficacy in our population. However, SLC1A1rs10815018 is associated with epilepsy and its generalized seizures. This result is expected since this glutamate transporter variants have been reported in one of the reflux epilepsies; the hot water epilepsy,[44] and other several neurodevelopmental disorders, such as schizophrenia,[45] obsessive-compulsive,[46,47] and Rett syndrome (RTT).[14] Furthermore, SLC1A1 was observed in patients with either focal or generalized epilepsy from four different regions (Brussels, Belgium, Dublin, and Ireland).[48] In addition, FAM131B rs4236482 is significantly associated in patients with epilepsy, and

particularly, in patients with focal onset seizures. On the other hand, Kampen et al reported the association of the FAM131B gene in a sixteen-year-old boy with generalized tonic-clonic seizures.[49] Considering its association with drug resistance in the study population, this represents the first step toward an intensive characterization of the FAM131Bvariations. Moreover, GPLD1 rs1126617 is also associated with the generalized onset epilepsy. Of the epilepsy type classification studied by Shazadi et al, four out of 16 SNPs were in strong linkage disequilibrium with each other, including rs2076317 and rs1126617 variants of the GPLD1 gene.[50] These findings shed light on the relation between SLC1A, GPLD, and FAM131B genes with epilepsy seizures classes and highlight the importance of patient classification with respect to their treatment response.

Conclusions

Overall, epilepsy is a common chronic neurological disorder affecting millions of people worldwide causing considerable morbidity and mortality.[51] This disease is affected by several factors, and genetic factors are believed to play a major role in epileptogenesis. This study presents for the first time some variants that affect disease development and its treatment as well in the Jordanian epileptic patients. Further pharmacogenetic studies are needed to identify other genetic factors that affect genetic susceptibility and treatment responsiveness outcomes to improve the efficacy and safety of epilepsy treatment. The findings need to be confirmed by the recruitment of a larger sample size and including further analysis exploring SNP-SNP, gene-gene, and haplotype–haplotype interaction, in addition to functionality studies to characterize the appearance of particular phenotypes.

Disclosure

The authors report no conflicts of interest in this work.

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